Fetal Alcohol Effects: A Review of the Current Literature and a Proposed Study of the Possible Additive Effects of Marihuana and Alcohol on the Fetus

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FETAL ALCOHOL EFFECTS: A REVIEW OF THE CURRENT LITERATURE
AND A PROPOSED STUDY OF THE POSSIBLE ADDITIVE EFFECTS
OF MARIHUANA AND ALCOHOL ON THE FETUS

by

Shirley Lange Kamp

A Thesis
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
requirements for the
Degree of Master of Arts
Department of Psychology

Western Michigan University
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The purpose of this paper was to review the current state of knowledge regarding the effects of alcohol ingestion during pregnancy, to determine the specific issues that remain under speculation, and to develop a theoretical research design which might aid in determining the role, if any, of marihuana in compounding fetal alcohol effects.

The literature reviewed indicated that alcohol creates a continuum of fetal effects from mild abnormalities to the full fetal alcohol syndrome; current marihuana studies suggest possible adverse effects on the fetus. The research model was based on this evidence, the well-documented usage of both drugs by women of childbearing age, and the lack of current studies that examine the additive effects of alcohol and marihuana. The proposed design was modeled after the most definitive studies in the literature pertaining to fetal alcohol effects.
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Although a number of sources were consulted while preparing this thesis, I am particularly grateful for the advice of my committee, professors Chris Koronakos, Malcolm Robertson, and Wayne Fuqua. I am also greatly indebted to Lee Kamp and Kristen Elliott-Willis for their invaluable assistance and support.

Shirley Lange Kamp
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Western Michigan University M.A. 1980

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Introduction

In the past decade the medical and scientific communities have published a wealth of information regarding the impact of alcohol use during pregnancy. Research indicates that alcohol ingestion creates a wide spectrum of fetal effects, ranging from mild behavioral and growth abnormalities to the full fetal alcohol syndrome (FAS). While the experts are not always in complete agreement and many questions remain unanswered, research continues, resulting in a more knowledgeable and aware public. The purpose of this paper is to review the pertinent literature in this area, determine the current state of knowledge, and present a theoretical research model.

Historical Citations

The incompatibility of alcohol and pregnancy has been noted throughout history. There are indications in the Bible (Judges 13: 3-4) that people were aware that alcohol may have an adverse effect if ingested during pregnancy. One of the myths of ancient Rome was the belief that intoxication at the time of conception would lead to the birth of a damaged child; the deformed blacksmith of the gods, Vulcan, was believed to be the result of such influence (cited in Green, 1974). Haggard and Jellinek (1942) cite an ancient Carthaginian ritual that prohibited the drinking of wine by the bridal couple on their wedding night to prevent
the conception of defective children. Rosett (1976) included the following observations in his review of the effects of maternal drinking on child development:

In 1621 Burton, in the Anatomy of Melancholy cited Aristotle's observation that "foolish and drunken and harebrained women most often bring forth children like unto themselves, morose and languid." In 1720, England lifted restrictions on distillation, and cheap gin flooded the country. In 1726, soon after the onset of the "gin epidemic," the College of Physicians reported to Parliament that parental drinking is a "cause of weak, feeble and distempered children." Morris, in 1759, attributed the drop in birthrate and the increase in sickly and inviable infants to parental alcoholism. Trotter wrote in 1813, "Can it be too gross to suppose the organs of generation must equally suffer in both sexes from frequent intoxication, and if offspring should be unfortunately derived from such a parentage can we doubt that it must be diseased and puny in its corporeal part and beneath the standard of a rational being in its intellectual facilities?" Morel, in 1857, published an elaborate theory of degeneracy which stated that parental drunkenness produced depravity, alcoholic excess, and degeneration in the first generation of offspring and progressively more severe symptoms in their children, until the fourth generation developed sterility, which caused extinction of the line. (p. 115)

Jones and Smith (1973) cite an 1834 report to the House of Commons by a select committee investigating drunkenness which indicated that infants born to alcoholic mothers sometimes had a starved, shrivelled, and imperfect look. In arguing against the inheritance of acquired characteristics, Sir Francis Galton wrote in 1889:

For example, a woman who was sober becomes a drunkard. Her children born during the period of her sobriety are said to be quite healthy; her subsequent children are said to be neurotic. The objections to accepting this as a valid instance in point are many. The woman's tissues must have been drenched with alcohol, and the unborn infant alcoholized during all its existence in that state. The quality of the mother's milk would be bad. The surroundings of a home under the charge of a drunken woman would be prejudicial to the health of a growing child. No wonder that it became neurotic. (p. 15)

**Early Human Studies of Fetal Alcohol Effects**

Some of the best early research on the deleterious effects of maternal alcoholism was published in 1899 by Sullivan, a Liverpool
prison physician. He studied 120 female inebriates of the Liverpool jail, who were screened to exclude those with histories of syphilis, tuberculosis, and degenerative disease. These 120 women bore 600 children of whom only 44 percent lived longer than 2 years of age; the other 56 percent either died before the age of 2 years or were stillborn. Sullivan also studied a comparison group of 28 women, all blood relatives of the female drunkards, who had married sober husbands and borne children. The infant mortality and stillborn rate was 2 1/2 times higher in the alcoholic women as compared to their own non-alcoholic relatives; only 24 percent of these latter offspring died by age two. Other findings by Sullivan are noteworthy: he reported that the death rate increased proportionately with the increasing parity of the alcoholic mother and also the effects of paternal sobriety were unrelated to the infant death rate in the offspring of alcoholic women. Sullivan felt that these findings clearly pointed to maternal intoxication as the primary source of damage to the fetus.

There were many similar reports after the turn of the century and Green (1974) cited the following in his review of early studies: In 1901, Ladrague claimed that children of alcoholics were "small and sickly"; Elderton and Pearson measured Edinburgh and Manchester school children in 1910 and found that children of alcoholic parents weighed less than those of "sober" parents, strongly implying a causal relationship; a 1944 study by Roe cited "innumerable reports" that indicated the rates of infant mortality, epilepsy, idiocy, and psychosis were high among offspring of alcoholics; Lecomte's 1950 report mentioned premature infants, increased stillbirths, and assorted deformities,
which were attributed to the effect of alcohol on the reproductive system; an increased frequency of prematurity and "inferior weight" and size of children of alcoholics was reported by Christiaens, Mizon, and Delmarle in 1960; and in 1961, Schaefer reported alcohol withdrawal symptoms in the 5-pound infant of an alcoholic Yukon Indian mother.

Haggard and Jellinek (1942) made the following assertions in their book, Alcohol Explored:

(1) the number of children in alcoholic families is greater; (2) alcoholic mothers have more miscarriages ("studies" were cited); (3) alcoholic mothers have almost twice the infant deaths of nonalcoholic mothers (figures from France, Finland, England, and Austria compared "alcoholic" and "temperate" families and the number of children who died before the fifth year). (cited in Green, 1974, p. 714)

Early Animal Studies of Fetal Alcohol Effects

Early research utilizing animal subjects produced little more definitive results and many contradictory findings. Green (1974) cited the following examples: In 1912, Pforringer claimed that alcohol produced central nervous system abnormalities and retarded development in the dogs he studied. In the same year, Nice reported increased fecundity but higher infant deaths in alcoholic white mice when compared to controls. In several studies conducted in 1916 and 1917, Pearl examined fowl exposed to ethyl alcohol fumes and reported that their offspring were physiologically superior. He attributed this to selective action on germ cells. Descendants of alcoholic guinea pigs were studied by Stockard and Papanicoulaou in 1916 and again in 1918, producing the following observations: smaller litters (later refuted by a 1922 study
by Durham & Woods); increased late prenatal deaths; increased total offspring deaths; and decrease in size and body weight of offspring. In a 1928 study utilizing descendants of alcohol-fume-treated rats, however, Hanson, Sholes, and Heys found that alcohol did not lower the mean body weight. In 1927, MacDowell and Lord reported an increased prenatal mortality rate in mice after long-term maternal exposure to alcohol vapor. Decreased litter size, an excess of underweight at birth, and greater mortality rate among the offspring of ethanol-treated mother mice were among Bluhm's 1930 findings. In 1932, Davenport noted that alcoholic rats gave birth to fewer pups, which were slower in mazes than controls. Mirone's 1952 report indicated no difference in number of offspring or birth weight among alcoholic mice, but did find a decrease in fertility. Pup development in mice did not appear to be adversely affected by ethyl alcohol according to a 1966 study by Thiessen, Whitworth, and Rodgers. In a 1971 report, Laale claimed that embryos of the zebra fish, on exposure to graded amounts of ethyl alcohol, showed developmental defects, including duplication of the spinal cord. This issue has never been resolved although similar studies were conducted in the past by Nice in 1917, Hanson and Handy in 1923, MacDowell in 1922, and Mirone in 1958.

Post-Prohibition Trends

The scientific community was certainly not in agreement regarding the effects of alcohol on the fetus, particularly after the repeal of Prohibition. Many of the earlier observations on the dangers of drinking during pregnancy became associated with the Temperance crusade and were
either discredited or ignored. The editors of the *Journal of the American Medical Association* assured readers in 1942 that even large doses of alcohol had not been proven harmful to unborn babies. The ninth edition of a widely used medical textbook, *Principles and Practice of Obstetrics* (DeLee & Greenhill, 1947) didn't even mention drinking alcohol. Books published for the general public followed the trend of medical and scientific publications. The original *Better Homes & Gardens Baby Book*, published in 1943, focused only on the caloric content of alcohol. The best seller, *Nine Months Reading* by physician Robert E. Hall (1959) indicated that alcoholic beverages were permissible during pregnancy if not ingested in excess. Dr. Marvin Block, in his 1962 book *Alcoholism*, wrote the following: "The numerous erroneous opinions that alcohol itself causes blindness, prematurity, insanity and stillbirth are untenable" (cited in Robe, 1977, p. 31). He suggested that malnutrition was the probable cause of these birth defects.

A 1955 pamphlet from the Yale Center for Alcohol Studies entitled "How Alcohol Affects the Body" stressed that "the old notions about children of drunken parents being born defective can be cast aside, together with the idea that alcohol can directly irritate and injure the sex glands" (Keller, 1959, p. 14). In his book *Life Before Birth* Ashley Montague (1965) stated that "it can now be stated categorically, after hundreds of studies covering many years, that no matter how great the amounts of alcohol taken by the mother - or by the father, for that matter - neither the germ cells nor the development of the child will be affected" (p. 114). This statement follows a section delineating the toxic effects of drugs taken during pregnancy and a warning that
pregnant women should avoid all drugs. As recently as 1972, a group of doctors at Boston Children's Medical Center published a comprehensive book for the public entitled *Pregnancy, Birth and the Newborn Baby*, in which they indicated that there is no reason to restrict alcohol in moderation during pregnancy.

**Critique of Early Research**

Much of the early research focused primarily on questions about the inheritability of alcoholism, not on the question of how the alcohol consumed by the mother might affect the fetus. There are other grounds for criticism of these studies: many researchers exclusively studied offspring of alcoholic fathers or failed to differentiate which of the "alcoholic parents" was alcoholic; it was often assumed by investigators that the "degeneracy" in children of alcoholics was the result of alcoholic damage to the germ cells or that it resulted from the neglect and abuse presumed to be inherent in the home environment of alcoholics; much of the work produced in the early part of this century stems from prohibitionist forces and the results often arose more from an effort to prove a point than from a desire for scientific validity; controls were often lacking or inadequate; and the criteria used to define alcoholism were inconsistent from one study to the next.
CHAPTER II

REVIEW OF CONTEMPORARY LITERATURE

Contemporary Human Research: The Seattle Studies

The modern history of what has become known as the fetal alcohol syndrome (FAS) actually began in 1969 with Dr. Christy Ulleland, a pediatric resident at Seattle's Harborview Medical Center. She became interested in infants who failed to thrive in spite of optimal medical care; the one common environmental factor that these infants shared was that they had alcoholic mothers. The fact that the infants continued to fail to thrive when given proper care suggested to Ulleland that the prenatal impact of the mother's alcoholism might be an important factor in their growth deficiency. She examined the records of all infants born at the Seattle hospital during an 8-month period, paying particular attention to those who were small for gestational age, were hospitalized for failure to thrive, or had alcoholic mothers. Twelve alcoholic mothers were identified; the proportion of undergrown babies (below the 10th percentile) born to these mothers was 83 percent as compared to 2.3 percent of the infants of non-alcoholic mothers. Developmental tests were given to 10 of the 12 babies: 2 were normal, 3 borderline, and 5 retarded. These findings were presented at two professional meetings (Ulleland, Wennberg, Igo, & Smith, 1970; Ulleland, 1972).

In early 1973, Seattle dysmorphologist David W. Smith examined one of the children identified by Ulleland; he noted in particular the boy's unusual facial features, but they did not fit a previously
labeled syndrome. Smith and Kenneth Jones, the dysmorphology fellow, then examined 8 of Ulleland's original patients and concurred that 4 of the 8 had the same condition. Three more children with the same characteristics were identified by Smith and Jones after they examined their own files; all had clear histories of maternal alcoholism. An eighth child was identified by Smith during a visiting lectureship at Akron, Ohio. Mental deficiency in varying degrees was identified by Smith and Jones and their Seattle colleagues as an important component of the yet un-named syndrome. Ann Pytkowicz Streissguth, a child psychologist, examined the small group of 8 children and found that none of them were performing within the normal range. In every case, social and motor performance was more in accord with mental age than chronological age. Five of the children displayed fine motor dysfunction, including tremulousness, weak grasp, and/or poor eye/hand coordination. Head rolling, head banging, or rocking was observed in 5 of the children tested. The complete clinical study of these children was published in *Lancet* (Jones, Smith, Ulleland, & Streissguth, 1973); the pattern of altered growth and morphogenesis described in these first 8 cases included the following:

1. Prenatal growth deficiency characterized by short birth length and low birth weight. Although the mean gestational age was 38 weeks, the mean birth length and birth weight were at the 50th percentile for gestational ages of 34 and 33 weeks, respectively.
2. Postnatal growth deficiency characterized by continuing failure to thrive. At age 1 these children's growth rate was only 65 percent of normal for length and 38 percent of normal for weight.
3. Craniofacial abnormalities, including microcephaly, short palpebral fissures, maxillary hypoplasia, and epicanthal folds.
4. Joint and limb anomalies, including altered palmar crease pattern.
5. Cardiac defects, primarily septal defects.
6. Mental deficiency. The mean IQ on standardized intelligence tests was 67 with a range from 83 to below 50.
7. Delayed motor development, both gross and fine motor, including tremulousness, weak grasp, and poor eye-hand coordination. (cited in Streissguth, 1976, p. 258)

The researchers believed at the time that theirs was the first published report of an association between maternal alcoholism and aberrant morphogenesis in the infants. However, later that year the work of Lemoine, Harousseau, Borteyru and Menuet (1968) was brought to the attention of David Smith by a European colleague. The findings of Lemoine et al., published in the French medical literature, had never appeared or been cited in the English language medical literature, but their results were strikingly similar to those of the Seattle researchers. The French study analyzed 127 offspring of alcoholic parents and found four outstanding characteristics: "Highly distinctive facial features; considerable growth retardation both in height and weight; high frequency of malformations; and psychomotor disturbances" (p. 2). The facial features, especially evident during the first 2 years of life, included a low forehead, sunken nasal base, short, turned up nose, retracted upper lip, receding chin, and badly set ears. Abnormal weight and height was also accentuated during the first 2 years of life, regardless of environmental conditions. The researchers were able to continue observation of 81 cases from ages 2 to 7 years and found that height averaged 9 cm below normal; weight differentiation from normal tended to decrease gradually. Malformations observed in 25 of the children, with frequency of appearance shown in parentheses are as follows:

Cleft Palates - one with a hare lip (5)
Ocular: Microphthalmia, cataract (3)
Malformations of the limbs
- Bilateral synostoses of the bones of the forearm (2)
- Retractions of the fingers into claws (2)
- Dislocated hip (1)
- Club foot (1)
Cardiopathies (7)
Visceral anomalies
- Diaphragmatic hernia (1)
- Pyloric stenosis (1)
- Costo-diaphragmatic and renal malformation (1)
- Polydystrophy syndrome (1)  (p. 3)

In describing psychomotor anomalies, Lemoine et al. found that although the infants appeared lively and animated at first glance, they were actually too lively, ceaselessly agitated, quarrelsome and irritable. Psychomotor development was retarded in a majority of the cases. The average child in the study group held his head up at 6 months, stood at 1 year, walked at approximately 20 months, and pronounced first words poorly. Lemoine et al. cited 70 as a characteristic IQ but gave no data on type of tests administered, ages of children examined, or range of scores.

Jones and Smith published a second paper in *Lancet* in November, 1973 in which the syndrome was named "fetal alcohol syndrome." Three additional cases were reported, including two identified at birth. The pattern of anomalies was very similar to that described in the earlier paper but additional findings were reported on the newborns. Both had serious respiratory problems and one had difficulty with biochemical adaption (hypoglycemia, hypocalcemia, and hyperbilirubinemia); 2 of the 3 infants had a cleft soft palate. One of the infants developed cyanosis at 5 hours of age and died at 5 days of age, resulting in the first necropsy report on a known case of fetal alcohol syndrome. The findings included small brain size, incompletely developed cerebral cortex, no corpus callosum, and serious disorientation of both neuronal and glial elements.
Two review articles have been published summarizing the clinical findings in the fetal alcohol syndrome (Jones & Smith, 1975; Jones, Smith & Hanson, 1976). Hanson, Jones, and Smith (1976) summarized findings on 41 clinical cases of fetal alcohol syndrome, primarily referred from the Seattle area, and their larger sample corroborated the findings from the first cases. All of the infants in the clinical cases were born to mothers who were chronically alcoholic according to National Council on Alcoholism standards (1972). The mothers frequently had secondary health problems and the exact amount of alcohol consumed during pregnancy was difficult to document, but the Seattle researchers unequivocally asserted that the women were alcoholic, usually of long-standing duration.

Jones, Smith, Streissguth, and Myrianthopoulos published a report in June, 1974 that was not a clinical study. Their sample was drawn from the Collaborative Perinatal Project of the National Institute of Neurologic Disease and Stroke, a national prospective study of 55,000 pregnancies in which offspring were followed up to 7 years of age. History of alcoholism during pregnancy was clearly substantiated in 23 subjects and 2 non-alcoholic control women were matched to each of the 23 alcoholic mothers; matching was done on the basis of socioeconomic status, education, age, race, parity, marital status, and geographic area of residence and all data were gathered blind. Four of the infants born to alcoholic mothers died during the first week of life, a mortality rate of 17 percent compared to 2 percent in the controls. Six of the 19 surviving children of alcoholic mothers had sufficient abnormal features to suggest the possibility of fetal alcohol syndrome; this was
not true for any of the control infants. Borderline to moderate mental deficiency (IQ 79 or below at age 7) was reported in 44 percent of the surviving offspring of alcoholic women, compared to 9 percent of the controls.

**Additional Reports of Fetal Alcohol Syndrome (FAS)**

There were numerous other sightings of the fetal alcohol syndrome following the publication of the Seattle findings. Palmer, Ouellette, Warner, and Leichtman (1974) reported 3 cases of FAS in one family—a girl and monozygotic girl twins who showed a pattern of prenatal onset of growth deficiency and developmental delay, microcephaly, small palpebral fissures, and multiple minor anomalies. Alcoholism was substantiated in the mother and the researchers concluded that the most likely explanation for the pattern of anomalies observed in the children was the mother's excessive alcohol intake during pregnancy.

Tenbrinck and Buchin (1975) reported on a case they studied at the Child Evaluation Center in Phoenix, Arizona. Alcoholism was documented in the mother and the child demonstrated continuing prenatal and postnatal growth and developmental deficits, as well as many of the other stigmata associated with the fetal alcohol syndrome. The researchers added the following to the list of abnormalities previously described by other authors:

A pale skin, despite a hemoglobin level of 10.5 gm/100 ml; prominent capillaries over the bridge of the nose and anterior chest wall; a narrow head with occiput slightly flattened; very fine hair; eyes slanting downward laterally, with a suggestion of hypertelorism; ears large and low-set; nose with flattened bridge and upturned nares; mouth turned down at the corners; palate highly arched; mandible small; considerable hyperextensibility; delayed bone age; and persistence of the left ureteropelvic junction obstruction." (p. 1147)
Also in 1975, Christoffel and Salafsky published a report on a pair of fraternal twins born to an alcoholic mother, who displayed the stigmata of the fetal alcohol syndrome. One twin was severely affected at birth while the other was only minimally affected, suggesting differences in susceptibility to the dysmorphogenic influence of ethanol.

Mulvihill, Klimas, Stokes, and Risemberg (1976) identified 7 cases of the FAS in newborn and older infants in one year; all the mothers had long-standing histories of alcoholism. Other researchers that confirmed the Seattle findings included Ferrier, Nicod, and Ferrier (1973), Hall and Orenstein (1974), Saule (1974), Barry and O'Nuallian (1975), Manske and Gross (1975), and Root, Reiter, Andriola, and Duckett (1975).

The Boston Studies

In 1976 a group of researchers from the Boston University School of Medicine and Boston City Hospital reported on their Maternal Drinking and Child Development Program. Their primary objective was the development of a model for alcoholism prevention in women coupled with research on the impact of maternal drinking on the offspring. Rosett, Ouellette, and Weiner (1976) pointed out that not all offspring of alcoholic women exhibit the group of morphologic anomalies described as the fetal alcohol syndrome, but stressed that these infants should be observed for functional, developmental, and behavioral disturbances even when gross anomalies are not apparent. In their report on the infants in the pilot study, Ouellette and Rosett (1976) found that only 1 of 9 babies born to heavy drinking mothers (classified by the Volume-Variability
Index of Cahalan, Cisin, & Crossley, 1969) was considered normal, single minor congenital anomalies were present in 4 of the 9 infants, and there was an increasing trend of hypotonia and jitteriness with increasing maternal alcohol intake. The offspring of these mothers also demonstrated a statistically significant decrease in all growth parameters. There was no increase in the frequency of medical illness among these infants to account for the findings. Ouellette and Rosett concluded that those infants previously identified by other researchers represented the most severely affected infants at one end of a bell-shaped curve and that a spectrum of structural, growth, and functional abnormalities could be found in the offspring of alcoholic women. In a later report detailing the operation of the Prenatal Clinic, Rosett, Ouellette, Weiner, and Owens (1977) concluded that heavy drinking women have a significantly higher chance of bearing abnormal children than moderate or rare drinkers. The complete fetal alcohol syndrome had not been observed but 11 percent of the infants born to heavy drinking women were microcephalic as compared with 0.4 percent in the other two groups; microcephalic infants are at risk for retarded motor and cognitive development. That same year, Ouellette, Rosett, Rosman, and Weiner published a study utilizing a group of 633 women from the Prenatal Clinic. Drinking patterns were again classified by the Volume-Variability Index as abstinent and rare drinkers, moderate drinkers, and heavy drinkers. The frequency of all abnormalities was twice as great in the offspring of heavy drinkers as the frequency of those in the other two groups. Thirty-two percent of the infants born to heavy drinkers displayed congenital anomalies, as compared to 9 percent in...
the abstinent group and 14 percent in the moderate group; however, a
specific pattern of anomalies was not noted.

**FAS and Intellectual Functioning**

Streissguth (1976b), in her report on psychologic handicaps in
children with the fetal alcohol syndrome, indicated that varying degrees
of mental retardation is probably the most striking disability among
these children. Those with the clear features of the fetal alcohol
syndrome were the most retarded, whereas those who were mildly affected
physically appeared less impaired mentally. The child with the highest
IQ in Streissguth's study group was labeled "questionable" for the
fetal alcohol syndrome; this child had fewer manifestations of the FAS
than did the other affected children in the group, yet she did have
some manifestations. Another child in the group had no clinical mani­
ifestations of the syndrome, although her mother was identified as
chronically alcoholic. This child's IQ was 80, which falls in the
borderline range of intelligence, leading Streissguth to conclude that
some offspring of chronically alcoholic women may have impaired
intellectual function, even in the absence of manifestations of the
fetal alcohol syndrome.

In a later report on intellectual functioning, Streissguth, Herman,
and Smith (1978) concluded that maternal alcoholism is related to a
continuum of dysmorphogenesis and mental dysfunction in affected
offspring. In their study, the severity of dysmorphogenesis ranged
from severely affected with full manifestations of the FAS to mildly
affected with only a few indications of the syndrome. Intellectual
development is directly related to dysmorphogenesis; the most severely affected children in this study also had the greatest intellectual handicap.

Additional FAS Characteristics

Other manifestations of the FAS have been reported since the original research findings were published. In a study on the ophthalmologic and systemic manifestations of the fetal alcohol syndrome, Altman's (1976) major findings were small eyes, telecanthus, normal interpupillary distance, and divergent strabismus. Clarren and Alvord (1976) studied brain malformations related to prenatal exposure to alcohol and found a previously unknown range of defects in morphogenesis, including extensive leptomeningeal neuroglial heterotopias. In a study by Clarren, Alvord, and Sumi (1977a) various abnormalities of brain morphogenesis were observed in a series of 13 offspring who were exposed to alcohol in utero and who died near or shortly after birth. One of the 4 offspring with frequent heavy alcohol exposure had hydrocephalus and a rudimentary brainstem and cerebellum; another had a leptomeningeal neuroglial heterotopia over a cerebellar folium. Two offspring with infrequent heavy alcohol exposure had abnormal brains: one was anencephalic and the other had an inflammation of the ependyma of the lateral ventricles. One of 6 offspring with light alcohol exposure had anencephaly.

Structural abnormalities of the brain were observed in 4 neonates exposed to large quantities of ethanol at frequent intervals during gestation in another study by Clarren, Alvord, and Sumi (1977b). Two
of the infants were hydrocephalic and all 4 brains showed similar malformations stemming from errors in the migration of neuronal and glial elements. Only 2 of the patients were diagnosed as having the fetal alcohol syndrome based on external criteria, suggesting that in some infants brain alterations may be the only significant effect of heavy ethanol exposure in utero.

Sander, Snyder, and Rosett (1977) analyzed 24-hour sleep-awake state distributions for 12 infants born to mothers with 3 different patterns of alcohol ingestion during pregnancy. The evidence presented indicated a detrimental effect of high alcohol intake during pregnancy on neonatal state regulation. These infants born to heavier drinkers showed a greater duration of indeterminate sleep and grossly abnormal patterning of sleep substages. They also exhibited a different quality of quiet sleep, typified by poorly stabilized respiratory amplitude, more frequent startles and more extended body movements, and irregular respiratory rate.

Renal anomalies related to the fetal alcohol syndrome have also been reported. Debeukelaer, Randall, and Stroud (1977) published a case history of renal insufficiency and anomalies of the urinary tract in a patient born to a chronic alcoholic mother; the symptomatology was traced to the pattern of defects associated with the fetal alcohol syndrome. Goldstein and Arulanantham (1978) described an infant with FAS who also had neural tube and renal anomalies; the authors suggested that the abnormalities in their patient supported the possibility that renal anomalies are part of the teratogenic effects of alcohol. Qazi, Masakawa, Milman, McGann, Chua, and Haller (1979) reported on 6 patients
with the FAS who had developmental abnormalities of the kidney. Although renal pathology was not of the same type in all cases, 4 of the patients had either unilateral or bilateral renal hypoplasia.

Spiegel, Pekman, Rich, Versteeg, Nelson, and Dudnikov (1979) investigated the orthopedic aspects of the FAS and found that certain anomalies were quite common and could aid in the initial diagnosis. The following were observed frequently: "hypoplastic toenails (100%), shortened fingers, usually the fifth finger (75%), radioulnar synostosis (50%), camptodactyly of fingers (50%), clinodactyly of toes (50%), and flexion contractures of the elbow (50%)" (p. 62).

Skeletal defects, particularly fusion of the cervical spine, may help to support the diagnosis of FAS in children, according to Dr. Patrick M. MacLeod, of the University of British Columbia (cited in Gonzalez, 1979). He and colleague David F. Smith found fusion of the cervical vertebral bodies, of the posterior elements, or of both, in 16 of 36 children who underwent skeletal surveys. Other defects found in a group of 43 children included radial ulnar synostosis, hypoplasia of the radial head, narrowing and distal tufting of the terminal phalanges, and abnormalities of the thoracic cage.

Contemporary Animal Studies

More recent and better controlled animal research has demonstrated that high levels of ethanol during pregnancy can be related to a variety of malformations and anomalies not unlike those found in the fetal alcohol syndrome. Papara-Nicholson and Telford (1957) found increased stillbirths, neonatal deaths, and low birth weights in the offspring of
alcoholic guinea pigs as well as poor locomotion, incoordination, and sucking and feeding difficulties. In 1967, Pilstrom and Kiessling (cited in Green, 1974) investigated long-term maternal ethanol ingestion and its effect on liver mitochondrial function and adenosine triphosphate activity in the rat fetus. They found a significant difference in birth weight, a greater mortality rate among offspring of treated mothers, and the mean body weight in the experimental offspring decreased continuously from birth to death, while control offspring grew normally.

Ethanol-induced morphogenesis in rat and chick embryo that included brain and spinal cord abnormalities was demonstrated by Sandor and Elias (1968), Sandor (1968), and Sandor and Amels (1971). Tze and Lee (1975) found a marked decrease in size and number of progeny produced by rats on high levels of alcohol before and during pregnancy. Work by Chernoff (1975) suggests a mouse model of the fetal alcohol syndrome, based on the findings of teratogenic and embryo-toxic effect of high levels of ethanol ingestion prior to and during pregnancy. Kronick (1976) reported similar results in his study utilizing pregnant mice.

Severe fetal malformations in the offspring of ewes exposed to high concentrations of ethanol have been reported by Mann, Bhakthavathsalan, Liv, and Makowski (1975a, 1975b). Bond and Digiusto (1977) found learning deficits in the offspring of pregnant Wistar rats fed a 35 percent ethanol diet throughout gestation. Marked physical and behavioral abnormalities were observed in the offspring of chronic ethanol-exposed female rats by Buckalew (1977); they exhibited growth-retardation, high post-weaning mortality, an altered sex ratio, hypersensitivity to auditory stimuli, fear responses to novel stimuli, and limited curiosity and exploratory behavior.
Shaywitz, Klopper, and Gordon (1976) investigated a syndrome resembling minimal brain dysfunction in rat pups born to alcoholic mothers. Body weight was significantly reduced from birth onward, maturation of righting responses and eye opening was markedly delayed, and impaired T-maze learning at 21 days and impaired shuttle box performance at 27 and 33 days was demonstrated. Martin, Martin, and Sigman (1977) found that chronic ethanol consumption by gravid rats produced changes in the survival, development, and operant performance of offspring. Differences between ethanol and control groups included number of neonatal deaths, growth-retardation to postnatal day 72, date of eye opening, distance traversed on day 15, contingent performance in the 1st week on continuous reinforcement, fixed ratio, and timing appetitive schedules, and number of shock initiations and ability to discriminate contingencies on punishment schedules. Henderson and Schenker's (1977) findings suggest that prolonged maternal alcohol intake has an adverse effect on newborn rat viability and growth as well as the total RNA, and to some extent, the DNA concentration of vital organs.

A pattern of malformations similar to those observed in human children with the FAS was produced in CBA and C3H female mice maintained on liquid diets containing 15-35 percent ethanol-derived calories (Chernoff, 1977). Prenatal death and maldevelopment increased with the level of alcohol intake; deficient occiput ossification, neural anomalies, and low fetal weight occurred with low ethanol diets, and cardiac and eye-lid dysmorphology with high ethanol diets. The pattern of malformations was characterized by a dose-response effect and indicated that
chronic maternal alcoholism is embryolethal and teratogenic in mice. A 1977 study by Randall, Taylor, and Walker added empirical support to the suggestion that ethanol is the direct teratogenic agent. Oral administration of ethanol as part of a nutritionally balanced diet produced physical anomalies in mice similar to those reported in other studies. Twice as many fetuses were resorbed by the alcohol-fed group than by the controls and experimental litters had at least one malformed fetus, while malformed fetuses were evident in only 5 of 29 control litters. The experimental fetuses weighed significantly less than controls and had a significantly higher incidence of skeletal, heart, and abdominal/urogenital anomalies.

Yanai and Ginsburg (1976) found that two inbred strains of mice whose parents had been fed alcohol were more susceptible to audiogenic seizures than either pair-fed or normally fed controls. A solution of 95 percent alcohol administered intraperitoneally to pregnant mice resulted in a significant increase in fetal deaths following treatment on gestation day 8 and 9 or 10 and 11 in the 1976 study by Kronick. Incidence of congenital anomalies increased following treatment on gestation days 8, 9, or 10.
CHAPTER III

UNANSWERED QUESTIONS

Although research on the fetal alcohol syndrome and related issues has increased dramatically since the original Seattle studies, there are many unanswered questions and areas of speculation. One of the most crucial points yet to be clarified is the level of alcohol necessary to compromise the fetus; at present it is not clear what is the lowest amount of alcohol needed to produce a teratogenic effect. Little (1976) found a significant relationship between alcohol and birth weight of offspring that was independent of nicotine in a prospective study of self-reports of alcohol ingestion in a group of middle-class pregnant women. Those who reported drinking over 1 ounce of absolute alcohol per average day had infants whose average birth weight was 180 grams less than the birth weight of infants whose mothers were very infrequent drinkers or abstainers. This well-controlled study is important in that these women were not alcoholics and did not consider themselves to have alcohol problems. In another report Little (1977) studied the association between moderate maternal alcohol intake and decreased birth weight in the offspring and found that maternal alcohol use before pregnancy and in late pregnancy is significantly related to infant birth weight; this association was independent of other variables, including tobacco use. Little suggested that reduction in birth weight with moderate maternal alcohol use may represent minimal damage on a spectrum of growth retardation, with minor alterations in growth at one end and fetal alcohol syndrome at the other extreme.

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A study in France on 9000 pregnant women showed a significantly decreased birth weight in offspring of mothers ingesting over 1.6 ounces of absolute alcohol daily even when other risk factors were controlled for (Kaminsky, Rumeau-Rouquette, & Schwartz, 1976). Mau and Netter (1974) prospectively studied 5000 pregnancies in Germany and found that moderate to high levels of alcohol consumption during pregnancy was related to shorter gestational ages in offspring after controlling for other relevant variables.

Infants of low-dosage social drinkers have been characterized by tremors, hand to mouth activity, and increased yawning and sneezing (Landesman-Dwyer, Keller, & Streissguth, 1977). Social drinking by women during pregnancy has also been associated with atypical behavior in newborn offspring based on the results of studies using the Brazelton Neonatal Assessment Scale (Streissguth, Martin, & Barr, 1977).

A study by Hanson, Streissguth, and Smith (1978) produced data which indicated that moderate levels of alcohol consumption during early pregnancy can have an adverse effect on the fetus. The data indicated a crude dose-response curve relating maternal alcohol intake to outcome of pregnancy; the researchers suggested that the risk of having a newborn child with the FAS increase proportionately with the average daily alcohol intake. Pioneer researcher Smith (1979) advises limiting alcohol consumption during any pregnancy or when conception is planned; while no major fetal effects have been noted at an intake of less than 4 drinks per day, a level of 2 drinks per day has produced infants averaging 60 to 160 grams below expected birth weight for gestational age. Clarren and Smith (1978) stress that lower levels of
alcohol consumption or less frequent use of alcohol carries an unknown risk and may be shown to be associated with less seriously affected children.

Another question that remains to be fully answered concerns the gestational stage at which the fetus is most vulnerable to the effects of alcohol. According to Jones et al. (1973) the pattern of malformations characteristic of the FAS probably develops during the first 11 weeks of gestation. In the first necropsy report by Jones and Smith (1973) the brain abnormalities that were found suggested that the damage was done before 80 days of gestation. Jones and Smith (1975) reaffirmed their opinion in a later paper; they suggested that structural damage begins very early in pregnancy, clearly during the first trimester.

Rosett et al. (1976) proposed that lower concentrations of ethanol during critical periods of gestation may result in functional disturbances of the developing central nervous system and other organs.

In their study on the brain abnormalities of 2 infants born to alcoholic mothers, Clarren and Alvord (1976) felt that the defects had occurred by the 75th day of gestation in the first patient and by the 40th day in the second patient. The findings of a similar study (Clarren et al., 1977a) suggested that the most critical period of teratogenesis is the first 85 days of gestation.

Ouellette et al. (1977) concluded that heavy drinking during the first trimester has the greatest effect on fetal maldevelopment, whereas heavy alcohol consumption near term may have a greater effect on fetal nutrition and size. Although there are not yet adequate data on the effects of alcohol during the second or third trimester alone, Smith
(1979) presents evidence that heavy exposure during the first trimester alone can cause serious problems: an evaluation was done on an 8 year old whose alcoholic mother had completely stopped drinking at the end of the third month of pregnancy; the child was hyperactive and had typical facial and other features of the fetal alcohol syndrome.

Has ethanol been pinpointed as the teratogenic factor in the FAS or are there other possible causes? There is extensive evidence that ethanol rapidly crosses the placental and blood-brain barriers of the fetus (Corrigan, 1976) and reaches approximately the same levels of concentration as those found in the mother (Jones et al., 1973). One baby with the fetal alcohol syndrome was noted to have the smell of alcohol on his breath at birth, the amniotic fluid from another infant had the odor of ethanol, and another affected baby had an ethanol determination on the cord blood at birth; the value was similar to the level found in the mother (Hanson et al., 1976).

It is also becoming apparent that the primary damage, particularly for the most severely affected infants, occurs in utero. Streissguth (1976a) reported that placing these children in excellent foster care homes and providing an infant stimulation program has not resulted in better learning skills or development; they continue to show a lack of catch-up growth, both physically and mentally, no matter how optimal the environment. Smith et al. (1976) concluded that although direct proof is lacking, the present evidence favors ethanol as the cause of the anomalies which constitute the fetal alcohol syndrome. Other researchers, including Palmer et al. (1974), Christoffel and Salafsky (1975), and Root et al. (1975) are in general agreement.
Fetal susceptibility to ethanol dysmorphogenesis may be an important variable; monozygotic twins born to an alcoholic mother showed slightly different characteristics of the syndrome (Christoffel & Salafsky, 1975). This suggests that the characteristic dysmorphism of the FAS is not genetic in origin, nor is it due to a genetic polymorphism of enzymes for ethanol metabolism. Genetics as a causative factor can also be ruled out on the basis of alcoholic mothers who have given birth to FAS babies, discontinued their drinking, and then produced normal children (Smith et al., 1976).

Maternal malnutrition is often raised as a possible cause, but there is no evidence from studies of severely malnourished women that nutritional deficiency alone can result in the type of malformations that are found in the fetal alcohol syndrome (Smith, C.A., 1947; Stein, Susser, Saenger, & Marolla, 1974). Furthermore, the prenatal growth deficiency in FAS infants is more severe with respect to birth length than to birth weight, a direct contrast to most studies of generalized maternal malnutrition, in which the neonates are underweight for their birth length (Jones et al., 1976). Extensive nutritional studies on one alcoholic woman at the time of birth of her severely affected infant failed to show evidence of any nutritional deficiency other than iron (Jones & Smith, 1973).

Spiegel et al. (1979) examined 8 patients with the FAS, all of whom had extensive endocrine, biochemical, and genetic work-ups; no abnormalities were found to explain the syndrome other than the teratogenicity of the maternal alcohol abuse. Growth hormone (GH) and somatomedin deficiencies have been ruled out as causative factors.
of the growth retardation in the FAS by Tze, Friesen, and MacLeod (1976).

There are several other factors that have not been eliminated as possible causative or additive factors, including fetal lead toxicity from untaxed alcohol (Sneed, 1977), placental dysfunction (Durandin & Rosso, 1976), and polymorphic and developmental isozymes of alcoholic dehydrogenase (Mulvihill & Yeager, 1976). In the absence of heavy alcohol use, neither heavy nicotine or caffeine use alone was shown to be related to the FAS (Hanson et al., 1978); while this does not rule out the possibility of an interactive effect, it does indicate that neither is the primary agent. Moderate maternal alcohol intake coupled with moderate to heavy cigarette smoking has been shown to exert an interactive and deleterious effect on learning in 2-day-old infants which was not predictable when the drugs were taken separately (Martin, Martin, & Lund, 1977).

There is the possibility that other factors, such as drug abuse, iron deficiency, vitamin deficiency, and a deficiency of trace metals may compound the teratogenic effect of ethanol on the fetus, but none of these agents alone has been demonstrated to produce the pattern of malformations characteristic of the fetal alcohol syndrome (Ouellette & Rosett, 1976). Hypoglycemia may also be a compounding factor or it may exert teratogenic action on its own; hypoglycemia is known to follow ingestion of alcohol and may play a significant role in the production of abnormalities. The role of paternal alcoholism is not clear, but it has been noted that at least one-fourth of the heaviest drinking women reported heavy drinking on the part of the baby's father (Rosett et al., 1976).
Other possible potentiating factors are altered intermediary metabolism and irregular medical care (Mulvihill et al., 1976), economic status, minority group status, anxiety, and stress (Green, 1974).
CHAPTER IV

POSSIBLE ADDITIVE EFFECTS OF ALCOHOL AND MARIHUANA

Current Trends in Alcohol and Marihuana Usage

Public and physician awareness of the problem and increased medical technology, including improvement in antepartum care (Luke, 1977) are two of the obvious reasons for the increasing identification of FAS-type infants. One other factor has also added to the statistics: in the past decade it has become much more socially acceptable for women to drink alcohol, in public places and in larger quantities. The stigma of alcoholism, even for women, is on the decline and this has allowed a relatively high-risk population of infants to be identified. There were indications as early as the mid-1960's that sex differences in amount and frequency of drinking were diminishing (Trice, 1966) and by the beginning of the next decade it was estimated that 6 to 9 million Americans used ethyl alcohol to such an extent that they might be considered "alcohol dependent" (Committee on Alcoholism and Drug Dependence, 1971). While women of all ages appeared to be increasing their alcohol consumption, the National Institute on Alcohol Abuse and Alcoholism (Keller, 1974) reported that the most striking increases were in the drinking practices of teen-aged girls. Demone and Wechsler (1976) studied the changing drinking patterns of adolescents since the 1960's and found a precipitous increase in drinking and intoxication in adolescent girls over the past decade.

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Another drug that has continued to gain social acceptance throughout the 1970's is marihuana, even though it is still an illicit substance in most states. The University of Michigan's Institute for Social Research conducted a national research and reporting program entitled "Monitoring the Future: A Continuing Study of the Life-Styles and Values of Youth" (Johnston, Bachman, & O'Malley, 1979). Their report covers the drug use and related attitudes of high school seniors in the United States from the classes of 1975 through 1978. They found an appreciable rise in marihuana use among these students without any concomitant increase in the proportion using other illicit substances. Fifty-nine percent of the class of 1978 had used marihuana at least one time during their lifetime; 50.2 percent had used marihuana in the past 12 months; 37.1 percent in the last 30 days, 10.7 percent of whom were daily users. It is important to note that these trends in overall use have occurred about equally among males and females. Among these same students, 93.1 percent had used alcohol at least once during their lifetime; 15.6 percent in the past year but not the past month; 72.1 percent in the past month, 5.7 percent of whom were daily users. Only 20 percent of these students associate much risk of harm with having one or two drinks almost daily and regular use of marihuana is judged to involve great risk by only 35 percent of the sample.

The majority of studies on the fetal alcohol syndrome and related disorders have attended to the issue of other drug use, but the focus has been primarily on narcotics, sedatives, amphetamines, hallucinogens, and cigarette smoking. However, evidence has been accumulating since the early 1970's that indicates marihuana may be more damaging to the body than previously believed by many experts in the field.
Marihuana Research: Human Studies

In a 1974 Science article, Maugh presented data accumulated over five years of research. The evidence suggested that the effects of marihuana are cumulative and dose-related, and that prolonged heavy use is associated with at least 6 different types of potential hazard:

(1) May cause chromosome damage that could affect the health of the user; (2) May cause disruption of cellular metabolism, including synthesis of DNA, and may interfere with the functioning of the immune system; (3) May mimic hormones or act on hormonal regulators to produce a variety of effects ranging from impotence and temporary sterility to the development of female-like breasts in men; (4) Is, with heavy use, severely debilitating to the bronchial tract and lungs; (5) Causes sharp personality changes that lead to a marked deterioration in what is normally considered good mental health; (6) And, most important, may cause potentially irreversible brain damage. (p. 683)

The primary evidence suggesting the possibility that exposure to cannabis causes damage to chromosomes has been developed at the University of Utah School of Medicine (Stenchever & Allen, 1972; Stenchever, Kunysz, & Allen, 1974). Leukocytes from 49 individuals who had used cannabis for an average of 3 years were examined and an average of 3.4 leukocytes with chromosome breaks per 100 cells per subject was found. This figure was more than twice as high as that observed in 20 matched individuals who did not use cannabis. The observed incidence of breakage is comparable to the damage associated with high doses of ionizing radiation (150 roentgens) and has the same potential for hazard. Gilmore, Lele, Robbins, and Maximilian (1971) found comparable increases in the incidence of chromosome damage in 11 individuals who used cannabis more than twice a month. Interference with the process of DNA synthesis could produce chromosome abnormalities and a study by Morishima and
Nahas (1976) presented convincing evidence in support of this possibility. Lymphocytes were obtained from 51 individuals who had used cannabis an average of 4 times per week for an average of 4 years. The lymphocytes were subjected to standard laboratory tests that measure their capacity to respond to mitotic stimulants; the researchers found that the incorporation of nucleic acids — and thus DNA synthesis — was about 40 percent lower in the lymphocytes from cannabis users than it was in comparable cells from non-users. Since lymphocytes are involved in the phenomenon known as cell-mediated immunity, it is possible that long-term cannabis use lowers the immune responsiveness of a user and thus makes him/her more susceptible to disease.

These studies lead to the speculation that marihuana products that accumulate in ovaries and testes may interfere with DNA metabolism of the germ cells; this raises the possibility that marihuana might have mutagenic effects (Nahas, 1975).

**Marihuana Research: Animal Studies**

Animal research has also produced significant findings. Harper, Heath, and Myers (1977) exposed Rhesus monkeys to marihuana smoke from cigarettes roughly equivalent to one joint per day. The monkey's brain cells showed striking structural changes, including abnormal deposits of opaque material in, and a widening of, the synaptic cleft between neurons. This could create a slowing down or interruption in the movement of brain messages.

It has been demonstrated that THC, the psychoactive constituent of cannabis, and its metabolites penetrate the placenta during the early
stages of pregnancy and appear in the rat fetus within 30 minutes after injection of the mother (Pace, Davis, & Borgen, 1971). Persaud and Ellington (1967) injected pregnant mice with 16 mg/kg of resin daily on days 1-6 of gestation, resulting in the death and resorption of all fetuses. A single injection caused no reduction in litter number but the offspring were stunted. THC at 50 mg/kg administered on days 12 and 13 of gestation to pregnant Swiss-Webster mice was followed by 9 percent fetal resorption rate (Mantilla-Plata, Clewe, & Harbison, 1974).

In rats, injection of 4:2 mg/kg of resinous extract on days 1-6 of gestation resulted in a high incidence of fetal resorption, malformed progeny, and stunting of normal survivors (Persaud & Ellington, 1968).

Studies utilizing pure THC as opposed to cannabis resin have produced no congenital abnormalities (Borgen, Davis, & Pace, 1971; Pace et al., 1971), leading researchers to speculate that cannabis resin probably contains an additional embryotoxic material of high potency which has not yet been identified. An experiment which supports this hypothesis was conducted by Gianutsos and Abbatiello (cited in Graham, 1976); an extract of cannabis was injected in a dose of 250 mg/kg on days 8-11 of gestation, the offspring were delivered and appeared to be normal. At 65 days of age the rats were tested in a simple maze and compared with the offspring of untreated rats of the same strain; the number of errors made and the time spent in the maze were recorded and the capacity to accomplish 3 error-free runs out of 4 trials was assessed. The rat offspring injected with cannabis extract were significantly inferior in performance to the control offspring.
Work with other species has confirmed the embryotoxic action of the resin. In studies utilizing hamsters, Geber and Schramm (1969a, 1969b) injected 25-300 mg/kg of cannabis extract on days 6-8 of gestation, examined the uterine contents on day 12, and described a high proportion of gross abnormalities, including head, spinal, and whole body edema and spina bifida. The percentage of teratogenic effects was dose-related.

The effects of THC and/or alcohol have been studied in developing chick embryos (Jakubovic & McGeer, 1976); THC and/or ethanol were injected repeatedly during incubation in 1 or 2 mg and 10 microliter amounts respectively. The body weights of the chicks decreased, liver weights increased, and there were apparent changes in specific brain and liver protein and RNA activity.

According to Cannabis and Health (Graham, 1976) the doses used in most of the animal research are unrealistic in terms of human consumption but maximal doses are always used when testing for teratogenic potential in new drugs. It is suggested that by such criteria, resin or extract of cannabis would be forbidden to women during the first 3 months of pregnancy.
It has not been demonstrated thus far that cannabis use is responsible for a pattern of birth defects or fetal malformations, nor is the scientific community completely in agreement, as outlined previously, that ethanol alone is completely responsible for the production of FAS-type symptoms. The prestigious *New England Journal of Medicine* recently published a letter (Mendelson, 1978) that emphasized the possibility that other drug use in addition to alcohol consumption may be responsible for increasing the number and/or severity of fetal and neonatal malformations. To this writer's knowledge, no study up to the present time has attempted to examine only the additive effects of marihuana and alcohol on the fetus, even though it is well-documented that the two are among the most widely used drugs in this country. The following is a proposed research study that might aid in clarifying the role, if any, of marihuana in the development and severity of FAS-symptomatology. The study will not actually be carried out because of financial and time constraints, but may serve as a model for similar research in the future. The purpose of this study would not be to prove causation or draw definitive conclusions about marihuana's role in the FAS, but to look instead at trends and significant differences in groups of infants with differing maternal intake histories. Two of the most important questions that remain unanswered are: (1) To what extent are the offspring of moderate or heavy social drinkers at risk?
(2) What are the compounding effects of alcohol with other drugs? This design attempts to explore both of these issues.

Selection of Subjects

Subjects would be selected from three sources: private physician's referrals, a prepaid medical care program (HMO), and a University or other large private hospital. Selection would take place during a period of 12-18 months to insure adequate sample size. Subjects from these sources would be predominantly white and middle-class, resulting in a lower prevalence of other drug use, elimination of stress from living in an unstable economic environment, more adequate nutritional status, and more moderate levels of alcohol consumption. Little, Schultz, and Mandell (1976) found that 2 percent of their middle-class pregnant women reported consuming over 1 ounce of absolute alcohol on an average daily basis and 7 percent reported consuming this amount prior to pregnancy. Streissguth et al. (1977) studied a similar group of middle-class pregnant women and obtained comparable results: 7 percent of their sample were heavy drinkers in the month prior to pregnancy, and 2 percent were heavy drinkers during the first 5 months of pregnancy, using 1 ounce or more of absolute alcohol per average day as the criterion for a heavy drinker.

In a study utilizing a poor, predominantly nonwhite sample, however, Rosett and Weiner (1975) reported much higher rates of alcohol consumption among pregnant women. They estimated that 8 percent of their sample averaged 8 ounces per day, with a range from 3 ounces to 32 ounces per day.
Screening of Subjects

Subjects would be required to meet the following criteria to be considered for the study: in prenatal care by the end of the 4th month of pregnancy; willing to sign a consent form indicating their voluntary participation; and no history of medical conditions which would affect the outcome of their pregnancy. It is unlikely that lack of subject participation would create difficulties; Rosett et al. (1976, 1977) obtained voluntary participation rates of 94 percent and 96 percent respectively; Ouellette et al. (1977) a 92 percent participation rate; Little (1977) a rate of 88 percent; and Hanson et al. (1978) a voluntary rate of 85 percent.

Subjects would be interviewed during their first prenatal visit and during the sixth and ninth months of pregnancy. This would allow for detection of any changes that might occur during pregnancy. The interview would be structured to obtain the following information:

1. Sociometric data-age, racial/ethnic background, education, income level, parity, number of abortions, and number of miscarriages.

2. Nutritional status would be evaluated on the basis of replies to the question, "What did you eat yesterday, and were yesterday's meals typical?" Responses would be analyzed according to the recommended dietary allowances of the National Research Council (1973). Adequacy of 9 nutrients would be assessed on the basis of the recommended diet for women 20 to 30 years old.

3. The initial interview would assess alcohol, marihuana, and other drug use for 2 time periods: one month prior to recognition
of pregnancy and after knowledge of pregnancy to the first prenatal visit. In most cases, the month preceding recognition of pregnancy would contain the first few weeks after conception, a potentially critical stage of gestation with regard to alcohol and other drug use. Subsequent interviews would assess usage during the intervening time periods from the first interview to the sixth month and from the sixth to the ninth month of pregnancy.

Alcohol use would be determined by the Volume-Variability Index of Cahalan et al. (1969), which would entail a 2-step operation. Each subject would be classified according to her average daily volume and these groups would be broken into subgroups according to how variable the subject's intake would be from day to day. Separate inquiry would be made about the use of wine, beer, and liquor. The monthly volume of alcohol could be calculated by multiplying frequency of use of each beverage by the various quantities that would usually be consumed; division by 30 would yield the daily volume. Cahalan et al. defines abstainers as those who drink at least once a year and infrequent drinkers as those who drink at least once a year but less than once a month. Those drinking at least once a month are divided on the basis of their average daily volume: low (0.05 - 0.58 drinks per day), medium (0.59 - 1.49 drinks per day), and high (1.5 or more drinks per day). Variability is defined as either high-maximum (5 or more drinks on an occasion) or low-maximum (those who never take as many as 5 drinks on an occasion). Six groups ranging from low-volume low-maximum through high-volume high-maximum result when the daily volume and the variability ratings are combined. The 4 groups which range from low-volume
high-maximum through high-volume low-maximum would be considered moderate drinkers for the purposes of this design.

Whenever possible a significant other, preferably the spouse, would also be questioned regarding the subject's marihuana use since there are no standard instruments or methods available to determine other drug use prior to and during pregnancy. These inquiries would be included in a questionnaire covering other aspects of the subject's life in order to camouflage their importance. If serious discrepancies arose, an average of the two responses would be used; it has been this writer's clinical experience that subjects often tend to underestimate use whereas family members overestimate.

Design

Subjects would be assigned to the following groups:

- **Group I**: Moderate Alcohol - High Marihuana Use
- **Group II**: Moderate Alcohol - Moderate Marihuana Use
- **Group III**: Moderate Alcohol - Low Marihuana Use
- **Group IV**: Moderate Alcohol - No Marihuana Use
- **Group V**: No Alcohol - No Marihuana Use

Only subjects assessed as moderate drinkers by the Cahalan method would be included in the experimental groups since the additive effects of marihuana use would be the area under investigation. The "No Alcohol" group would contain abstainers and infrequent drinkers as defined previously. Marihuana use would be defined as follows:
High: 12 marihuana cigarettes or more per month
Moderate: 5 - 11 marihuana cigarettes per month
Low: 1 - 4 marihuana cigarettes per month
No Use: Abstainers and those who would have smoked 3 marihuana cigarettes or less in the past 12 months

Diagnostic Criteria

All infants included in the study group would be examined within 24-48 hours after birth by two independent pediatric neurologists with no prior knowledge of mother's history, no details of pregnancy or delivery, and no knowledge of the other physician's findings. The infants would be rated according to the following criteria, which are those most often used in fetal alcohol effects studies as diagnostic aids:

Congenital anomalies, major and minor (Marden, Smith, & McDonald, 1964)
Growth abnormalities (small for gestational age, pre- or post-mature)
Functional abnormalities (jittery, hypotonic, poor suck)
Birth length, birth weight, and head circumference would be expressed in percentiles; these would be determined by the use of standardized anthropometric charts for newborns and the Lubchenco Tables (Lubchenco, Hansman, & Boyd, 1966). Gestational age would be determined by Dubowitz criteria (Dubowitz, Dubowitz, & Goldberg, 1970). Apgar scores would be determined at 1 minute and 5 minutes after birth.
Follow-Up Measures

Developmental, motor, and behavioral studies would be conducted at 8 and 18 months, including the Bayley Test to indicate mental and motor age, the Vineland Social Maturity Quotient, and the Denver Developmental Evaluation. If further follow-up was possible, IQ testing would be conducted at age 4 (Stanford-Binet, form L-M) and at age 7 (Wechsler Intelligence Scale for Children). Testing at these ages would be desirable because the extent of prenatal insult might not be apparent until an age when higher level cognitive functioning would be measurable.
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