109. O. L. Kedrovskii, in *Translations of French and Soviet Papers Presented at Second Panel on the Peaceful Uses of Nuclear Explosions, Vienna, Austria, 18-22 January, 1971* (UCRL-trans-10543, NTIS, Springfield, Va., 1971); I. D. Morokhov, Ed., *Nuclear Explosions for Peaceful Purposes* (UCRL-trans-10517, NTIS, Springfield, Va., 1971); B. I. Nifontov, D. D. Protopopov, I. E. Sitnikov, A. V. Kulikov, *Underground Nuclear Explosions* (Atomizdat, Moscow, 1965) (in Russian); A. R. W. Wilson, in *Proceedings of the 4th International Conference on the Peaceful Uses of Atomic Energy* (United Nations, Geneva, and IAEA, Vienna, 1972), vol. 7, pp. 211-231.
110. H. J. Dunster, H. Howells, W. L. Templeton, in *Proceedings of the 2nd U.N. International Conference on the Peaceful Uses of Atomic Energy* (United Nations, Geneva, 1958), vol. 18, pp. 296-308.
111. This case would also require either that an extremely large area had been contaminated by $^{137}$Cs ( > 100 times that for $^{90}$Sr), or that overlap had occurred between high-level (millicuries per square meter) $^{137}$Cs and $^{90}$Sr contamination zones (caused by a shift in wind direction during the accident) in order to produce the $^{90}$Sr/$^{137}$Cs activity ratios (> 100:1) reported in terrestrial radioecology study areas. If such $^{137}$Cs-contaminated areas actually existed, one might legitimately ask three questions: (i) Why is there a preponderance of $^{90}$Sr research papers in the Soviet literature? (ii) Why have Soviet scientists used data from their own long-term research on $^{90}$Sr to forecast its migration in soils (*44*) but, in a similar exercise, used British data (*112*) to forecast $^{137}$Cs migration? (iii) Why were the first $^{137}$Cs data in Soviet soil radioecology studies not reported until 10 years after application (*12*) and only $^{144}$Ce and $^{90}$Sr data reported earlier (*13,14*)?
112. V. M. Prokhorov, *Sov. Soil Sci. No. 11* (1975), p. 724; H. M. Squire and L. J. Middleton, *Radiat. Bot.* **6**, 413 (1966).
113. S. J. Rimshaw, "Fission product calculations," unpublished material, Oak Ridge National Laboratory, Oak Ridge, Tenn., 24 February 1958.
114. J. A. McBride, E. B. Sheldon, W. S. Frank, J. C. Bresee, in *Proceedings of the 3rd International Conference on the Peaceful Uses of Atomic Energy* (United Nations, New York, 1965), vol. 13, pp. 194-203; *Operational Accidents and Radiation Exposure Experience Within the United States Atomic Energy Commission, 1943-1975* (WASH-1192 Rev., Division of Operational Safety, U.S. Atomic Energy Commission, Washington, D.C., 1975); R. Gillette, *Science* **181**, 728 (1973).
115. J. N. Fairlie and A. J. W. Hitchman, *A Report on the Effects of the Chemical Explosion of December 13, 1950 at Chalk River Nuclear Research Laboratories* (AECL-1687, Atomic Energy of Canada, Ltd., Chalk River, Ontario, January 1963).
116. M. A. Cook, *The Science of High Explosives* (Reinhold, New York, 1958); R. M. Hainer, in *Fifth International Symposium on Combustion* (Reinhold, New York, 1955), pp. 224-230.
117. C. H. Johansson and P. A. Persson, *Detonics of High Explosives* (Academic Press, New York, 1970).
118. *Operation Castle—Final Report Project 4.1, Study of Response of Human Beings Accidentally Exposed to Significant Fallout Radiation* (WT-923, AEC Technical Information Service, Oak Ridge, Tenn., 1954).
119. We thank Z. A. Medvedev for focusing our attention on this challenging and important subject; A. T. Gresky, S. J. Rimshaw, and E. G. Struxness for technical advice and assistance in obtaining important reference materials; the efficient courteous staff of the Central Research Library at Oak Ridge National Laboratory, especially E. P. Nunn, O. H. Russell, and C. B. Andrews; and other colleagues at Oak Ridge: F. T. Binford, R. E. Blanco, J. O. Blomeke, E. A. Bondietti, R. H. Cooper, N. H. Cutshall, C. W. Francis, W. F. Harris, S. G. Hildebrand, J. M. Holmes, A. D. Kelmers, L. T. Newman, D. E. Reichle, C. R. Richmond, J. P. Witherspoon, and R. G. Wymer. Research sponsored by the Office of Health and Environmental Research, U.S. Department of Energy, under contract W-7405-eng-26 with Union Carbide Corporation. Publication No. 1500, Environmental Sciences Division, Oak Ridge National Laboratory.

# Teratogenic Effects of Alcohol in Humans and Laboratory Animals

Ann Pytkowicz Streissguth, Sharon Landesman-Dwyer
Joan C. Martin, David W. Smith

Historically, alcohol has often been noted to have an adverse effect on offspring. The Bible, Judges 13:7, says: "Behold, thou shalt conceive and bear a son: and now drink no wine or strong drink." In early Carthage there was reported to be a prohibition against the bridal couple drinking on their wedding night for fear of producing a defective child. According to Aristotle, "Foolish, drunken and harebrained women most often bring forth children like unto themselves, morose and languid," and in 1834 a report to the British House of Commons said: Infants of alcoholic mothers often have a starved, shriveled, and imperfect look (*1*).

In 1899, Sullivan (*2*) reported the first empirical work on the fetal effects of maternal drinking during pregnancy. Female drunkards in the Liverpool jail had a stillbirth and infant death rate of 56 percent, more than double that of nonalcoholic female relatives. Noting that the outcomes of successive pregnancies were increasingly adverse as a woman's alcoholism progressed, Sullivan concluded that "maternal intoxication" was the main source of damage to the fetus.

Despite these early warnings, little further research was reported during the next 50 years. Haggard and Jellinek (*3*), reflecting the prevailing attitude in 1942, attributed developmental problems in children of alcoholic mothers to poor postnatal nutrition and chaotic environmental circumstances rather than to intrauterine exposure to alcohol. But by 1957 (*4*), a medical thesis, filed in Paris and apparently never published, described quite clearly the malformations, growth deficiency, and poor development of foundling home children whose mothers were alcoholic.

In this article we discuss the work of the past 10 years that implicates alcohol as a teratogen, describing data from three sources: clinical studies, prospective human studies, and research with experimental animals. Alcohol is of particular interest as a teratogen because of its wide use, and the wide range of effects on offspring exposed in utero. Malformations, intrauterine death, growth retardation, central nervous system abnormalities, and behavioral deficits have all been demonstrated in humans and laboratory animals exposed to alcohol in utero. Mental retardation is the most pronounced behavioral effect of heavy intrauterine exposure to alcohol.

Alcohol, like other drugs with a molecular weight between 600 and 1000, passes freely across the placental barrier (*5*), and concentrations of alcohol in the fetus are at least as high as in the mother (*6, 7*). Prior to the 1940's it was assumed that the uterus was virtually impervious to harmful extrinsic factors circulating within the mother (*8*). However, full realization of the teratogenic potential of environmental agents came with the thalidomide tragedy, and now alcohol joins the list of agents with demonstrated teratogenic effects.

## Fetal Alcohol Syndrome

In 1968, in a relatively obscure French medical journal, Lemoine and colleagues (*9*) described 127 offspring of alcoholics, emphasizing their remarkable similarity of facial characteristics, growth deficiency, and psychomotor disturbances. Lemoine said the children resembled each other to such a degree that the diagnosis of maternal alcoholism could be made from examination of the child.

Drs. Streissguth and Martin are professors and Dr. Landesman-Dwyer is assistant professor in the Department of Psychiatry and Behavioral Sciences, and at the Child Development and Mental Retardation Center and the Alcoholism and Drug Abuse Institute, and Dr. Smith is professor in the Department of Pediatrics and at the Child Development and Mental Retardation Center, University of Washington, Seattle 98195.


0036-8075/80/0718-0353$02.00/0 

*Summary.* The teratogenicity of alcohol has been demonstrated in humans through clinical studies, behavioral studies, and epidemiologic studies, and in animals through controlled laboratory experiments. In humans exposed to alcohol during gestation the effects can range from fetal alcohol syndrome in some offspring of chronic alcoholic women to reduced average birth weight in offspring of women reporting an average consumption of two to three drinks or more per day. The behavioral effects of such exposure may range from mental retardation in children with fetal alcohol syndrome to milder developmental and behavioral effects in infants born to social drinkers. In animals, exposure to alcohol in utero may result in death, malformation, and growth deficiency as well as behavioral and developmental abnormalities. The mechanisms of impairment and related risk factors are yet to be elucidated.

Five years later, Jones and Smith and co-workers (*10*) at the University of Washington independently described a similar pattern of malformations in eight unrelated children born to chronically alcoholic mothers. Although initially referred for failure to thrive and developmental delay, these children displayed a constellation of particular facial features, growth deficiency, and mental retardation that Jones and Smith termed the fetal alcohol syndrome (FAS). This identification of a recognizable pattern of malformation, which clearly implicated the prenatal period as the time of insult, stimulated interest in the toxicity of alcohol. Within the next few years, several hundred case reports (*11*) were published in the medical literature of many countries, including Germany, France, the United States, Ireland, Sweden, South Africa, Canada, and Australia.

The facial characteristics in FAS (Fig. 1) include short palpebral fissures (eye slits), low nasal bridge, epicanthic folds, short nose, indistinct philtrum (the ridges running between the nose and the mouth), narrow upper lip, small chin, and flat midface. Other eye anomalies, such as ptosis (drooping eyelids) and strabismus (crossed eyes), have been noted as well as some minor malformations of the external ear. Although many of these features might occur in normal persons, it is the cluster of characteristics that is diagnostically important for FAS. Fetal alcohol syndrome has been recognized in children of all races; Fig. 2 shows the comparability of FAS facial characteristics despite differences in racial heritage. Minor joint anomalies, altered palmar crease patterns, and minor genital anomalies have also been reported; heart defects occur in about 30 percent of children with FAS. Tables 1 and 2 summarize the prevalence of these features in 245 clinical patients with FAS (*11*).

The growth deficiency typical of FAS is of prenatal onset, and postnatal catch-up growth generally does not occur. Children with FAS are usually below the third percentile in height, weight, and head circumference. As they develop, the reduced adipose tissue becomes more pronounced, and as children they are often very thin.

The central nervous system effects include retarded mental and motor development, tremulousness, hyperactivity, and poor attention spans. Small brain size and brain malformations (Fig. 3) have been noted at autopsy, as well as abnormal migration of neural and glial cells out over the surface of the brain (*12, 13*). Havlicek and others (*14, 15*) have noted abnormal electroencephalogram patterns in newborns and children with FAS.

Fetal alcohol syndrome has been diagnosed in infants and in adults (*10, 16*). The facial characteristics and growth deficiency have been the primary diagnostic criteria in the newborn, although a variety of functional deficits have also been noted, including tremulousness, hypotonia, hyperactivity, and hyperacusis (heightened sensitivity to sound) (*17*). Weak sucking ability and other feeding difficulties, failure to thrive, and delayed development also have been reported during the first year of life (*10, 18*).

Although FAS has attracted much interest because of its unique and easily recognizable constellation of features, it is becoming increasingly evident that maternal alcoholism is related to a whole spectrum of effects (*19*). Even in the absence of typical FAS, a variety of other adverse effects of alcohol have been reported. Two recent studies (*15, 20*) have confirmed Sullivan's (*2*) early work showing higher neonatal and infant mortality in offspring of female alcoholics, as well as increased risk for infants with low birth weight. Although one group of investigators (*15*) reported an increased risk of epilepsy in infants born to alcoholic mothers, epilepsy has not been a frequently reported concomitant of FAS.

*Mental handicaps.* Mental retardation, hyperactivity, slow development, and perceptual-motor disturbance are frequently noted in clinical reports of children with FAS. In IQ studies of children with FAS in Germany (*21*), France (*22*), Sweden (*15*), and the United States (*16*), the findings were remarkably similar. The average reported IQ of children with FAS is around 68 (mildly retarded), but the range of IQ scores is wide. A few children with FAS may have normal intelligence, but most have significant mental handicaps. As indicated in Table 3, increasing severity of the physical characteristics of FAS is associated with decreasing intellectual performance (*16, 21, 22*). These IQ scores are for children with a diagnosis of FAS; the risk for mental retardation in children who do not have an FAS diagnosis, but who are born to alcoholic mothers, would be expected to be much lower.

Only a few IQ studies have been conducted on the same children over time. One child with FAS who was studied in our clinic from birth to 5 years (Fig. 4),

Table 1. Principal features of FAS observed in 245 affected persons. [Table reproduced from Clarren and Smith (*11*), courtesy of the *New England Journal of Medicine*]

| Feature | Manifestation |
|---|---|
| Central nervous system dysfunction | |
| Intellectual | Mild to moderate mental retardation* |
| Neurologic | Microcephaly*; poor coordination and hypotonia† |
| Behavioral | Irritability in infancy*; hyperactivity in childhood† |
| Growth deficiency | |
| Prenatal | Less than 2 standard deviations for length and weight* |
| Postnatal | Less than 2 standard deviations for length and weight*; disproportionately diminished adipose tissue† |
| Facial characteristics | |
| Eyes | Short palpebral fissures* |
| Nose | Short, upturned†; hypoplastic philtrum* |
| Maxilla | Hypoplastic† |
| Mouth | Thinned upper vermillion*; retrognathia in infancy*; micrognathia or relative prognathia in adolescence† |

*Feature seen in > 80 percent of patients. †Feature seen in > 50 percent of patients.

showed no improvement in IQ, despite good care in a foster home since birth and multiple remedial services. Although one follow-up study reports mild improvement in the most mildly affected cases (*22*), other studies of small groups of children with FAS show no significant change in IQ over time (*15, 23*). The ages of the children tested, genetic factors, and environmental circumstances may all play a role in the outcome of FAS.

Several investigators have described cognitive or intellectual deficits in children born to alcoholic mothers but lacking the characteristics of FAS. This is not surprising, because teratogenic agents can produce behavioral deficits in experimental animals, even in the absence of structural defects (*8, 24*). Shaywitz *et al.* (*25*) have described a small group of children, all born to alcoholic mothers, who have minimal brain dysfunction but generally normal intelligence. Olegard *et al.* (*15*) have described infants born to alcoholic mothers who had abnormal evoked-response encephalograms in the absence of other FAS characteristics and in the absence of low birth weight. Clarren *et al.* (*12*) reported brain malformations in autopsied offspring of a small group of alcoholic and "binge" drinking mothers; some of these offspring showed no FAS characteristics. Two recent studies of children born to alcoholic mothers (*20, 26*) show significantly lower IQ scores in children of alcoholic mothers compared to controls matched on a variety of relevant variables, even though most of the children did not have an FAS diagnosis. Unfortunately, the contributions of certain postnatal environmental factors associated with maternal alcoholism are difficult to sort out in human studies. Future studies should focus on outcomes in children raised by nonalcoholic foster parents to fully separate the relative contributions of prenatal and postnatal influences.

*Prevalence.* Two questions must be addressed regarding the prevalence of FAS: What is the prevalence of FAS among children of alcoholic mothers and what is the prevalence of FAS in the general population? On the basis of data from the National Perinatal Collaborative Study, Jones and colleagues (*20*) reported that six children of 23 chronically alcoholic mothers could be retrospectively diagnosed as having FAS. However, the alcoholic mothers in this study were primarily from the lowest socioeconomic classes, and this 32 percent prevalence rate of FAS among alcoholic mothers may pertain only to those from comparable backgrounds. Olegard and colleagues in Sweden (*15*) conducted a prospective study identifying alcoholic women during pregnancy and reported a 33 percent prevalence rate for the full syndrome and a 76 percent rate for partial effects. Majewski, Bierich, and colleagues (*21*) conducted extensive retrospective studies of children of alcoholic mothers in Germany and reported a 26 percent frequency of FAS. However, these workers noted that the frequency was 43 percent among the most severe alcoholics and 20 percent among women with milder alcoholism. They concluded that the critical issue is not the exact amount of alcohol consumed by the alcoholic mother during pregnancy, but rather the chronicity of her alcoholism. Majewski's sample, like that of Jones *et al.*, also contained many alcoholic women from the lower social classes. Unpublished work in our own clinic suggests that the frequency of FAS may be lower when we sample a volunteer group of recovered alcoholic women of higher social class and educational background who reported being alcoholic during a given pregnancy. The prevalence of FAS reported in studies of alcoholic mothers is influenced by such factors as sample selection and demographics as well as by the definitions for alcoholism and FAS that are used.

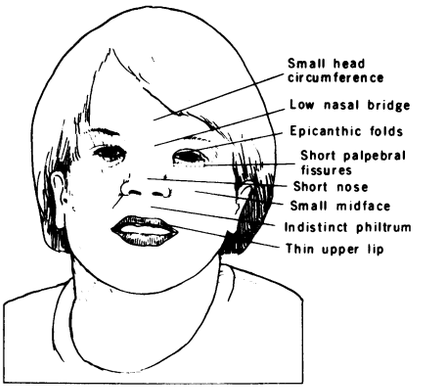


Fig. 1. Facial features that are characteristic of FAS.

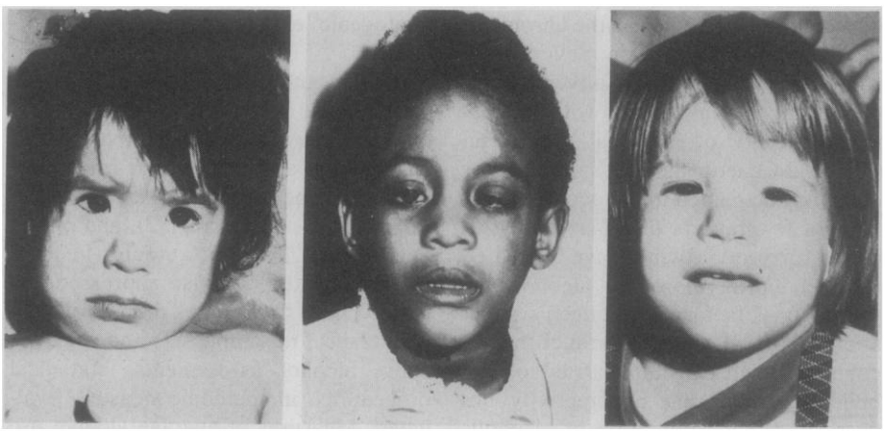

Fig. 2. Children with FAS of three racial backgrounds: (left) American Indian, (center) black, and (right) white. All are mentally retarded.

Table 2. Associated features of FAS observed in 245 affected persons. Features described as frequent were reported in 26 to 50 percent of patients; features described as occasional were reported in 1 to 25 percent of patients. [Table reproduced from Clarren and Smith (*11*), courtesy of the *New England Journal of Medicine*]

| Area | Frequent | Occasional |
|---|---|---|
| Eyes | Ptosis; strabismus; epicanthal folds | Myopia; clinical microphthalmia; blepharophimosis |
| Ears | Posterior rotation | Poorly formed concha |
| Mouth | Prominent lateral palatine ridges | Cleft lip or cleft palate; small teeth with faulty enamel |
| Cardiac | Murmurs, especially in early childhood, usually a result of atrial septal defect | Ventricular septal defect; great vessel anomalies; tetralogy of Fallot |
| Renogenital | Labial hypoplasia | Hypospadias; small rotated kidneys; hydronephrosis |
| Cutaneous | Hemangiomas | Hirsutism in infancy |
| Skeletal | Aberrant palmar creases; pectus excavatum | Limited joint movements, especially fingers and elbows; nail hypoplasia, especially fifth polydactyly; radioulnar synostosis; pectus carinatum; bifid xiphoid; Klippel-Feil anomaly; scoliosis |
| Muscular | | Hernias of diaphragm, umbilicus, or groin; diastasis recti |

The question of the prevalence of FAS in newborns in the general population must be addressed through systematic prospective studies in which newborn infants are examined for characteristics of FAS. In northern France (*22*), the birth prevalence of FAS was reported to be one in 1000 live births when only the most severe cases were counted, but one in 400 if milder cases were included. These figures are very comparable to those reported from Sweden (one in 600 births) (*15*), and from Seattle (one in 750 births) (*27*).

Although chronic maternal alcoholism with heavy drinking during pregnancy has been a consistent factor in reported cases of FAS, some other factors may exist which predispose a given woman to producing affected offspring, and these risk factors warrant further study. The higher prevalence of affected cases within the lower socioeconomic classes suggests that some social class–related factors, such as poor nutrition, smoking, and additional drug use, may increase the risk of FAS. Other risk factors may be alcohol-related, such as the chronicity of the mother's alcoholism. Several case studies show increasingly adverse pregnancy outcomes associated with increasing chronicity of maternal alcoholism (*21, 28*). Genetic factors in mother or child may be related to the occurrence of FAS; a few reports of differentially affected dizygotic twins have appeared (*28, 29*). Furthermore, the alcoholic father as a risk factor has not been systematically studied, despite the fact that alcoholic women are often married to alcoholic men and that hyperactivity has been reported in offspring of alcoholic fathers (in studies failing to adjust for alcoholic mothers) (*30*).

If we conclude that current knowledge suggests a prevalence of FAS of about one per 750 births in the general population, and if we assume that neonates diagnosed as having FAS will indeed have subsequent retarded development, then this would make FAS one of the most common forms of mental retardation with a known etiology. Although FAS is clearly associated with chronic maternal alcoholism, the effects of individual drinking patterns, nutrition, other drug use, genetic factors, metabolic differences, paternal alcoholism, and other possibly correlated risk factors are less well understood.

## Prospective Studies on the Effects of Maternal Drinking

Although clinical studies have focused on the consequences of chronic maternal alcoholism, information is rapidly accumulating on the effects of a wider spectrum of maternal drinking, including social drinking. Studies of the consequences of lower and more variable amounts of alcohol exposure are important because the lower limits of the teratogenic effects of alcohol are unknown.

In 1974, the National Institute of Alcohol Abuse and Alcoholism (NIAAA) funded three major prospective studies on maternal alcohol use and pregnancy outcome: one in Boston (*31*), one in Loma Linda, California (*32*), and one in Seattle (*33*). Two prior studies in Paris (*34*) and Seattle (*35*) also addressed this issue. These five studies differed widely with respect to sample size and constituency, alcohol assessments, statistical procedures, and outcome measures evaluated. Measures of average alcohol use were derived from self-reports obtained through interview or questionnaire. The criterion for a "heavy" drinker varied considerably across studies: in the Seattle studies (*33, 35*), "heavy" drinkers were those who reported 1 ounce or more of absolute alcohol per day on the average (equivalent to two or more drinks of wine, liquor, or beer per day); in the Paris study (*34*), "heavy" drinkers reported 40 or more centiliters of wine daily (equivalent to about 1.6 ounces or more of absolute alcohol per day); and in the Boston study (*31*), "heavy" drinkers reported 45 drinks or more per month and sometimes five drinks or more per occasion.

In all of these prospective studies the "heavy" drinking group was defined solely on the basis of self-reported consumption rather than on whether or not the women were alcoholic or had alcohol-related problems. The lower limit of "heavy drinker" in each study was well within the quantity of consumption generally construed to be "social" drinking.

Because the use of alcohol is correlated with smoking and smoking is also related to adverse pregnancy outcome (*36*), it is necessary to adjust or control for smoking in studies of alcohol teratogenesis. Most, but not all, of the prospective studies addressed this issue. Despite many differences in sample characteristics and procedures, the conclusions of the prospective studies were similar, with 12 reports indicating that alcohol use by pregnant women is associated with adverse effects on offspring (*31, 33–35*).

*Intrauterine growth.* Intrauterine growth is negatively associated with maternal alcohol intake, even after adjustment is made for other variables such as smoking, caffeine, parity, and gestational age. Kaminski *et al.* (*34*), reported that greater alcohol use is related to lower infant birth weight and placental weight. Heavy drinkers (women drinking an average of at least 1.6 ounces of absolute alcohol per day during pregnancy) have infants averaging 59 grams less than offspring of lighter drinkers. Little (*35*) reported that women drinking an average of 1 ounce or more of absolute alcohol per day during the eighth month of pregnancy delivered babies averaging 160 grams less than offspring of lighter drinkers. In our prospective study, we have also found that increased alcohol use is significantly related to decreased birth weight, the length of the infant at birth, and the head circumference (*37*), after adjusting for other relevant variables.

*Stillbirths.* The French investigators (*34*) found a significant relationship between maternal drinking and stillbirth rates. The unadjusted stillbirth rates of 9.9 per 1000 for light drinkers and 25.5 per 1000 for heavy drinkers were significantly different. Certain risk factors,

Table 3. Studies of intellectual function in FAS. The severity of diagnosis is indicated by Roman numerals, with I representing the least severe.

| Country | Reference | Sample size | IQ (mean and range) | Relation of IQ to severity of diagnosis | Hyperactivity |
|---|---|---|---|---|---|
| France | Lemoine *et al.* (*9*) | 127* | About 70* | | Yes |
| | Dehaene and coworkers (*22*) | 22 | 66 (33 to 122) | Yes | Yes |
| Germany | Majewski *et al.* (*21*) | 18 | 82 (47 to 123) | I: IQ = 91<br>II: IQ = 79<br>III: IQ = 66 | Yes |
| United States | Streissguth *et al.* (*16*) | 20 | 65 (16 to 106) | I: IQ = 82<br>II: IQ = 68<br>III: IQ = 58<br>IV: IQ = 55 | Yes |

*It is unknown whether this represents actual test scores and, if so, the number of children tested from among the total sample.

when combined with heavy alcohol use, resulted in even higher stillbirth rates. These included greater maternal age, higher parity, lower social class, and smoking. In nonsmokers, heavy alcohol intake more than doubled the risk of stillbirths, while women who both drank heavily and smoked had the highest stillbirth rates—50.5 per 1000.

*Congenital malformations.* Kaminski *et al.* (*34*) did not detect a relationship between maternal drinking and rate of major congenital malformations. This is not surprising because major malformations have not been noteworthy even in children with FAS. Their data on minor malformations have not yet been reported.

In the Boston study (*31*), infants were examined by a pediatric neurologist who reported increased rates of congenital anomalies associated with heavy maternal alcohol use: 32 percent of the heavy drinkers' infants had major or minor anomalies compared to 14 percent for moderate drinkers and 9 percent for light drinkers. Multiple congenital anomalies were found in 20 percent of the heavy drinkers' offspring, more than four times the rate for light drinkers. For reasons that are not entirely clear, Ouellette and co-workers (*38*) did not note a specific pattern of anomalies suggestive of FAS.

In the Seattle longitudinal study, Hanson *et al.* (*27*) evaluated and categorized newborns according to FAS characteristics and growth deficiency. Standardized blind evaluations were conducted on 163 newborns, half of whom had been born to heavier drinkers and half to controls (who drank infrequently or abstained). The women's reports of drinking in early pregnancy were significantly related to a pattern of growth deficiency and minor malformations associated with FAS. As Table 4 indicates, the percentage of abnormal infants for each group of mothers was directly related to the amount of maternal drinking. It must be noted, however, that only two of these infants were diagnosed as having the full syndrome, and the mothers of both of them had an independent clinical diagnosis of alcoholism. The other nine infants were called "abnormal" on the basis of their growth deficiency and the presence of some FAS characteristics, but they did not have the full syndrome. As Hanson *et al.* point out, the predictive validity of such a diagnosis is not known, but follow-up studies are under way.

Clarren and colleagues (*12*) examined a small number of brains obtained at autopsy from children with a diagnosis of FAS, including some from the Seattle study. Of particular interest is that these workers found leptomeningeal neuroglial heterotopias (abnormal cell migration) in the offspring of two women who described themselves as infrequent drinkers who had occasional binges. It is not clear from these data whether this means (i) that large doses of alcohol at infrequent intervals can produce brain malformations; (ii) that these women gave inaccurate accounts of their actual drinking habits; or (iii) that other factors, which may or may not be related to binge drinking, may produce these brain malformations. Further research is needed in this area.

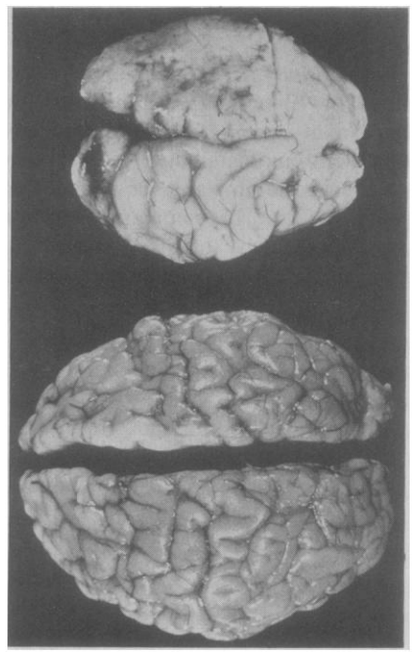

Fig. 3. Comparison of the brain of a normal newborn with the brain of an infant with FAS who died 5 days after birth. [Photograph courtesy of S. Clarren] Note the small size of the brain from the infant with FAS and that the gyral pattern is obscured by a leptomeningeal neuroglial heterotopia.

*Neonatal behavioral effects.* Behavioral teratology is relatively new to the field of teratology (*24*). Traditionally, the teratogenicity of an agent has been evaluated in terms of physical malformations, whereas adverse pregnancy outcomes in epidemiologic studies have focused on measures of growth, morbidity, and mortality. However, the behavioral deficits associated with FAS (mental retardation, learning problems, hyperactivity, and attentional deficits) make behavioral studies of particular interest in evaluating the effects on offspring of moderate maternal alcohol use.

The Seattle study (*33*) focused primarily on the behavioral consequences of social drinking, with newborn behavior evaluated through several independent procedures. Although the predictive validity of newborn behaviors is unknown, the longitudinal design should permit investigation of this question. From the interviewed sample of 1529 Seattle women, a cohort of 500 offspring was selected for detailed behavioral evaluation: 250 whose mothers were the heaviest drinkers and 250 whose mothers drank alcohol infrequently or not at all.

All of the infants were examined under standardized conditions by independent teams of examiners who had no knowledge of parental drinking history, medical diagnosis, or infant performance on other tests. The data were analyzed primarily by multiple regression techniques, with adjustments being made for effects of nicotine, caffeine, parity, and other relevant variables. On their first day of life, the infants were examined with the Brazelton Neonatal Assessment Scale (BNAS) and systematic observations were made of the infants' naturally occurring behaviors. On the second day, data were obtained regarding operant learning and baseline sucking behavior.

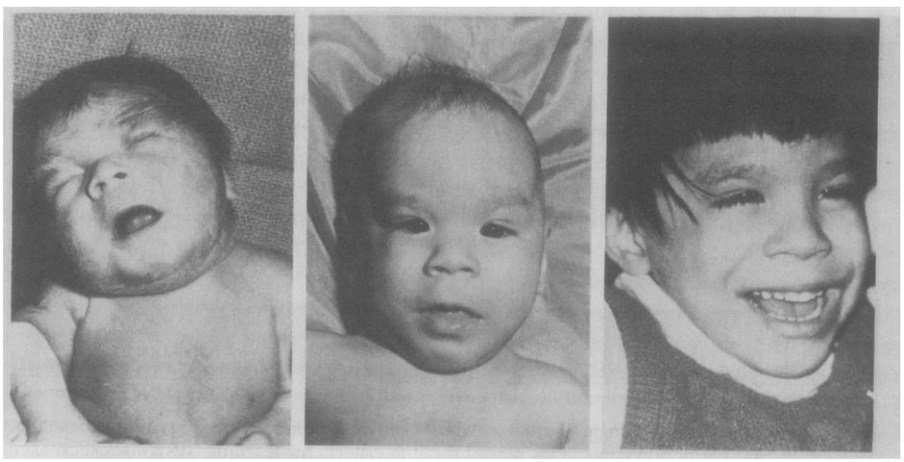

Fig. 4. Child with a diagnosis of FAS photographed at birth, at 8 months, and at 4½ years; the child's IQ was 40 to 45 at each evaluation from 8 months on.

On the BNAS (*39*), significant differences were found on two of the six behavioral clusters evaluated. Infants of mothers who were heavy drinkers had poorer habituation scores (that is, they were not as quick to tune out redundant stimuli) and lower levels of arousal. The habituation finding is of particular interest in view of the hypersensitivity to sounds (hyperacusis) that has been reported clinically in infants with FAS (*16*).

The naturally occurring behaviors of a subset of 124 infants were coded by Landesman-Dwyer *et al.* (*40*), by means of an electronic data acquisition system to preserve the time and sequence of all events. Of the 16 summary behavior codes examined, infants exposed to more alcohol were significantly more likely than controls to display; (i) increased body tremors, (ii) increased time with eyes open, (iii) increased head orientation to the left (an atypical position in newborns), (iv) increased hand-to-mouth behavior, and (v) decreased vigorous body activity (Fig. 5).

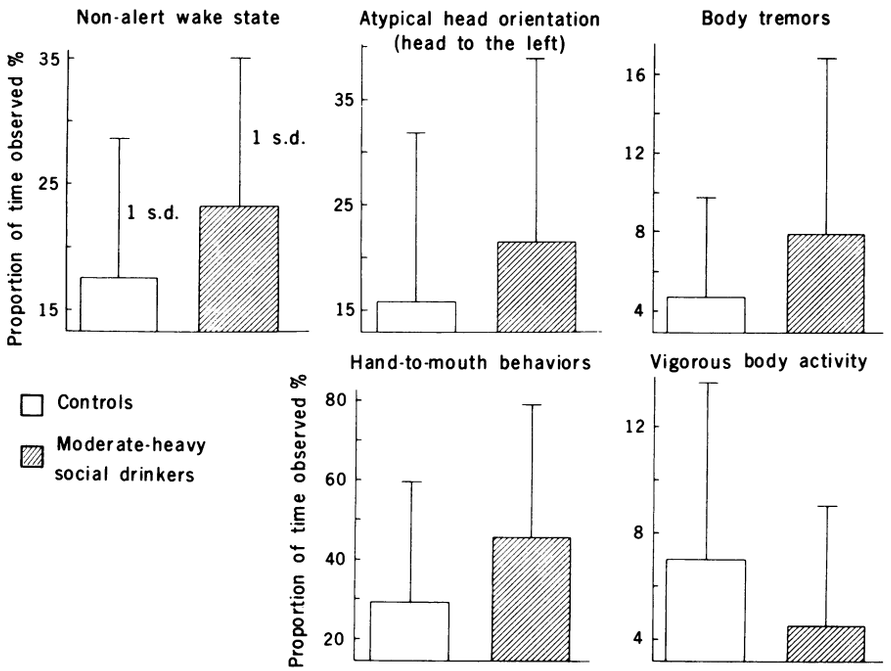


Fig. 5. Findings from the naturalistic observation study. All comparisons depicted here are significantly different in multiple regression analyses, adjusting for maternal nicotine use and sex, birth weight, and birth order of the infant.

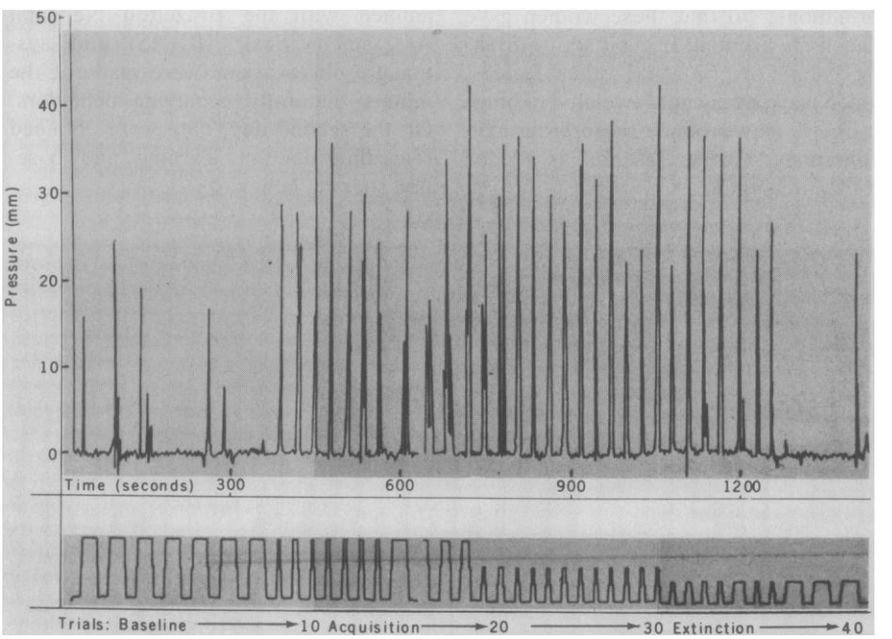


Fig. 6. Sucking record of an individual newborn showing number of sucks during baseline, acquisition, and extinction trials. This record met the criteria for learning: responses increased in the presence of a reward (acquisition trials) and decreased when the reward was withdrawn (extinction trials).

Operant learning studies involved two paradigms: head-turning and sucking behavior (*41*). In these studies, the infant received a sip of glucose water as a reward for the prescribed response (either a head turn to the nonpreferred side or sucking on a nonnutritive nipple). Figure 6 depicts a sucking record from the operant learning study. Similar findings were obtained for both head-turning and sucking experiments: infants whose mothers both smoked and drank heavily during pregnancy performed significantly more poorly on both learning tasks. The relation of these measures to learning during the school-age years is not known, but is being evaluated in the longitudinal design.

Measures of sucking behavior (*42*) were obtained from 151 infants by means of a pressure transducer attached to a nonnutritive nipple, as in the learning study. Data were recorded on a tape recorder and computer-analyzed. Infants of mothers who drank heavily during pregnancy had significantly weaker sucking pressure; this is of particular interest because poor sucking and feeding difficulties have been reported clinically in infants with FAS, and sucking pressure is directly related to milk intake.

In addition to using the specially designed codes for behavioral variables described above, certain medical indices of newborn status were obtained from the hospital records of 1429 infants whose mothers were interviewed during pregnancy (*43*). On three of these, there was a higher frequency of occurrence among infants born to heavy drinking mothers compared to offspring of control mothers: (i) need for ventilatory resuscitation, (ii) heart rate abnormalities, and (iii) lower Apgar scores. The Apgar is a commonly used clinical tool for rating newborn status at delivery. The 10-point scale represents a summation of ratings on color, crying, respiration, responsiveness, and muscle tone. Significantly more infants of heavy drinking mothers had 1-minute Apgar scores of 3 or below and 5-minute Apgar scores of 8 and below.

From the Boston prospective study, Ouellette, Rosett, and colleagues (*31*), reported that infants of heavy drinkers were significantly more jittery than offspring of control mothers. Sander *et al.* and Rosett *et al.* (*44*) reported data from

a pilot study of 31 newborns receiving 24-hour monitoring in a special bassinet. They concluded that the regulation of state (the presence of predictable patterns of sleep and waking activity) is not as well-organized in infants of heavy drinkers, although the actual time spent in different stages of sleep does not differ. Maternal smoking was not adjusted for in either of these studies (*31*, *44*), so it remains as a potentially confounding variable.

In terms of effects on later development, two reports are relevant. Maternal alcohol use during pregnancy has been related to small but significant decrements in mental and motor development in 8-month-old infants (*45*), and to decreased attentiveness in 4-year-old children (*46*). In these two studies, statistical adjustments were made for several other variables such as gestational age, birth order, and maternal smoking.

The prospective studies of social drinking during pregnancy indicate that increased maternal alcohol use is related to a variety of adverse pregnancy outcomes. These include increased intrauterine growth deficiency, stillbirths, congenital malformations, and a variety of functional measures including low Apgar score, heart rate abnormalities, jitteriness, poor sucking ability, low activity, poor habituation, poor performance on operant conditioning, atypical head orientation and other behaviors associated with poor functioning of the central nervous system. The breadth of the findings and the number of studies reporting comparable results are important factors in evaluating the strength of the effect. However, some caveats must be mentioned.

1) All of the studies of social drinking have been based on self-reported maternal alcohol intake; the relationship of these scores to actual intake is unknown. Although one study (*47*) has shown good test-retest reliability over a 1-week interval and no systematic tendency toward reporting more or less alcohol consumption on the second interview, the question of validity has not been addressed.

2) The lower limit of alcohol necessary to produce a harmful effect has not been determined. Furthermore, patterns of alcohol use both between women and within women are so variable during pregnancy that any attempt at quantification represents only a rough estimation. To date, adverse effects have not been reported at less than two drinks per day on the average. The significance of binge as opposed to regular drinking has not been systematically addressed.

3) Alcohol use is positively correlated with smoking and other personal characteristics that may influence risk. While smoking has been adjusted for in most of the studies described above, other possible risk factors, such as poor nutrition and use of prescription and nonprescription drugs, are more difficult to evaluate. Some of these factors can be dealt with more precisely in studies on experimental animals.

Table 4. Maternal alcohol consumption and neonatal outcome. Children were classified as abnormal if two of the following four criteria were met, in addition to either criterion iii or iv: (i) weight or length or both < third percentile; (ii) head circumference < third percentile; (iii) short palpebral fissures (< 1.8 cm in infants ≥ 36 weeks of gestational age); (iv) multiple dysmorphic features characteristic of FAS (such as broad, low nasal bridge, epicanthic folds, long philtrum, small nails, limitation of joint movement). [Data from Hanson *et al.* (*27*)]

| Maternal alcohol consumption | | | Abnormal newborns with some features of FAS | |
|---|---|---|---|---|
| AA* | Drinks per day | *N* | Percentage | *N* |
| ≥ 2.0 | (≥ 4 drinks per day) | 16 | 19 | 3† |
| 1.0 to 2.0 | (2 to 4 drinks per day) | 54 | 11 | 6 |
| < 1.0 | (≤ 2 drinks per day) | 93 | 2 | 2 |

*AA = Average ounces of absolute alcohol consumed per day, in month preceding recognition of pregnancy, according to self-report. †Two of these three newborns had enough FAS characteristics to receive an FAS diagnosis; their mothers also had a clinical diagnosis of alcoholism.

## Animal Models for Teratogenic Effects of Alcohol

The third major body of evidence implicating alcohol as a teratogen comes from reports of experiments with laboratory animals. Animal models are particularly important because of the opportunity to control for factors seldom accounted for in human studies, including control of timing and dose of alcohol exposure, control of nutrition through pair-fed controls, control of the postnatal environment through cross-fostering, and consideration of individual differences through cross-strain comparisons. The mouse (*48*), guinea pig (*49*), beagle dog (*50*), rat (*51*), and pigtail macaque (*52*) are among the species being studied as models for the teratogenicity of alcohol.

*Structural and physiological effects.* Reduced size of litter and of offspring are frequently found with high dosages of alcohol during gestation (*48*, *49*). Many morphological effects are also found, but these are not consistently replicated across species. In the mouse, investigators have produced eye defects (*53*), cardiac and neural abnormalities (*48*), digit anomalies, and cardiovascular, urogenital, and head malformations (*54*) by administering large doses of alcohol. In the rat, microcephaly and a shriveled appearance have been noted, as well as developmental retardation, malformation, and delayed ossification following a very small dose of alcohol (*51*). Abel (*55*), however, found no gross malformations at birth nor any learning differences with a comparable dose. In the guinea pig (*49*), whose neural development is complete at birth, shallow fissures, abnormally flat gyri, and cellular lesions in cortex and basal ganglia were found in the offspring of mothers given oral doses of ethanol, although no external structural anomalies were described. Methodological differences between experimenters in terms of the time period during gestation that alcohol is administered, the dose, the route of administration, and the strain of animal used, contribute to the difficulties encountered in reproducing experimental results. However, species differences may also be responsible for the lack of consistency. Although it may not be possible to induce teratogenic effects in the rat as reliably as in the mouse, it is relatively easy to induce structural change in some mouse strains.

Neurochemical, hormonal, and neural anomalies may occur as a consequence of ethanol exposure and have a profound effect on offspring function even in the absence of gross morphological change. Decreased protein synthesis (*56*), delayed myelination of fetal brain (*57*), and lowered concentrations of serotonin in the brain (*58*) have been reported in offspring of alcohol-fed rats. More such studies are needed to determine the mechanisms underlying functional deficits.

*Developmental and functional effects.* Measures of function studied in animals include: (i) developmental and growth indices, (ii) activity, (iii) stress paradigms, and (iv) appetitive or learning paradigms. Stress paradigms are of particular interest because of the assumption that neurally compromised organisms will not tolerate stress as readily as will noncompromised individuals. To date, behavioral teratology studies have been done primarily on rodents, and alcohol

has usually been administered only during the period of organogenesis.

*Developmental effects*. Decreased birth weight and litter size in offspring of alcohol-fed animals have been found by many investigators (*48, 59, 60*), although not by all (*7, 51*). In the laboratory of one of us (J.C.M.), it was found that increased neonatal deaths as well as growth retardation continuing until adulthood occurred in some studies of rats exposed to alcohol in utero (*60*). In other studies, these differences were not found (*61*), possibly because of differing methods of alcohol administration and differing amounts of drug available to the fetus. We have uniformly found longer gestational periods for alcohol-treated rat dams, although Ellis *et al.* (*62*) failed to find this in the mouse. We have also found some evidence for developmental delay, but not all measures differentiate groups. Eye-opening tends to be delayed no matter what administration method is used. Papara-Nicholson and Telford (*49*) found not only decreased birth weight in newborn guinea pig offspring, but also poor locomotion, and sucking and feeding difficulties as well as incoordination, increased stillbirths, neonatal deaths, and retardation of myelination.

*Hyperactivity*. Hyperactivity in the offspring of mothers given alcohol during pregnancy has been reported by several investigators, including ourselves (*63–65*). Since the methods of alcohol administration have included both intubation and liquid diet, and the activity has been measured by a variety of methods such as activity wheels, observer counts of rearing and approach, and squares crossed in an open field, we can be fairly confident that the results are valid. Krsiak's group (*58*) found lowered concentrations of serotonin in the brains of offspring from dams given alcohol, although brain catecholamines (dopamine and norepinephrine) were not depleted. This may be particularly relevant because a recent review (*66*) links lowered activity of the serotonergic system to hyperactivity in humans. In addition, the Krsiak study eliminated the possible effect of individual versus group housing (which has been shown to influence brain monoamine levels), and our study (*63*), by cross-fostering the offspring, eliminated possible postnatal maternal influences. Offspring exposed to alcohol in utero are more active than controls, regardless of whether they are raised by natural or foster mothers, a finding that replicates the clinical reports of hyperactivity in children with FAS (*16*).

*Learning effects*. These have been reported by many investigators, beginning with an early study reporting inferior learning ability in a water maze and greater emotionality in rats whose mothers received alcohol during pregnancy (*67*). Phillips and Stainbrook (*59*) tested visual discrimination in an apparatus designed to present four stimuli simultaneously; the offspring exposed to alcohol in utero were inferior in learning set formation, which tests conceptualization, or "learning to learn." Bond and Di Giusto (*65*) found such offspring impaired in their ability to learn to avoid a noxious stimulus. Riley *et al.* (*68*), using several different paradigms, reported difficulty with response inhibition and reversal learning in offspring of alcohol-fed rats, behaviors perhaps analogous to the uninhibited behaviors seen in some children with FAS (*16*).

In our own laboratory (*60*), operant studies, in which the receipt of food depends on an animal's ability to learn the pattern of timing or to expend a given amount of effort, have shown that rats exposed to alcohol in utero are slower to learn on the simple schedules when alcohol is also continued during lactation. Alcohol administered only during the nursing period did not have as severe an effect. Pair-fed controls were used to control for undernutrition, since alcohol is caloric. The offspring exposed to alcohol in utero performed more efficiently on schedules that rewarded a slower rate of response. A punishment schedule, in which the rats had to turn on the shock themselves before they could operate a bar to receive food pellets, showed that offspring exposed to alcohol during gestation and nursing had trouble learning the problem; their behavior totally disintegrated at the highest shock level.

From the literature on animal studies, we see a confirmation of the work conducted with humans on the teratogenic effects of alcohol. In addition to producing malformations and increased offspring mortality, intrauterine exposure to alcohol in laboratory animals produces growth deficiency and learning deficits that might be construed as analogous to the developmental and intellectual impairment noted in children with FAS. Furthermore, the literature on laboratory animals clarifies the nutritional issue to some extent. Pair-fed controls have been used in many of the animal studies, and the results have suggested that it is the alcohol that is the prime teratogenic agent, not the poor nutrition. However, even pair feeding does not control for changes in metabolism and utilization of basic nutrients which may be affected by alcohol. To our knowledge, no one has investigated the role of poor nutrition as a risk factor that might increase the likelihood of an effect in alcohol-fed animals. Such studies of possible synergistic effects might help to explain the preponderance of children with FAS among the lower social classes.

Animal experiments also show the importance of the host in determining the effect produced by a teratogenic agent. Chernoff (*69*) found that alcohol-fed mice had more resorptions and more malformed offspring than pair-fed controls, but the effects were strongest in a mouse strain that has low alcohol dehydrogenase activity and is a slow metabolizer of alcohol. As there is still considerable question as to why some alcoholic mothers produce affected offspring and others do not, studies such as these can help explain some of the genetic factors that may be involved.

## Conclusions

The research and clinical studies reviewed here clearly indicate that alcohol is a teratogen. However, the mechanisms through which the effects are produced remain unclear. The question of whether it is the direct effect of alcohol on morphogenesis or the effect of a breakdown product, such as acetaldehyde (*70*), awaits further study. Likewise, risk factors that may exacerbate an effect, such as poor nutrition, exposure to other drugs, and individual differences in alcohol metabolism, are poorly understood.

There appears to be a dose-response curve for intrauterine alcohol exposure. The effects on offspring range from birth weight and functional deficits at the lower doses to FAS and increased offspring mortality at the higher doses (such as among offspring of chronic alcoholics). A safe level of alcohol use during pregnancy has not been established, although birth weight decrements in human beings have been found at levels corresponding to about two drinks per day on the average.

*Public policy*. These findings have important implications for public policy. On 1 June 1977, following the first federally sponsored workshop on FAS, Ernest P. Noble, then director of NIAAA (*71*), issued a health caution on FAS, warning that adverse effects were found corresponding to about six drinks per day on the average and that the effects at lower levels remained uncertain. Immediately, a statement on FAS was made to 200,000 health care professionals through the *Morbidity and Mortality*

*Weekly Report* circulated by the Center for Disease Control (*72*). In September 1977, Donald Kennedy, then commissioner of the Food and Drug Administration (FDA), authorized publication of a statement on FAS in the FDA *Drug Bulletin* (*73*).

On 15 November 1977, Kennedy urged the Bureau of Alcohol, Tobacco, and Firearms (BATF) to initiate rulemaking to require that labels be put on bottles regarding alcohol use during pregnancy. On 31 January 1978, the Senate Subcommittee on Alcoholism and Drug Abuse held hearings on the question of bottle labeling and FAS (*74*), and on 17 March 1978, BATF solicited public response to the question (*75*). In January 1979, BATF decided against bottle labeling partly because of the complexity of the message that would be required (*76*). BATF did require that the liquor industry fund an educational campaign, to be evaluated in 2 years, warning mothers of the dangers that drinking poses to their unborn children (*75*).

On another front, NIAAA has funded two demonstration and prevention projects (*77*) to develop education materials and media campaigns regarding alcohol and pregnancy, and to develop systems for providing information and referral services to pregnant women drinking at risk levels. Several states, including Wisconsin, South Carolina, Virginia, Texas, and Illinois, have also taken the initiative and developed educational and service programs for FAS. The National Council on Alcoholism has made FAS a focus for research funding, the National Foundation-March of Dimes has been active in educational programming for FAS, and the Bureau of Indian Affairs made FAS top priority for the Year of the Child.

The teratogenic effects of alcohol are clearly established in humans and animals, although many questions remain unanswered. Two key issues, now, are to elucidate the mechanisms of impairment and to increase public awareness.

#### References and Notes


1. R. H. Warner and H. L. Rosett, *J. Stud. Alc.* **36**, 1395 (1975).
2. W. C. Sullivan, *J. Ment. Sci.* **45**, 489 (1899).
3. H. W. Haggard and E. M. Jellinek, *Alcohol Explored* (Doubleday, New York, 1942).
4. J. Rouquette, thesis, University of Paris (1957).
5. E. J. Calabrese, *Pollutants and High Risk Groups* (Wiley, New York, 1978).
6. J. E. Idanpaan-Heikkila, G. E. Fritchie, B. T. Ho, W. M. McIsaac, *Am. J. Obstet. Gynecol.* **110**, 426 (1971); P. V. Dilts, Jr., *ibid.* **107**, 1195 (1970).
7. P. S. Weathersbee and J. R. Lodge, *J. Reprod. Med.* **21**, 63 (1978).
8. J. G. Wilson, in *Handbook of Teratology*, J. G. Wilson and F. C. Fraser, Eds. (Plenum, New York, 1977), pp. 47–74.
9. P. Lemoine, H. Harrousseau, J. P. Borteyru, J. Menuet, *Ouest Med.* **25**, 477 (1968) (English translation available from National Clearinghouse for Alcohol Information, Department STIAR, P.O. Box 2345, Rockville, Md. 20852).
10. K. L. Jones and D. W. Smith, *Lancet* **1973-II**, 999 (1973); _____, N. Ulleland, A. P. Streissguth, *ibid.*, **1973-I**, 1267 (1973); K. L. Jones and D. W. Smith, *Teratology* **12**, 1 (1975).
11. S. K. Clarren and D. W. Smith, *N. Engl. J. Med.* **298**, 1063 (1978).
12. S. K. Clarren, E. C. Alvord, S. M. Sumi, A. P. Streissguth, D. W. Smith, *J. Pediatr.* **92**, 64 (1978).
13. F. Majewski, H. Fischbach, J. Peiffer, J. R. Bierich, *Dtsch. Med. Wochenschr.* **103**, 895 (1978).
14. V. Havlicek, R. Childiaeva, V. Chernik, *Neuropaediatrie* **8**, 360 (1977); A. W. Root, E. O. Reiter, M. Andriola, G. Duckett, *J. Pediatr.* **87**, 585 (1975).
15. R. Olegard *et al.*, *Acta Paediatr. Scand. Suppl.* **275**, 112 (1979).
16. A. P. Streissguth, C. S. Herman, D. W. Smith, *J. Pediatr.* **92**, 363 (1978).
17. S. Pierog, O. Chandavasu, I. Wexler, *ibid.* **90**, 630 (1977).
18. A. P. Streissguth, *Am. J. Epidemiol.* **107**, 467 (1978).
19. D. W. Smith, *Pediatr. Rev.* **1** (No. 6), 165 (1979).
20. K. L. Jones, D. W. Smith, A. P. Streissguth, N. C. Myrianthopoulos, *Lancet* **1974-I**, 1076 (1974).
21. F. Majewski, J. R. Bierich, H. Loser, R. Michaelis, B. Leiber, F. Bettecken, *Muench. Med. Wochenschr.* **118**, 1635 (1976) (English translation available from National Clearinghouse for Alcohol Information, Department STIAR, P.O. Box 2345, Rockville, Md. 20852); F. Majewski, *Nervenarzt* **49**, 410 (1978); J. R. Bierich, *Internist* **19**, 131 (1978).
22. P. Dehaene, C. Samaille-Villette, P. Samaille, G. Crepin, R. Walbaum, P. Deroubaix, A. P. Blanc-Garin, *Rev. Alcool.* **23**, 145 (1977) (English translation available from National Clearinghouse for Alcohol Information, Department STIAR, P.O. Box 2345, Rockville, Md. 20852); C. Samaille-Villette and P. Samaille, *J. Nat. Neonatol.* **37** (21 May 1977); P. Dehaene, M. Titran, G. Crepin, G. Delahousse, P. Fasquelle, C. Samaille-Villette, P. Samaille, *Nouv. Presse Med.* **6**, 1963 (1977).
23. A. P. Streissguth, C. S. Herman, D. W. Smith, *Alc. Clin. Exp. Res.* **2**, 165 (1978).
24. D. E. Hutchings, in *Studies of Development of Behavior and the Nervous System:* vol. 4, *Early Influences*, G. Gottlieb, Ed. (Academic Press, New York, 1978), pp. 7–30.
25. S. E. Shaywitz, D. G. Cohen, B. A. Shaywitz, *Pediatr. Res.* **12**, 375 (abstr. 71) (1978).
26. A. P. Streissguth, R. E. Little, C. Herman, S. Woodell, *Alc. Clin. Exp. Res.* **3**, 197 (1979).
27. J. W. Hanson, A. P. Streissguth, D. W. Smith, *J. Pediatr.* **92**, 457 (1978).
28. H. Manzke and F. R. Grosse, *Med. Welt* **26**, 709 (1975).
29. K. K. Christoffel and I. Salafsky, *J. Pediatr.* **87**, 963 (1975).
30. G. S. Omenn, *Ann. N.Y. Acad. Sci.* **205**, 212 (1973); N. R. Morrison and M. A. Stewart, *Am. J. Psychiatry* **130**, 791 (1973); R. J. Cadoret, L. Cunningham, R. Loftus, J. E. Edwards, *J. Pediatr.* **87**, 301 (1975).
31. H. L. Rosett, E. M. Ouellette, L. Weiner, E. Owens, *Ann. N.Y. Acad. Sci.* **273**, 118 (1976); E. M. Ouellette and H. L. Rosett, *ibid.*, p. 123; _____, N. P. Rosman, L. Weiner, *N. Engl. J. Med.* **297**, 528 (1977); H. L. Rosett, E. M. Ouellette, L. Weiner, E. Owens, *Obstet. Gynecol.* **51**, 41 (1978); H. L. Rosett, personal communication.
32. J. Kuzma and T. Phillips, Loma Linda Medical School, Loma Linda, California.
33. A. P. Streissguth, J. C. Martin, D. C. Martin, *Univ. Wash. Alcoholism and Drug Abuse Institute Tech. Rep. No. 78-01* (1978); also see (*27, 28, 39–42, 44, 46*).
34. M. Kaminski, C. Rumeau-Rouquette, D. Schwartz, *Rev. Epidemiol. Med. Soc. Santé Publique* **24**, 27 (1976) [English translation by R. E. Little and A. Schinzel, *Alc. Clin. Exp. Res.* **2**, 155 (1978)]; M. Kaminski, personal communication.
35. R. E. Little, *Am. J. Public Health* **67**, 1154 (1977).
36. S. Landesman-Dwyer and I. Emanuel, *Teratology* **19**, 119 (1979).
37. D. C. Martin, H. M. Barr, A. P. Streissguth, unpublished data.
38. K. L. Jones and D. W. Smith, *New Engl. J. Med.* **298**, 55 (1978); E. M. Ouellette, *ibid.*
39. A. P. Streissguth, D. C. Martin, H. M. Barr, paper presented at the American Psychological Association Meeting, San Francisco (1977).
40. S. Landesman-Dwyer, L. S. Keller, A. P. Streissguth, *Alc. Clin. Exp. Res.* **2**, 171 (1978).
41. J. C. Martin, D. C. Martin, C. Lund, A. P. Streissguth, *ibid.* **1**, 243 (1977).
42. D. C. Martin, J. C. Martin, A. P. Streissguth, C. A. Lund, in *Currents in Alcoholism*, M. Galanter, Ed. (Grune & Stratton, New York, 1979), vol. 5.
43. A. P. Streissguth, H. M. Barr, D. C. Martin, S. Woodell, *Alc. Clin. Exp. Res.* **2**, 201 (1978).
44. L. W. Sander, P. Snyder, H. L. Rosett, A. Lee, J. B. Gould, E. Ouellette, *ibid.* **1**, 233 (1977); H. L. Rosett, P. Snyder, L. W. Sander, A. Lee, P. Cook, L. Weiner, *Dev. Med. Child Neurol.*, in press.
45. A. P. Streissguth, H. M. Barr, D. C. Martin, *Alc. Clin. Exp. Res.*, in press.
46. S. Landesman-Dwyer, A. Ragozin, R. E. Little, abstracts of individual papers, Society for Research in Child Development (1979), p. 122.
47. A. P. Streissguth, D. C. Martin, V. E. Buffington, *Ann. N.Y. Acad. Sci.* **273**, 458 (1976).
48. C. F. Chernoff, *Teratology* **11**, 14A (1975); C. L. Randall, W. J. Taylor, D. W. Walker, *Alc. Clin. Exp. Res.* **1**, 219 (1977).
49. D. Papara-Nicholson and I. R. Telford, *Anat. Rec.* **127**, 438 (1957).
50. F. W. Ellis and J. R. Pick, *Pharmacologist* **18**, 190 (1976).
51. S. Sandor and D. Amels, *Rev. Roum. Embryol.* **8**, 101 (1971); W. J. Tze and M. Lee, *Nature (London)* **257**, 479 (1975).
52. R. H. Elton and M. E. Wilson, *J. Stud. Alc.* **38**, 2181 (1977).
53. J. B. Kronick, *Am. J. Obstet. Gynecol.* **124**, 676 (1976).
54. C. L. Randall, in *Alcohol and Opiates: Neurochemical and Behavioral Mechanisms*, K. Blum, D. Bard, M. Hamilton, Eds. (Academic Press, New York, 1977), p. 91.
55. E. L. Abel, *Psychopharmacology* **57**, 5 (1978).
56. A. K. Rawat, *Res. Commun. Chem. Pathol. Pharmacol.* **12**, 723 (1975).
57. N. P. Rosman and M. J. Malone, *Neurology* **26**, 365 (1976).
58. M. Krsiak, J. Ellis, N. Pöschlová, K. Masek, *J. Stud. Alc.* **38**, 1696 (1977).
59. D. S. Phillips and G. L. Stainbrook, *Physiol. Psychol.* **6**, 75 (1978).
60. J. C. Martin, D. C. Martin, G. Sigman, B. Radow, *Dev. Psychobiol.* **10**, 435 (1977).
61. J. C. Martin, unpublished research.
62. J. Ellis, M. Krsiak, N. Pöschlová, K. Masek, *Act. Nerv. Super.* **18**, 220 (1976).
63. J. C. Martin, D. C. Martin, G. Sigman, B. Radow, *Physiol. Psychol.* **6**, 362 (1978).
64. L. Branchey and A. J. Friedhoff, *Ann. N.Y. Acad. Sci.* **273**, 328 (1976); see also (*58*).
65. N. W. Bond and E. L. Di Giusto, *Psychol. Rep.* **41**, 1269 (1977).
66. D. A. Brase and H. H. Loh, *Life Sci.* **16**, 1005 (1975).
67. N. M. Vincent, *Am. Psychol.* **13**, 401 (1958).
68. E. P. Riley, E. A. Lochry, N. R. Shapiro, J. Baldwin, *Pharmacol. Biochem. Behav.* **10**, 255 (1979); E. P. Riley, E. A. Lochry, N. R. Shapiro, *Psychopharmacology* **62**, 47 (1979).
69. C. F. Chernoff, *Teratology* **13**, 223 (1977).
70. P. V. Veghelyi and M. Osztovics, *Experientia* **34**, 195 (1978); _____, E. Szaszavsky, *Br. Med. J.* **2**, 1365 (1978).
71. Department of Health, Education and Welfare, press release, 1 June 1977.
72. *Morbidity and Mortality Weekly Rep.* **26**, 1978 (1977).
73. *Drug Bull.* **7**, 18 (1977).
74. Hearing before the Subcommittee on Alcoholism and Drug Abuse of the Committee on Human Resources, U.S. Senate, 95th Congress, 2nd session on S.1464, 31 January 1978.
75. Progress report concerning the Advance Notice of Proposed Rulemaking on Warning Labels on Containers of Alcoholic Beverages and Addendum, Department of the Treasury and Bureau of Alcohol, Tobacco, and Firearms, February 1979.
76. R. J. Smith, *Science* **203**, 858 (1979).
77. R. E. Little, A. P. Streissguth, G. M. Guzinsky, A Demonstration Project to Prevent Fetal Alcohol Syndrome and Intervene in Female Alcohol Abuse During Pregnancy, NIAAA No. 1H84 AA03736-01; A. Baxter, The Fetal Alcohol Syndrome Prevention Program, NIAAA No. 1H84 AA03922-01.


78. We thank K. Warren (NIAAA) and D. Bast (NCALI) for technical support, G. Owen for graphics, and M. Leamon and S. Hughes for secretarial assistance. Partial financial support was from HEW grant AA01455-05 from the National Institute of Alcohol Abuse and Alcoholism, PHS grant 15253 from the Bureau of Community Health Services, Maternal and Child Health and Crippled Children Services, and the University of Washington Child Development and Mental Retardation Center, PHS grant HD02274 from the National Institute of Child Health and Human Development.