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Title: AN INVESTIGATION INTO THE RELATIONSHIP BETWEEN THE FETAL ALCOHOL SYNDROME AND SHOCK-ELICITED AGGRESSION IN RATS

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Over the past 20 years, investigations into the causation and possible effects of the fetal alcohol syndrome have flourished. As clearly indicated by the review of literature, the use of alcohol by women, and more specifically by pregnant women, has increased dramatically. Maternal alcohol drinking may affect the offspring via growth and developmental deficiencies, cognitive impairment, and various behavioral impairments. Thus, the intent of numerous animal studies has been to closely simulate human conditions, investigate factors in each category mentioned above, and hence, provide data to help educate women about the dangers involved to their offspring if maternal drinking should occur during pregnancy.

The primary purpose of the present study was to investigate the relationship between fetal alcohol syndrome and shock-elicited aggression in rats. Additionally, activity behavior and open-field exploratory

behavior was measured. A free-feeding procedure and surrogate fostering of offspring were used as controls. The results of the activity testing indicated that males were significantly more active than the females, with no significant difference between fetal-alcohol and non-fetal-alcohol animals. The exploratory testing revealed that females displayed significantly more exploratory behavior than males. However, significant differences between groups within male and female categories did exist. These differences were due to the high levels of exploration shown by animals that had remained with a mother that continued to receive alcohol until their weaning. Overall, the results of the shock-elicited aggression testing indicated that males did not differ significantly from females. However, both males and female fetal-alcohol animals were significantly higher than the non-fetal-alcohol animals in both aggressive response data and response-time data.

AN INVESTIGATION INTO THE RELATIONSHIP BETWEEN THE FETAL ALCOHOL SYNDROME AND SHOCK-ELICITED AGGRESSION IN RATS

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CHAPTER 1

INTRODUCTION

The potential teratogenic effects of alcohol have been suspected for centuries. For example, Aristotle observed that drunken women often bore feebleminded children (see, Abel, 1980; Warner & Rosett, 1975). Evidence from ancient Carthage indicated that wine was forbidden bridal couples on their wedding night so that defective children might not be conceived (see, Little, 1979; Warner & Rosett, 1975). Most notable during England's gin epidemic of the 18th century a select committee of the British House of Commons was established to investigate "drunkeness," prior to the establishment in the same year of an Alcoholic Liscensure Act. Evidence presented to that committee indicated that infants born to alcoholic mothers sometimes had a "starved, shriveled and imperfect look" (see, Jones & Smith, 1975; Little, 1979). In 1899 a significant piece of research by Sullivan investigated 120 female alcoholics at the Liverpool Prison. He documented an increased frequency of early fetal death and early infant mortality in their offspring, which was a rate of two to two and one-half of children born to sober women (see, Jones & Smith, 1975; Little, 1979).

Continuing beyond the Prohibition Era in this century, interest in the use of alcohol during pregnancy waned. The topic of maternal drinking during pregnancy was generally regarded as one of little scientific interest. Even as late as the 1940's and 1950's government reports and books on pregnancy claimed that there were no known ill

effects of alcohol to the fetus (Streissguth, 1977). Not until 1957 did attention refocus on this major problem. Discussion of these findings, however, were published in foreign journals and went virtually unnoticed in the United States. For example, a 1968 French study by Lemoine reported that 127 children born to alcoholic parents displayed frequent abnormalities of growth deficiency, unusual facies, and a 25% incidence of malformations (in particular, cleft palate and cardiac malformations). Also, psychomotor retardation associated with "agitation" and "character disturbance" often occurred (Jones & Smith, 1975). The first information, to appear in English speaking journals which described the problems of alcohol on the fetus and neonate, was reported by Ulleland (1972). In this study the author reported that low birth rate, small head circumference, and mental retardation were evident among ten children from a sample of twelve whose medical records were randomly selected from files of women reported as being alcoholics.

Until 1973, most health professionals had attributed the learning and development problems often found in children of alcoholics to a disruptive home life and poor caretaking. Then the dramatic identification of Fetal Alcohol Syndrome (FAS) by Jones and Smith in 1973 awakened the scientific community to the potential dangers of heavy maternal alcohol use. Working at the University of Washington in Seattle, Jones and Smith identified eight children with similar patterns of growth deficiency, altered morphogenesis, and mental deficiency. The mothers had been chronic alcoholics and drank heavily during pregnancy. Continued studies suggested that the exposure to alcohol in utero was the primary cause of their growth deficiency, malformation, and retardation (Streissguth, 1977). The identification of a specific pattern of

malformation and the labeling of the syndrome was an important step in bringing attention to this tragic and preventable form of mental deficiency.

Maternal Alcohol Consumption

It is estimated that there are 18 million Americans who are heavy alcohol consumers, i.e., they consume about five to six drinks per day (Abel, 1980; Chambers & Griffey, 1975). According to Barnes and Russell (1977), heavy drinkers are typically associated with the male population. However, differences in the amount and frequency of alcohol consumption between males and females is gradually disappearing. In fact, women in the age range of 18 to 34 years of age may comprise an overly representative percentage of alcohol abusers. In fact, female drinking rates are rising so rapidly that it is felt that they will catch and eventually surpass male drinking rates if the current trend continues (Bowker, 1977). Although the increased use of alcohol by females is alarming, even more disturbing is the number of pregnant women who are consuming large amounts of alcohol. Little, Schultz and Mandell (1976) estimated that 2% of middle-class pregnant women consume as many as two drinks per day. Rosett, Ouellette, Weiner, and Owens (1978) reported even higher levels of alcohol consumption among women in low socio-economic classes. They estimate that 13% of these women are heavy alcohol consumers.

It is difficult to discuss levels of risk to the fetus because impairment may vary according to the stage at which the fetus was exposed. The same amount of alcohol may produce a variety of outcomes or differing amounts of alcohol may produce similar outcomes. According to Dobbing (1976) there are two critical periods in the development of

the human fetus when the brain is most vulnerable to teratological agents. Within the first trimester, between the twelfth and eighteenth weeks of gestation, neuronal multiplication occurs. During this period the consumption of alcohol could cause disruption in the development of the central nervous system. The second period occurs during the third trimester and continues through the first eighteen months after birth. This period coincides with the dendrite branching and formation of synaptic connections. The association between critical periods in development, different patterns of maternal drinking, and possible outcomes are discussed below.

Several studies (Hanson, Streissguth, & Smith, 1978; Martin, Martin, Sigman, & Radow, 1977; Streissguth, 1977) have reported that drinking, either before pregnancy or prior to recognition of pregnancy, is linked to a variety of neonatal problems. Such effects occur even with an average of only two drinks per day, and regardless of whether the drinking is daily or irregular. One ounce of absolute alcohol (two drinks) daily before pregnancy is associated with low birth weight (Little, 1977). Little (1977) and Hanson et al. (1978) documented studies on moderate drinking (two to four drinks per day) during pregnancy. Intrauterine growth retardation, lowered birth weight, was reported, decreased body activity, increased tremor (Landesman-Dwyer, Keller, & Streissguth, 1977), and poor habituation (Streissguth, 1977) were reported. Hanson et al. (1978) have stated that the range of one to two ounces of absolute alcohol per day may cause as many as 10% of the offspring to run the risk of having recognizable signs of clinically apparent altered growth and morphogenesis at birth. Heavy drinking (i.e., more than four drinks per day), further increases the risk of

stillbirth. Kaminski (1978) found that there were 3.7% more stillbirths among women who drank 2.4 or more ounces of absolute alcohol per day than among those who drank less than 1.6 ounces daily. Consumption of this quantity of alcohol per day increases risk of spontaneous abortion during the first trimester (Sokol, 1979). Likewise, Harlap (1979) found that there is also an increased risk or alcohol-induced abortion in the second trimester. Sander (1977) reported sleep disturbances, such as abnormal patterning of sleep substages and requiring a longer time to sleep and to awaken, in infants born of heavy drinking mothers. Poor muscle tone, jitteriness, and poor sucking response in the newborns are other possible risks (Ouellette, Rosett, Rosman, & Weiner, 1977). Jones, Smith, Streissguth, and Myrianthopoulos (1974) reported that high levels of drinking also significantly decreased intellectual development in the offspring, this deficit appears to persist. During this second trimester fetal alcohol effects become a serious risk, with effects such as failure to thrive, tremulousness, hyperactivity and irritability occurring (Streissguth, Herman, & Smith, 1978).

Placenta Transport of Alcohol and Its Effects on the Developing Fetus

The ingestation of alcohol into the body results in an immediate diffusion of the alcohol across cell membranes. This distribution occurs equally through all body tissue and assumes equal proportion to tissue water content (Abel, 1980). Until the development of the placenta, little alcohol will reach the fetus by way of maternal circulation. However, after placental formation it has been discovered that in both humans and animals the alcohol will pass from mother to fetus, with fetal concentration approaching maternal concentration (Abel, 1980; Dilts, 1970). In the fetus, alcohol is distributed in the

amniotic fluid, placenta liver, pancreas, kidney, lung, thymus, heart, and brain (Abel, 1980). Further research by Wallgren and Barry (1970) states that the highest alcohol concentration in the brain occurs in the gray matter, which has greater water content.

The use of intravenous alcohol to prevent premature labor stimulated research on the acute effects of alcohol on the fetus as the mother comes close to term. It was found that, because of immaturity of fetal hepatic enzymes, fetal blood alcohol concentration falls at a rate slower than that of the mother. As a result of these studies (Dilts, 1970; Mann, Bhakthavathasalan, & Liu, 1975), it was concluded that the use of alcohol to suppress labor may be hazardous to the fetus because it becomes progressively asphyxiated. These observations suggest that comparable effects may also occur in the fetus as a result of brief but intense exposure to alcohol, i.e., "binge drinking."

Further, Nichols (1967) and Pierog, Chandavasu, and Wexler (1977) have shown that chronic effects of utero exposure to alcohol results in severe withdrawal shortly after birth. Withdrawal signs appear similar to those of adult delirium tremors and include hyperactivity, sweating, and prolonged twitching for several days after birth. The only alternative to this experience would be for the mother to stop drinking before delivery. In this case the fetus would undergo withdrawal while still in the womb (Gordis & Kreck, 1977).

During the period in utero, the fetus receives nutrients which are essential for growth and development. Due to poor nutritional habits associated with many chronic alcohol consumers, deficiencies in protein, B-complex vitamins, and minerals (e.g., magnesium, potassium, zinc) also effect the environment of the fetus during pregnancy (Neville, Eagles,

Samson, & Olson, 1968). There has been a great deal of evidence that maternal malnutrition can result in cognitive impairment in offspring. One major observation noted by Olson (1973) is the deficiency of folate acid among women who consume heavy amounts of alcohol. Such a deficiency of this important amino acid results in malformations and mental retardation of the developing fetus. However, Jones et al. (1974) indicated that inadequate maternal nutrition, a side effect of alcoholism, cannot completely account for the physical malformations seen in FAS children.

Although maternal nutrition plays an important role in fetal development, it is necessary to mention the other factors that can have effects upon the growth of the fetus; genetic susceptibility, other drug use, maternal ill health, poverty, and psychological stress (Abel, 1980). The combination of one or several of these inherent or environmental factors with alcohol abuse has been a confounding variable in FAS studies.

Incidence and Morphological Characteristics of Fetal Alcohol Syndrome

Hanson et al. (1978) estimated that FAS affects at least one to two live births per 1000 in the United States each year. Approximately three to five live births per 1000 display partial expression of the syndrome. Clarren and Smith (1978) argue that these figures underestimate the actual extent of the problem. The authors conclude that lack of medical attention, as well as misdiagnosis (particularly children evidencing partial expression), make it difficult to determine reliable incidence figures. Perhaps the most valid information available concerning FAS is the clinical research and anecdotal reporting

which describes the physical and intellectual characteristics of the condition.

Children with FAS present a distinct pattern of congenital malformations. Lemoine, Haronsseau, Borteryu, and Menuet (1968) was the first to describe the details, later highlighted by Ulleland (1972) and Jones, Smith, Ulleland, and Streissguth (1973). These symptoms are distinct in appearance and are directly associated with alcohol teratogenicity.

In a composite of 1970's research findings of the symptoms of FAS characteristics were present across four major dimensions: 1) central nervous system dysfunctions; 2) growth deficiencies; 3) characteristic clusters of facial anomalies; and 4) variable major and minor malformations (Clarren and Smith, 1978; Ferrier, Nicod, & Ferrier, 1973; Hanson et al., 1976; Jones et al., 1974; Jones & Smith, 1973; Lemoine et al., 1968; Mulvihill & Yeager, 1976; Palmer, Ouellette, Warner, & Leichtman, 1974; Streissguth, 1977; and Ulleland, 1972). More specifically, these characteristics are as follows:

- central nervous system depression
- hip dislocation (a possible result of low activity in utero)
- acidosis
- limb and joint deformaties
- delayed respiration at birth lasting up to five minutes
- delirium tremers
- bone cell membrane
- high-pitched cry
- large anterior fontanelle
- neonatal seizures
- jitteriness
- poor sucking reflex
- increased yawning and sneezing
- increased hand-to-mouth activity
- microcephaly
- occassional anencephaly (absence of skull)
- drawn facial appearance
- midfacial and mandibular growth deficiency
- retrusive maxilla (resultant flattened profile)
- short palpebral fissures

- epicanthal folds
- stralismis
- myopia
- hypoplastic upper lip and thinned vermillion
- diminished to absent philtrum
- ptosis
- decreased adipose tissue
- growth deficiencies in both weight and height
- short nose
- low bridge
- anteverted nostrils
- occassional cleft lip and palate
- posterior rotation of the helix
- alteration in conchal shape
- naemanglomas (nonmalignant tumors of the blood vessels)
- hypertonicity
- cardio-vascular defects
- hyperactivity
- hypoplastic nails
- irregularities of genitalia
- limited joint movement
- aberrant palmer creases
- diaphragmatic abnormalities

In addition, Streissguth et al. (1978) reported that the children born to alcoholic mothers often evidence little interest in food, increased sleep disturbances, diminished REM and quiet sleep period, and demonstrate lower levels of body movement. Further, Sander (1977) suggested that the greater the amount of alcohol consumed by the mother during pregnancy, the greater the intensity of the sleep disturbances. An interesting observation by Landesman-Dwyer et al. (1977) is the occurrence of FAS children sleeping with their head to the left, typically children sleep with their head primarily to the right.

Although the reader is able to generalize many of the associated handicapping conditions expressive of physical abnormalities (e.g., visual, motor, etc.), a pattern of mental retardation appears consistently in this disorder as the direct result of maternal alcohol consumption. Mulvihill and Yeager (1976) may be correct in stating "mental retardation is the most serious defect and probably the most sensitive

manifestation of maternal alcohol abuse". With alcohol having a major impact on the development of the central nervous system in the fetus, it is expected that mental retardation would be evident in FAS children. Clarren and Smith (1978) have observed 85% of all children diagnosed as having FAS score below two standard deviations on standardized test instruments. Jones and Smith (1973) reported I.Q.'s between 50 and 83. Streissguth (1976) established intellectual functioning levels for these children to be from borderline intelligence to severe mental retardation. Lemoine et al. (1968) also noted that this population exhibited delayed language development, as well as short attention span.

Children's environmental influences after birth should be made aware of, although mental retardation appears to be highly correlated with maternal alcohol consumption. Prenatal alcohol consumption may have an effect on the parent-child interaction. Jones et al. (1974) reported that FAS children raised by their parents tend to have significant lower I.Q.'s than those raised in foster home environments.

Animal Studies

Abel (1980) and Chernoff (1977) have both sited that numerous experimental studies on animals dating back to the latter part of the 19th century have occurred with the results often being contradictory and unconvincing. In general, these early preclinical studies found that in utero exposure to high doses of ethanol resulted in decreased litter size, decreased size and birth weight of each offspring, and increased postnatal deaths of neonates (Abel, 1978; Green, 1974). However, the absence of vehicle-treated or pair-fed control groups characterized many of the early experimental designs, thus neglecting the evaluation of such possible effects as injection trauma and maternal

undernutrition. A second flaw was the failure to remove newborn pups from their natural mothers and to assign them to surrogate mothers to avoid possible confounding of postnatal maternal bheavior (Abel, 1980). Although the animal studies have had problem areas, it is essential that more sophisticated controls continue to be developed in an attempt to more closely simulate human conditions. Thus, through many years of research it has been determined that before any definite conclusions can be drawn from the results of animal studies, the experiment must include (a) pair-fed controls and (b) surrogate fostering of offspring.

Pair-feeding techniques include alcohol administered via a liquid diet or intragastrically with the assumption that the nutritional intake or alcohol-treated and control animals is equivalent. Abel (1980) stated that pair-feeding only partially solves the problem of alcohol-related undernutrition, because the alcohol may affect the absorption of nutrients into the body and/or across the placenta to the fetus. Nevertheless, it is still felt by many investigators that pair-feeding is an important control for assessing secondary aspects of alcohol intake.

Abel (1980) and many others feel that the removal of offspring from their alcohol-treated mothers should occur as soon as possible after birth and be assigned to non-drug-treated mothers. Failure to do so could introduce the influence of alcohol-related impairment of maternal behavior. It has been noted that maternal withdrawal from alcohol may affect maternal behavior toward offspring. For example, Abel (1980) and Flandera and Norakova (1974) both observed greater cannibalism from the mothers who were given alcohol throughout pregnancy and whose offspring were withdrawn from alcohol at birth compared to pair-fed or ad lib

control mothers. Excessive alcohol may also disrupt lactation, causing a reduction in the milk supplied to the nursing infant (Abel, 1975; Altman, 1970). There are indications in rats that drinking blocks secretion of oxytocin, thereby preventing milk ejection. Since alcohol can affect both the milk ejection reflex and maternal behavior it seems inevitable that the most beneficial means of studying early postnatal effects of alcohol on infant animals would be through alcohol vapor inhalation.

In addition to pair-fed controls and fostering the offspring, another important consideration in animal studies is how large of a drug dose is to be given. In a recent survey by Abel (1980) it was found that the majority of animal studies, alcohol is placed in a liquid diet in a concentration of 6% - 7% volume to volume alcohol or in the drinking fluid in a concentration of 10% volume to volume alcohol. This method has an advantage of sustaining alcohol in the body, this is often a critical variable and an important consideration in animal studies. However, consumption levels are very difficult and misleading when compared with human consumption levels. Henderson and Schenker (1977) and Chernoff (1977) findings suggest that a more valid basis of comparison than the amount of alcohol consumed is blood alcohol concentration (BAC), since it is influenced by maternal rates of metabolism which are ultimately under genetic control.

Size and weight are relatively easy parameters to measure. Thus, early pre-clinical studies have suggested that prenatal exposure to alcohol resulted in decreased size and body weight and increased postnatal mortality (see, Abel, 1980; Martin et al., 1977; Streissguth, 1977; Tze & Lee, 1975). Abel (1980) suggests that more recent studies

tend to support the earlier findings concerning reduced birth weight. However, the effects on litter size is not consistent. Tze and Lee (1975) observed reduction in average litter size for alcohol-treated females, while other investigators have not reported similar effects (Chernoff, 1977; Kronick, 1976; Martin et al., 1977). Further, several investigators have reported fetal malformations and increased postnatal mortality in animals prenatally exposed to alcohol (Martin et al., 1977; Tze & Lee, 1975). However, these results are misleading because animals exposed to alcohol in utero were not removed after birth and given to non-treated mothers. As already noted, failure to separate the offspring could produce problems involved with both maternal behavior and milk production. When surrogate fostering is used, no evidence of increased postnatal mortality in animals was observed in animals exposed prenatally to 1 and 2 g/kg/day of alcohol (Abel, 1978), but at 4 and 6 g/kg/day of alcohol there was a significant increase in mortality rate (Abel & Dintcheff, 1978).

A general consideration in testing behavioral consequences of in utero exposure to alcohol, is the possibility that behavioral differences may result from impaired sensory ability, motor coordination, physical size; rather than direct impairment of cognitive functioning (Barlow & Sullivan, 1975). The measurement of effects of prenatal exposure to alcohol on emotionality relies on the open-field test. There is some disparity of results in this area. Some investigators have reported increased activity in the open field, while others have reported the absence of significant differences (Abel & York, 1979). Abel (1978) in his experimental studies included pair-fed controls and cross-fostering of offspring after birth, while most other studies did

not include both important variables. It is essential to notice that maternal behavior is clearly a factor that influences the emotionality of offspring in adulthood. The study suggested the possibility of a dose-response effect between prenatal alcohol exposure and subsequent adult emotionality. At doses of 1,2, and 4 g/kg/day, no effect of in utero exposure to alcohol was observed on open-field activity. However, following exposure to 6/g/kg/day of alcohol, animals reared less in the open-field and had longer stepdown latencies than pair-fed controls (Abel, 1978; Abel & York, 1979).

The effects on learning and memory in rats who were prenatally exposed to alcohol was observed by Bond and DiGusto (1978). These investigators reported inferior two-way shock avoidance learning in these animals. However, Hebb-Williams maze learning does not appear to be affected by prenatal exposure to alcohol (Abel, 1980). In this study offspring were cross-fostered but pair-fed controls were not included. In contrast to these studies, Abel (1978) reported no significant differences, in a variety of learning/memory tasks, between rats whose mothers were treated with 1 or 2 g/kg/day of alcohol throughout pregnancy. This experiment included both pair-fed and ad lib control groups and offspring were placed with, surrogate mothers immediately after birth.

Aggressive behavior of mice prenatally exposed to alcohol has been studied. The results of these studies have been equivocal. Krsiak (1977) suggested that mice exposed to alcohol in utero throughout gestation were significantly more aggressive and restless in social interactions than control offspring. The alcohol treated offspring displayed attacks, tail rattling and locomotion directed toward the partner or the

observational cage, and these behaviors increased rapidly when the social interactions were repeated. The increased aggressiveness and locomotor unrest were associated with a depletion of brain serotonin which is partly due to the alcohol during gestation. On the other hand, Yanoi and Ginsburg (1976) reported that mice, whose mothers were given unrestricted access to water containing 10% volume to volume ethanol throughout gestation and for the first two weeks following the birth of the pups, were significantly less aggressive than non-treated offspring. It should be noted however, that in neither study was provision made for pair-feeding or surrogate fostering.

Other investigations of animals exposed prenatally or shortly after birth to alcohol have focused upon structural anomalies. The following are examples of some investigations that have been conducted using laboratory animals to closely simulate what would happen to humans in similar conditions: 1) In 1968, Sandor and Elias (see, Abel, 1980) studied chick embryos to determine the effects of alcohol on the developing central nervous system. Upon administering alcohol 72 hours after incubation these researchers noted deformed brain vesicles and spinal cords and abnormal somite development in many of the chicks; and 2) in an experiment conducted in 1977 by Druse and Hafteig, Sprague-Dawley rats were utilized to determine alcohol effects on fetal development. A liquid diet of 6.6% volume to volume ethanol was administered prior to and throughout gestation, and resulted in offspring with significantly smaller brains than control rats.

An experimental study conducted by Chernoff (1977) employed mice to assess the alcohol effect on fetal growth. The findings note that mice who received liquid diets containing alcohol for 30 days prior to and

throughout gestation produced offspring who exhibited various malformations of the central nervous system. Dilated brain ventricles and absence of corpus callosum were also absent.

Fetal Alcohol Syndrome: Conclusion

In summary, the literature reports that alcohol abuse is increasing among women. With more women of childbearing age using alcohol, the number of children born with FAS can be expected to increase. Fetal Alcohol Syndrome is characterized by physical malformations and more frequently, cognitive impairment. The FAS children are the offspring of mothers who have consumed varying amounts of alcohol at some period during pregnancy. At present, no minimal safety limits have been determined.

Research on FAS is presently taking place in both laboratory and clinical environments. A variety of animal species, anecdotal reporting of FAS children, and autopsy examinations are among the strategies being used to evaluate causation and effective methods of intervention.

Without question, there would appear to be a myriad of factors that could (should?) be researched in future FAS studies. Unfortunately, it is simply not possible to combine all the relevant parameters into one comprehensive study. Hence, the present study was designed to investigate only one factor, aggression.

In addition to the research reported by Krsiak (1977) and Yanoi and Ginsburg (1976) which attempted to relate FAS mice and aggressiveness, several recent reports have also attempted to relate alcohol-induced hypoglycemia (low blood sugar level) and shock-elicited aggression. More specifically, Tramill, Turner, Harwell and Davis (1981) based on numerous reports, initiated an experiment predicting that a single injection of ethanol would result in an increase in blood-glucose levels

(hypoglycemia) in nonfasted subjects and a decrease in glucose levels (alcohol-induced hypoglycemia) in animals fasted for a period of days. The findings did suggest that an acute challenge of a moderate amount of ethanol can induce a hypoglycemic state in the fasted white rat. Based upon a series of studies (Davis, Cronin, Meriwether, Neideffer, & Travis-Neideffer, 1978; Davis, Gussetto, Tramill, Neideffer, & Travis-Neideffer, 1978; Davis & Rossheim, 1980; Neideffer, Davis, & Travis-Neideffer, 1980) showing a significant negative relationship between insulin-induced hypoglycemia and shock-elicited aggression, two recent reports (Tramill, Turner, Sisemore, & Davis, 1980; Tramill, Wesley, & Davis, 1981) have attempted to relate alcohol-induced hypoglycemia and shock-elicited aggression. Tramill et al. (1980 & 1981) have noted that the findings reporting the effects of alcohol on aggression in animals are inconsistent. More specifically, it has been shown (Tramill et al., 1980; Tramill et al., 1981) that sedation and inhibition of aggression resulting from alcohol injections have occurred in domestic cocks, white mice, Siamese fighting fish and white rats. However, other investigations (Tramill et al., 1980; Tramill et al., 1981) have reported an increased rate of aggressive responding after an alcohol injection. Tramill et al. (1980 & 1981) noted that the inconsistencies in the investigations may be due to the variety of animal subjects, species-specific differential responses to the alcoholic challenges, varying injection dosage levels, and the different aggression tasks utilized. Thus, the Tramill et al. (1981) study attempted to investigate the effects of ethanol single-animal, on shock-elicited aggression responding in animals maintained on a controlled diet. The results of this study suggested that chronic injections of a 30% ethanol solution

at low and moderate dose levels tended to increase aggressive responding in rats. Whereas, high-dosage levels of ethanol resulted in the response of inhibition.

As the above-mentioned studies dealt with adult animals exposed to alcohol-injestion procedures after reaching maturity, any relationship to the FAS cannot be directly assessed. However, given the negative relationship between blood-sugar level and aggression established by these insulin and alcohol studies, it seems reasonable to propose the existence of a relationship between the FAS and shock-elicited aggression. Certainly, the Krsiak (1977) and Yanoi and Ginsburg (1976) studies utilizing mice as subjects suggest that some type of relationship between the FAS and aggressive responding in the single, restrained-animal situation. The present experiment was designed to specifically evaluate: (1) the development of the FAS in the albino rat, and (2) what, if any, relationship exists between the FAS and shock-elicited aggression.

CHAPTER 2

METHOD

Subjects

Eleven pregnant albino rats, purchased from the Holtzman Company, Madison, Wisconsin and their offspring served as subjects. Throughout the gestation period, six of the mothers were given 10% alcohol in their water, while the other five received plain water. All pregnant females were individually caged with the water and food available on a free-feeding basis. Immediately upon birth fifty-seven of the pups were cross-fostered, 34 were fetal-alcohol (FAS) offspring (19 male, 15 female) and 23 were non-fetal alcohol (NFAS) offspring (8 male, 15 female). Eight fetal-alcohol pups (1 male, 7 female) and 23 non-fetal-alcohol pups (16 male, 7 female) remained with their natural mothers. In addition, one mother was continued on the alcohol-water mixture until weaning of her eleven offspring (5 male, 6 female) at 21 days of age. This pattern of cross-fostering or non-cross-fostering formed the basis for specific group formation and designation. More specifically, Group FAS-CF contained fetal-alcohol animals that were cross-fostered, Group FAS-NCF contained fetal-alcohol animals that were non-cross-fostered, Group NFAS-CF contained non-fetal-alcohol animals that were cross-fostered, Group NFAS-NCF contained non-fetal-alcohol animals that were non-cross-fostered, and Group FAS-E contained those fetal-alcohol animals that remained with the natural mother who continued to receive the 10% alcohol solution until the weaning of the pups.

Apparatus

Activity Test. A Lafayette (Model 86010) activity platform and a Lafayette single impulse counter (Model 58022) were used to measure activity.

Exploratory Test. An open-field chamber (27" wide x 45" long), constructed of 11 3/8" high wooden sides was used to evaluate exploration. The floor of the chamber was separated into 15, 9" squares.

Shock-Elicited Aggression Test. The experimental apparatus was similar to the rat-restraining device, described by Tramill, Turner, Sisemore, and Davis (1980), used for measuring shock-elicited aggression testing. The apparatus consisted of an opaque plastic tube, measuring 21.5cm in length and 7.5cm in diameter. The tube was stabilized on a wooden platform to facilitate placement of the subject into the tube and to permit removal of fecal material and urine that accumulated during testing. At the enclosed end of the tube a 1.4cm hole allowed the subject's tail to be extended from the apparatus and secured to a wood restraining rod by adhesive tape. The other end of the tube was open. The tail electrodes were two pieces of Number 14 copper wire, permanently attached to the rod 7cm apart. When the rod was in place it served the dual purpose of a restraining device to prohibit escape from the apparatus and an electrode carrier. A 2.0-mA shock source was provided by a Stoelting shock generator (Model 21670).

A Lafayette omnidirectional lever (Model 80111), served as the aggression target. The lever was mounted on the wooden platform, perpendicular to the open end of the restraining tube. When in place, the lever extended across the open mid-portion of the tube. The lever was 1.5cm from the tube and required a movement of 1cm to activate the

attached microswitch. Activation of the microswitch caused closure of relay circuitory, which in turn, activated a Lafayette (Model 5707PS) impulse counter, and a Lafayette (Model 54014) 1/100 second timer.

Procedure

From birth until weaning the subjects were reared in 10-gallon aquariums with either the natural or cross-fostered mother present. Upon weaning the pups remained in the aquariums in their respective litters, but the mother was removed. The litters were maintained until the forty-fifth day when the pups were sexed and placed in separate cages. On the 81st day following birth experimentation began. During the entire maturation period each pup was weighed daily. Food and water were available to all animals on an ad libitum basis.

The first day of testing consisted of exploratory and activity testing. The exploratory test measured open-field behavior for a one-minute period. The subject was placed in the center of the open-field chamber. As soon as the subject's feet touched the floor, the timer was started. The subject was free to wander about the chamber while the number of squares entered were counted (the body must be ½ way into a square to count) and recorded. Each subject was also tested for one minute in the activity test. The subject was placed in the center of the apparatus with the power being turned on simultaneously. At the end of the one-minute, the power was turned off and the activity data was recorded.

Twenty-four hours later, shock-elicited aggression testing began. Each individual testing session consisted of securing the designated subject in the restraining tube five minutes prior to the application of shock. This five-minute period served as habituation to the apparatus.

The subject, then received shock administration for five minutes. During this time, 100 2.0-mA shocks of 300 mSec duration were administered at three-second intervals. The number of responses and the total time of aggressive responding shown by each subject during the five minute test session was recorded.

CHAPTER 3

RESULTS

For clarity of presentation the results will be presented in three separate sections: Analysis of activity data, analysis of exploratory data, and analysis of shock-elicited aggression data. The number of subjects in each experimental group is shown in Table 1 in the Appendix.

Analysis of Activity Data

The mean activity scores for each group is shown in Table 2. As only one subject was available for testing in the male FAS-NCF group, the data for this animal was not included in statistical analysis. Hence, separate analyses of variance comparing the various experimental treatments were performed for males and females. The analysis of the male-subject data failed to yield significance, F (3,44) = 1.28, $p > .25$. Likewise, the analysis of the female-subject data failed to yield significance, F (3,45) = 1.40, $p > .25$. However, an overall comparison (non-directional t test) of male and female scores indicated that male subjects displayed significantly higher, t (97) = 4.66, $p < .001$, activity scores than did females.

Analysis of Exploratory Data

The mean exploratory score for each group is shown in Table 3. Separate analysis of the male- and female-subject data indicated that significant group differences existed for both males, F (3,44) = 3.59, $p < .05$, and females, F (3,45) = 4.01, $p < .05$. The Newman-Keuls technique was employed to ascertain specific differences. In each case

these tests indicated that subjects in both FAS-E groups displayed significantly ($p < .01$) higher exploratory scores than the other groups, which, in turn, did not differ from each other. The overall comparison of male versus female exploratory scores (nondirectional t test) indicated that females displayed significantly, t (97) = 5.04, $p < .001$, higher exploratory scores than did males.

Analysis of Shock-Elicited Aggression Data

Prior to analysis, the response data for each subject was transformed to a $\log_{10}$ (X_i + 1) measure in order to achieve normality of distribution. Further, the time score for each subject was divided by the total number of responses to yield a time-per-aggressive-response score. These transformed scores were used for analysis purposes.

Mean aggressive responses are shown in Table 4. Separate analysis of the male and female data yielded a significant group effect in both cases: males, F (3,44) = 7.95, $p < .01$, females, F (4,45) = 5.72, $p < .01$. Specific contrasts were evaluated with the Newman-Keuls procedure. For both males and females the fetal alcohol animals were significantly ($p < .01$) more aggressive than the non-fetal alcohol animals. However, there were no significant differences shown in comparisons of fetal alcohol groups with each other, or non-fetal alcohol groups with each other. As with the activity and exploratory data, nondirectional t tests were employed to ascertain differences between males and females. The results of this analysis indicated that males and females did not differ in terms of aggressive responding, t (97) = 1.13, $p > .20$.

Mean time per aggressive response scores are shown in Table 5. As with the aggressive-response data, separate analysis of variance of the male and female data yielded significance: males, F (3,44) = 4.82,

$p < .01$; females, $F\ (4,45) = 5.64$, $p < .01$. Subsequent Newman-Keuls analysis indicated that, for both males and females, the amount of time spent per aggressive response was significantly ($p < .01$) higher for the fetal alcohol groups than for the non-fetal alcohol groups. Further comparisons indicated that the fetal alcohol groups and non-fetal alcohol groups did not differ among themselves. Likewise, overall male versus female comparisons failed to yield significance, $t\ (97) = 1.25$, $p > .20$.

CHAPTER 4

DISCUSSION

As previously mentioned, there are many behavioral consequences that could be explored when considering the effects of in utero exposure to alcohol. However, the primary purpose of the present study was to investigate the relationship between the fetal alcohol syndrome and shock-elicited aggression. Additionally, open-field exploratory behavior and activity behavior were measured.

To facilitate the validity of the obtained data, the experiment included the control procedure of surrogate fostering of offspring. Abel (1980) stated that removal of offspring from alcohol-treated mothers should occur immediately after birth and that the pups should be assigned to non-alcohol-treated mothers. Failure to remove the offspring could introduce the influence of alcohol-related impairment of maternal behavior. Otherwise, a possible confounder could be introduced. Further, the withdrawal from alcohol may also affect maternal behavior toward offspring. Thus, one mother remained on the 10% alcohol solution and retained her own pups until weaning. It was observed that this mother displayed poor maternal instincts (i.e., improper feeding habits, urinating on pups, and failing to clean them). In corroboration of Abel (1980), and Flandera and Norakova (1974), cannibalism of one pup was observed in this litter.

Another important variable, in addition to cross-fostering, was determination of the alcohol dosage to be administered during pregnancy.

In compliance with a recent study by Abel (1980), a concentration of 10% volume to volume alcohol was added to the water of five mothers. This method has the advantage of sustaining alcohol in the body. Physical observations, such as, decreased size and weight, litter size, and increased postnatal mortality were observed in the fetal-alcohol animals. Further, it should be noted that one complete fetal-alcohol litter was stillborn. Additionally, it was observed that all of the fetal-alcohol litters were born subsequent to the non-fetal-alcohol litters. As mating for all animals was done at the same time by the supplier, this observation would appear to suggest another possible effect produced by in utero exposure to alcohol. Also, it should be noted that the offspring of the mother continued on the alcohol-water solution after birth were significantly smaller than all other pups. This observation suggests that failure to separate offspring could produce problems involved with both maternal behavior and milk production.

With regard to the three behavioral measures that were recorded, the results would appear to be somewhat equivocal. Measurement of exploratory and activity behavior have not resulted in consistent results in previous studies. Some have reported increased activity, while others have reported an absence of significant differences (see, Abel & York, 1979). As already noted, the results of present study indicated the separate groups within each gender failed to differ with regard to the activity measures. However, when an overall comparison of the male versus female scores was made, the male subjects displayed significantly higher activity scores. This pattern of results would appear to suggest that prenatal exposure to alcohol does not significantly affect activity.

The exploratory data presents a somewhat different picture. Here it was found that both the male and female FAS-E groups explored significantly more than the other groups. Further, unlike the activity data, it was shown that females explored significantly more than did the male subjects. The results of the exploratory data would not seem to coincide with the activity data. This incompatibility suggests another avenue for future research.

According to Krisak (1977), mice exposed to alcohol in utero throughout gestation were significantly more aggressive and restless in social interactions than control offspring. Certainly the present shock-elicited aggression data are in accord with the Krisak (1977) data. More specifically, it was shown that the fetal-alcohol animals, whether or not they were cross-fostered, were more aggressive than the non-fetal-alcohol animals. It was encouraging to find that both aggressive measures yielded comparable data. As these two responses provided somewhat different measures of aggression, their comparability certainly lends to the credibility of the results of the present experiment. In view of the exploratory and activity data discussed above, it was somewhat surprising to find that males did not differ in some manner from females in terms of aggressive behavior. This result further reinforces the above comment suggesting the need for further research relating fetal alcohol effects to the behavioral measures taken in the present experiment. More specifically, this pattern of results strongly suggests the need for the use of multiple dependent-variable measures in future experiments. The interrelations of such multiple measures should provide important new insights into fetal-alcohol effects.

As suggested, it is apparent that many facets of the fetal alcohol syndrome still need further exploration. Such investigations are needed in the areas of growth and development, as well as behavioral effects. However, one must remember that the fetal alcohol syndrome has just recently become an interest of many researchers in the laboratory and/or clinical setting. Unfortunately, Abel (1980) has stated that studies utilizing animals, in contrast to human data, do not present uniform data patterns and that animal studies, thus far, have been disappointing in terms of advancing our knowledge concerning fetal alcohol syndrome. Although differences in length and method of alcohol administration, species and strain differences, and differences in test conditions, may exist, the production of consistent results will certainly go a long way toward convincing skeptics, such as Abel, of the value of animal research in this area. Certainly the comparability of the data from the Krisak (1977) experiment using mice as subjects and the present aggression data generated by rat subjects suggests that animal experimentation is potentially capable of producing such consistent data.

In a broader sense, it is hoped that the results of this study will help to further elaborate the importance of maternal drinking and its potentially tragic outcomes. It would appear that if we can educate women, through the findings of laboratory and clinical research, this preventable form of mental deficiency and growth and developmental retardation may begin to diminish in future generations.

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APPENDIX: TABLES

Table 1

Number of Subjects Per Treatment Condition
By Sex

Sex	FAS-CF	FAS-NCF	NFAS-CF	NFAS-NCF	FAS-E
Male	19	1	8	16	5
Female	15	7	15	7	6

FAS-CF = Fetal Alcohol Cross-Fostered

FAS-NCF = Fetal Alcohol Non-Cross-Fostered

NFAS-CF = Non-Fetal Alcohol Cross-Fostered

NFAS-NCF = Non-Fetal Alcohol Non-Cross-Fostered

FAS-E = Fetal Alcohol Extended

Table 3

Mean Exploratory Scores

Sex	FAS-CF	FAS-NCF	NFAS-CF	NFAS-NCF	FAS-E	Total Weighted Mean
Male	13.05	X	13.21	13.31	18.00	13.67
Female	17.73	17.08	16.20	16.28	21.50	18.00

FAS-CF = Fetal Alcohol Cross-Fostered

FAS-NCF = Fetal Alcohol Non-Cross-Fostered

NFAS-CF = Non-Fetal Alcohol Cross-Fostered

NFAS-NCF = Non-Fetal Alcohol Non-Cross-Fostered

FAS-E = Fetal Alcohol Extended

Table 4

Mean Aggression Responses

Sex	FAS-CF	FAS-NCF	NFAS-CF	NFAS-NCF	FAS-E
Male	1.73	X	.77	.83	1.75
Female	1.79	1.71	.78	.97	1.87

FAS-CF = Fetal Alcohol Cross-Fostered

FAS-NCF = Fetal Alcohol Non-Cross-Fostered

NFAS-CF = Non-Fetal Alcohol Cross-Fostered

NFAS-NCF = Non-Fetal Alcohol Non-Cross-Fostered

FAS-E = Fetal Alcohol Extended

Table 5

Mean Time Per Aggressive Response

Sex	FAS-CF	FAS-NCF	NFAS-CF	NFAS-NCF	FAS-E
Male	2.87	X	1.16	1.01	2.75
Female	2.61	2.65	1.28	1.15	2.88

FAS-CF = Fetal Alcohol Cross-Fostered

FAS-NCF = Fetal Alcohol Non-Cross-Fostered

NFAS-CF = Non-Fetal Alcohol Cross-Fostered

NFAS-NCF = Non-Fetal Alcohol Non-Cross-Fostered

FAS-E = Fetal Alcohol Extended