Pergamon

Neurotoxicology and Teratology, Vol. 17, No. 4, pp. 445–462, 1995

0892-0362/95 $9.50 + .00

0892-0362(94)(95)00001-1

Maternal Risk Factors in Fetal Alcohol Syndrome: Provocative and Permissive Influences

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Received 20 April 1994; Accepted 16 December 1994

ABEL, E. L. AND J. H. HANNIGAN. *Maternal risk factors in Fetal Alcohol Syndrome: Provocative and permissive influences.* NEUROTOXICOL TERATOL **17**(4) 445–462, 1995.—We present an hypothesis integrating epidemiological, clinical case, and basic biomedical research to explain why only relatively few women who drink alcohol during pregnancy give birth to children with alcohol-related birth defects (ARBDs), in particular, Fetal Alcohol Syndrome (FAS). We argue that specific sociobehavioral risk factors, e.g., low socioeconomic status, are permissive for FAS in that they provide the context for increased vulnerability. We illustrate how these permissive factors are related to biological factors, e.g., decreased antioxidant status, which in conjunction with alcohol, provoke FAS/ARBDs in vulnerable fetuses. We propose an integrative heuristic model hypothesizing that these permissive and provocative factors increase the likelihood of FAS/ARBDs because they potentiate two related mechanisms of alcohol-induced teratogenesis, specifically, maternal/fetal hypoxia and free radical formation.

Fetal Alcohol Syndrome (FAS) Alcohol-related birth defects Etiology Mechanisms Risk Risk factors Free radicals Hypoxia Smoking Binge drinking SES Nutrition (Undernutrition) Ethnicity Race Genetics

FETAL Alcohol Syndrome (FAS), a pattern of anomalies occurring in children born to alcoholic women consisting of (a) pre- and/or postnatal growth retardation, (b) morphological anomalies, and (c) central nervous system (CNS) dysfunction (72,111,236,275) is now recognized as a leading nongenetic cause of mental retardation (14,143) and other serious physical and cognitive anomalies (4,9). Prenatal alcohol exposure may also give rise to individual alcohol-related birth defects (ARBDs), including spontaneous abortion, heightened stress reactivity, decreased immune function, attention problems, hearing impairment, delayed development, altered play behavior, and a host of other anomalies (e.g., 4,9,35,54,140,154, 184,237,256,272, 273,275,279,287,311,314,327).

This review focuses on FAS because there are specific criteria for its diagnosis. Attributing individual ARBDs, other than FAS, to prenatal alcohol exposure for any single patient is problematic because any single anomaly may also be the result of innumerable factors other than alcohol. On the other hand, analogues of individual ARBDs have been produced in animal models (e.g., 4,9,19,54,80,183,227,232,233), arguing cogently that these various outcomes in humans are plausible consequences of in utero alcohol exposure.

Based on a wide-ranging but necessarily circumscribed literature, we discuss the selective occurrence of FAS in various populations. This selectivity for FAS is not unlike the selectivity associated with other effects of chronic alcohol abuse, such as cirrhosis, which develops in relatively few heavy drinkers or alcoholics (185). On the basis of the disparities in the occurrence of FAS, we draw inferences about potential predisposing sociobehavioral risk factors for FAS which we call "permissive" factors. We argue that these permissive factors provide the context within which vulnerability to alcohol's teratogenic effects are increased. We then describe how these permissive factors create a biological milieu that is "provoca-

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tive" for FAS. This biological milieu is provocative because it increases cellular susceptibilities to alcohol's toxic effects. Finally, we draw inferences from the relationships between these permissive and provocative factors to support an integrative hypothesis focusing on hypoxia and free-radical damage which, we argue, accounts for the selective occurrence of FAS.

We begin our review with an examination of the epidemiological literature, which as stated previously, clearly indicates a nonuniform occurrence of FAS in different populations.

INCIDENCE, PREVALENCE, AND INFERENCE: FAS IS NOT AN EQUAL OPPORTUNITY BIRTH DEFECT

The latest conservative estimate for the incidence of FAS in the western world is 1.02 cases per 1,000 live births (10). This estimate is based on 29 prospective epidemiological studies and is considerably higher than our previous estimate of 0.19 cases per 1,000 live births, based on considerably fewer studies (15,16). Nearly all of the cases contributing to this rate, however, have come from the United States where the rate is 1.95 per 1,000, compared to 0.09 cases per 1,000 from the rest of the world (10). If instead of calculating an overall rate per 1,000 cases, one averages the incidence rate from each of these 29 studies, the mean incidence rate is 0.60 per 1,000, and the median rate for these studies is zero cases per 1,000, which is also the mode. These disparities among these three estimates, and the disparity between the mean and the median, indicate FAS occurs considerably more often (or less often) at some sites than others. In other words, FAS is not an equal opportunity defect.

The estimated incidence of FAS among women who drink "heavily" (as defined by consumption of 5 or more drinks per occasion, an average of 2 or more drinks per day, a positive MAST score, or a clinical diagnosis) is about 4.3% of all live births (10). This relatively low rate of occurrence among a population seemingly most at-risk for FAS likewise suggests FAS is not an equal opportunity birth defect. Because ARBDs in individual children cannot be unambiguously attributed to prenatal alcohol exposure, estimates for their incidence/prevalence are highly speculative.

Although it has been argued FAS is underdiagnosed (72,166), there is little evidence to support this assumption. As a result of increased awareness of FAS among health care professionals, the possibility of FAS going unrecognized shortly after live birth seems unlikely. Studies by Clarren and his associates (26,55), and by our group (13) indicate the pattern of facial anomalies in young children with FAS is distinctive. The unusual facial features are related to amount of maternal drinking (13,241), although individual anomalies vary (111) and identification becomes more difficult when individuals reach puberty (272,279). The low rate of FAS among infants of heavy drinking women, therefore, does not appear to be due to underdiagnosis.

One inference from the relatively low rate of occurrence of FAS, even among infants of "heavy" drinkers (4.3%), is that factors in addition to alcohol consumption during pregnancy affect the expression of FAS. We propose two categorical types of factors: permissive and provocative.[2] By *permissive* factors, we mean predisposing behavioral, social, or environmental characteristics (e.g., alcohol consumption patterns, socioeconomic status, culture) that can produce certain biological conditions. These conditions, in conjunction with heavy drinking, increase fetal vulnerability to alcohol's teratogenic effects. By *provocative* causes, we mean the biological conditions (e.g., high blood alcohol levels (BALs), decreased antioxidant status) resulting from these permissive factors, which create the internal milieu responsible for the increased fetal vulnerability to alcohol at the cellular level. In our model (Fig. 1), for example, "smoking" behavior is a permissive factor because it results in the introduction of the products of tobacco smoke into the body. The products of this tobacco smoke are provocative factors because they exert a direct biological impact on specific, causal mechanisms of FAS/ARBDs (e.g., hypoxia and free-radical damage). We argue that the interplay between these permissive and provocative factors relate directly to the mechanisms and magnitude of alcohol's effects on developing tissues and explain why a relatively small proportion of alcoholic women give birth to a disproportionate number of reported FAS cases (7,15,16,63,72,137,165). The next sections discuss these permissive and provocative factors in detail.

Permissive Factors

Alcohol intake pattern. Both the amount and pattern(s) of alcohol consumption are permissive factors in the etiology of FAS. The more alcohol consumed, and the more quickly it is consumed, the higher the blood alcohol level (BAL). The higher the BAL, the more likely a given fetus will reach a biological "threshold" for FAS, even though it may not be possible to define that threshold for individuals or groups.

All teratogens, including alcohol, produce their effects within a range of exposures (4,9,11,215): Below one level there may be no observable damage to the conceptus (4,11,183,246); above another level, there may be various anomalies such as the individual ARBDs of lowered birth weight, postnatal growth retardation, microcephaly, or decreased cognitive function (58,70,96,241,246,279). At very high levels, a teratogen may be embryo- or fetotoxic (30,144,317), thereby providing an upper limit on the number of potential live births with exposure to that teratogen. In nonhuman primates, abortions from alcohol begin to occur following exposures in the first trimester of the 164-day gestation period, of about 200 mg/dl (19,54,256), corresponding to consumption of about 8.5 drinks within a 4-h period (one drink per half hour) for a 55 kg (120 lb) woman (295). Different outcomes are dependent not only on the amount of alcohol exposure but also on the time during pregnancy when alcohol exposure occurs (4,9,37,214).

Alcohol consumption patterns have been characterized in terms of average alcohol consumption per day, average monthly occasions of drinking, average drinks per drinking occasion, maximum drinks per occasion, frequent heavy drinking, problem drinking, combinations of quantity-frequency variability, and bingeing (5 or more drinks on any occasion) (e.g., 12, 71,241,279). Although average alcohol consumption per day is one of the most commonly used indices for determining risk, few Americans drink daily (153). Average daily consumption is a derived measure, and potentially misleading (240), especially in describing "thresholds," because it ignores episodic patterns of high levels of consumption (71). For example, in North America, the greatest amount of alcohol is commonly consumed on weekends (12), and drunkenness is socially tolerated to a much greater extent than in Mediterranean countries where wine and beer are consumed mainly with meals, and where drunkenness is discouraged (31,134).

An average daily consumption of 2 drinks per day may reflect just that, or it may reflect consumption of 7 drinks on

[2] One of us (EA) has encountered these terms in a similar context but cannot find the appropriate reference.

each Friday and Saturday night (240). Because it is a basic tenet in teratology that once a threshold for toxicity is exceeded, the extent of embryo/fetal damage is a function of the amount of exposure to a teratogen (8), exposures to brief but high blood alcohol levels ought to cause more cellular damage than exposures to more prolonged, lower levels of exposure (253). The number of drinks per occasion, or the related measures of maximum drinks per occasion, frequent heavy drinking, or number of "binges" are, therefore, more relevant for assessing fetal exposure and potential damage than exposures derived from average consumption levels, especially when those averages may be inflated by discrete binges (37,245, 246,253,276,279). Drinks per occasion is also more compatible with evidence from the experimental literature comparing episodic versus sustained exposure to alcohol (see below). However, this generalization may only hold true for some aspects of development, such as brain development or function and less so for other effects such as decreased birth weight or postnatal growth (cf. 71,142,291).

Race/socioeconomic status. Most of the FAS cases identified in epidemiological studies from the United States have been diagnosed in inner city hospitals where the populations were predominantly African-American and uniformly characterized by poverty (2.29 cases per 1,000 live births), compared to sites where the populations were primarily Caucasian and middle class (0.26 per 1,000) (10). The 11 FAS children originally described by Jones and Smith (143), for instance, were racially divergent, e.g., Caucasian, African-American, and Native American but similar in that all 11 mothers were living on welfare. About 40% of the 133 African-American and Hispanic lower SES infants studied by Bingol and her group had FAS, compared to only 2.7% with FAS among the 109 infants born to a group of Caucasian upper middle class alcoholics in New York (32). Nearly all of the FAS mothers studied by Sokol et al. (140,267,270) were on welfare. Day et al.'s patient population in Pittsburgh were equally divided between African-Americans and Caucasians, but were overwhelmingly characterized by poverty (family income averaged less than $400/month) (71). Most of the subjects in the Georgia Alcohol and Pregnancy Research Project were African-American and were likewise poverty stricken (average income of $372/month) (264). The two FAS cases from the Hanson et al. study (112) that contributed to the middle class estimate, were both African-American. Had they been eliminated from the analysis as being nonrepresentative of the "predominantly white, middle class and well-educated" sample (112), the estimated incidence for middle class Caucasians would have been zero. In surveillance studies suggesting the rate of FAS may be seven times higher among African-Americans and 30 times higher among Native Americans than among Caucasians, racial group is confounded with poverty (16,49).

African- and Native Americans are disproportionately characterized by poverty (annual incomes of less than $10,000/year) (293). Although race and SES are often inextricably confounded (61), most studies of FAS risk factors have focused on race as a biological factor and have largely ignored SES. Race, however, has meaning primarily as a social concept; biologically, it has been shown to be less meaningful in the present context (316). Racial variations in susceptibility to health-related problems rest on a misconception that race reflects biological homogeneity and that the genes determining race are linked to those affecting health (316). The assumption that African-Americans are at increased risk for FAS because of any unique genotype has not been supported by evidence to date (10).

Even a recognized single gene disorder such as sickle-cell anemia, which is frequently cited as evidence of a racially homogeneous disorder is not unique to Africans or African-Americans. Although certainly more common among African-Americans, the genetic trait also occurs among Caucasians of Mediterranean background. Occurrence of sickle-cell trait is dependent not on race but on geographical origin. Peoples from areas where malaria is common have a higher prevalence of the trait (316). A variety of genetic studies, including DNA analyses, indicates *intragroup* genetic variability among African-Americans is greater than the *intergroup* genetic variability between African-Americans and Caucasians (61,316). A research focus on genetic differences between populations, therefore, may divert attention from socioeconomic or environmental contributions to disease in general and to poor infant outcome in the case of FAS in particular.

Whereas a lower threshold for FAS has been reported for African-Americans compared to Caucasians (4 vs. 6 drinks per day, respectively) (267), this apparent differential susceptibility does not necessarily relate to different genotypes among racial groups for several reasons. First, threshold estimates based on self-reported drinking are unreliable, especially when obtained from problem drinkers (72,84,141,170). We do not know if people from different racial or SES backgrounds, pregnant or otherwise, differ in denial or distortion of self-reported drinking behavior (161). We do know, however, that as a group, African-American women are more likely to be abstainers than are Caucasian women (46). Among women who do drink, African-American women are more likely to drink heavily and to develop alcohol-related problems than Caucasian women (239). African-American, Native American, and Caucasian alcoholics also differ in drinking patterns. African- and Native American alcoholic women tend to drink more in fewer bouts per week (i.e., bingeing), whereas Caucasian alcoholic women are more likely to drink constantly throughout the week (69,113,175,176). It is the number of drinks per occasion and the attendant higher peak BALs, rather than a relatively constant lower BAL, that appears to be a major risk factor for ARBDs (37,214,215,245,276,279). The higher BALs associated with binge-like drinking compared to sustained consumption of the same amount of alcohol by alcoholics could put infants of African- and Native American women at relatively greater risk for FAS. This would imply that cultural factors influencing drinking patterns have a major permissive contribution to racial group differences in the incidence of FAS.

Having shown that low SES appears to be a major permissive factor in FAS, this does not mean genetic factors are not also involved. Differential sensitivity to FAS/ARBDs in dizygotic twins (47,52,204,249,278) and a high concordance for FAS/ARBDs among monozygotic twins (278) suggest a genetic basis for individual vulnerability to alcohol's teratogenic effects (47,52,204,249,278). However, differential sensitivities to in utero alcohol exposure are also found in genomically identical inbred mice (99).

Genetic factors influencing vulnerability to FAS may include differences in the various isoforms of alcohol dehydrogenase (ADH), the enzyme that metabolizes alcohol to acetaldehyde (38,39,61,102,289). However, there is no convincing evidence for a racial predisposition to FAS based on these different isoforms. One small study published in abstract form, reported that five African-American children with FAS had a higher than expected frequency of a rare ADH form, but included no racial control group (271). Another abstract found no association between the occurrence of "atypical

ADH and ALDH genotypes" and the clinical features of FAS (87).

It is also unlikely that African-Americans are at increased risk for FAS because of differences in the isoforms of aldehyde dehydrogenase (ALDH), the enzyme that converts acetaldehyde to acetate. There is an inactive form of ALDH (ALDH2*2), which leads to the build-up of acetaldehyde following alcohol consumption and an accompanying characteristic cutaneous vasodilatory "flush," tachycardia, and nausea. However, that inactive form of ALDH is present in Asians and not in African-Americans, Native Americans, or Caucasians (38,39,61,102,289). Because alcohol itself is capable of reducing fetal growth and inducing malformations in a dose-dependent manner without conversion to acetaldehyde (43, 56,219), acetaldehyde is not a necessary contributing factor in FAS/ARBDs. It is possible that differences in other biological parameters related to responsivity to alcohol, e.g., differential absorption, neural sensitivity, or cell membrane composition, may underlie alcohol's pharmacological (103,167) and teratogenic effects (129). However, there is no convincing evidence African- or Native Americans are at greater risk for FAS/ARBDs than Caucasian-Americans because of some genotypic population differences for any biological factor.

On the other hand, African-Americans are at greater risk than Caucasian-Americans for many causes of mortality and for several specific health-related problems, such as hypertension, obesity, type II diabetes, and low birth weight (61). It seems unlikely such a heterogeneous pattern of increased susceptibilities to health problems is due to genotype. A more probable hypothesis is that these racial group differences are due to the more consistent influences of culture and low SES (e.g., 61,126). For example, the higher prevalence of hypertension among African-Americans could be due to higher dietary sodium intakes compared to Caucasians, which, in turn, could be related to socioeconomic differences between these two groups (cf. 316).

Low SES itself contributes to many adverse pregnancy-related outcomes (61,130,200,217,254). Apparent racial differences in poor perinatal outcome, mortality and developmental disabilities—independent of alcohol abuse—are markedly influenced by SES and these differences often cease to be statistically significant when SES is taken into account (61,130,200,217). In the United States, the mortality rate for infants born to African-American mothers with low SES is about twice as high as the rate for college-educated African-American mothers, a difference comparable to that among Caucasians (254). African-American infants born in more segregated cities have higher infant mortality rates compared to those born in less segregated cities. As differences between social classes narrow, differences in infant mortality rates decrease (130,200,217,254). Because of these considerations, we believe low SES, rather than biological factors related to race, is the major permissive factor for FAS. Because genes are easier to characterize and study than SES (61), and because race is highly related to SES (61), permissive sociobehavioral factors related to SES may have been largely ignored in FAS research in favor of research aimed at identifying possible race-related genetic susceptibilities (cf. 32,49,267,268). FAS does occur in people of all races, but it occurs predominately in low SES populations regardless of race (10,14,16,112, 143,236,268).

Culture/ethnicity. Another major permissive factor for the occurrence of FAS that has been underexplored is ethnicity. We define ethnicity, in accord with the definition proposed by Warren et al. (306), as "self-perceived membership in populations defined by diverse criteria, including common ancestry, nationality, culture, language, and physical appearance." Differences among ethnic groups and cultures with respect to social or behavioral characteristics may increase the risk for FAS for one group over another. The difference in alcohol consumption patterns noted previously between African-American and Caucasian women in the United States (46, 69,113,175,176) is one such example.

In addition to site-related differences in the incidence of FAS noted within the United States, there are also differences among Western countries. For example, FAS appears to be much more common in Germany and the United States than in Italy or Great Britain (14,112,143,216,281,321), even though total per capita alcohol consumption is similar for these countries (134,198,218,221,326). It is unlikely these national differences are attributable to differential recognition since, as noted above, FAS is relatively easy to diagnose (13,26,55). Large epidemiological studies of ARBDs have been conducted in Great Britain (216,281,321) and it seems unlikely FAS would remain unrecognized in these studies.

Artifactual explanations for the higher incidence of FAS in the United States include differences in medical training of diagnosticians or in the inclination of physicians to label patients with a diagnosis. FAS may be more commonly reported in the United States than in countries such as England, for instance, because English physicians assign diagnostic labels to patients less often than their American colleagues (257). This difference may reflect the more "aggressive" way medicine is practiced in America compared to other countries. For example, vaginal hysterectomies are more common in Germany and subtotal hysterectomies are more common in France, whereas total abdominal hysterectomies are more common in the U.S. (208). Because of a more "aggressive" approach to medical diagnosis and treatment, in general, American physicians may be more likely than their British colleagues to make a diagnosis of FAS. Differences in criteria used to diagnose cases (172,236,299), differences in the importance given to specific features (e.g., 55), and biases on the part of diagnosticians in labelling cases within ethnic groups (235) may also contribute to reported differences in incidences at various sites. For example, more negative labels in psychopathology tend to be given to African-American than Caucasian patients (320).

Other cultural factors can influence a physician's decision to diagnose a child with FAS or not. For example, some states have laws specifying that occurrence of FAS is de facto evidence of maternal neglect or child abuse (136) and making it a misdemeanor for a physician or other health care provider not to report a case of FAS to the authorities (296). Diagnostic status also serves as a criterion for government aid (282) and medical care and labeling decisions may vary for children in needy families. One biologically based explanation is that cultural differences in diet or other factors among populations account for these differences, an idea developed later when we discuss how mechanisms of alcohol teratogenesis are related to risk factors.

Smoking. The final major permissive factor for FAS is smoking. Smoking is a permissive factor in that it causes the products of tobacco smoke to be taken into the body. There is no doubt these products themselves contribute to adverse pregnancy outcome, especially decreased birth weight (73, 118,152,155,294). Although alcohol consumption is highly correlated with smoking behavior among pregnant women (42,70,118,152,159,203,216,277,281,294,297,321), assessments of the impact of alcohol on pregnancy outcome have not al-

ways adequately addressed the problem of nonrandom assignment of subjects with different smoking histories in clinical or epidemiological studies. For example, in a truly randomized study design, each light, moderate, and heavy alcohol consumption group should have the same number of light, moderate, and heavy smokers. But because smoking and drinking are highly correlated, there are usually relatively few heavy drinkers-light smokers compared to heavy drinkers- heavy smokers. Although the concurrent influences of alcohol and smoking can be examined statistically to assess the independent effects of each alone, when there are too few subjects who are both heavy drinkers and light smokers or light drinkers and heavy smokers, additivity or synergism may not be detectable due to poor statistical power (61).

An alternative procedure for assessing the interaction between alcohol and smoking is to stratify alcohol users on the basis of smoking level. When this is done, it is clear that considerably more alcohol must be consumed to cause a significant decrease in birth weight when a women does not smoke than if she does (11). In their study of 2,803 births from a healthy Northern-European population considered at low risk for pregnancy complications, Verkerk et al. (297) found alcohol consumption had no significant effect on birth weight or gestational age unless the mother also smoked. Similar results were reported by Wright et al. (321), Brooke et al. (42), and Sulaiman et al. (281) for populations in England. An analysis of 23 prospective studies in this area derived an apparent threshold for significantly decreased birth weight at an average alcohol consumption of 2 or more drinks per day—but only among smokers (11). In several other studies, robust interactions were reported between maternal smoking and drinking in humans and between nicotine and alcohol administration in animals (42,159,203,216,281,321).

We conclude smoking cigarettes is a permissive factor in FAS. Furthermore, as we argue below, whereas low SES is a primary risk factor for FAS, the reason FAS and specific ARBDs such as decreased birth weight sometimes occur in higher SES groups is that the mothers of these infants were smokers. The common link between low SES and smoking is that they provoke a common biological milieu which increases susceptibility to alcohol's teratogenic action as we explain in the next section.

Relationships Between Permissive and Provocative Factors

Our model for the relationship between the four major sociobehavioral permissive factors identified above: alcohol intake pattern, low SES, ethnicity/culture, and smoking behavior, and the provocative biological factors they provoke are schematized in Fig. 1. The explanation for these interdependencies follows:

Alcohol intake pattern and blood alcohol levels (BALs). A very high level of alcohol consumption during a single drinking occasion, such as in bingeing, results in higher peak BALs than sustained alcohol intake even when similar total amounts of alcohol are consumed. Studies by West's group (37, 214,215) have clearly shown that a critical factor in alcohol-induced CNS damage in rats exposed during a developmental period equivalent to the third trimester brain growth spurt in humans is peak BAL, rather than total daily amount of alcohol exposure. Studies by Streissguth's group likewise suggest that peak BALs, rather than total daily exposure, is the critical factor affecting brain development and function in children (245,276). This means that high peak BALs appear to be a key provocative cause of FAS. In our model, culturally influenced patterns of drinking, such as bingeing, that effectively increase peak BALs, are permissive factors for FAS, and the result of such bingeing—a high BAL, is its provocative counterpart. The high BAL directly "provokes" the biological changes that result in FAS.

Low SES and alcohol-related health problems. The population most at risk for FAS is overwhelmingly poverty stricken (10,14,16). Whereas FAS does occur in all races (10), those study populations with the largest number of FAS patients are all characterized by poverty (10). For instance, 83% of the mothers in the Detroit population studied by Jacobson and coworkers were on welfare (140). This population has one of the highest rates of FAS in the United States (269). Other studies, as cited previously, likewise indicate a very high, if not exclusive occurrence of FAS/ARBDs among the socioeconomically disadvantaged, regardless of race (10). Some of the environmental and social correlates of poverty that are directly provocative, or that exacerbate other provocative factors for FAS, include inadequate diet or poor nutrition, inner city residency, psychological stress, high parity, smoking, and other drug abuse. The most prominent of these are described next in some detail, and others are included in the model (Fig. 1).

Undernutrition. In all cases of FAS reported in the literature (see reviews by 9,10,14,16,111), the mothers involved were characterized by undernutrition (reflected in low prepregnancy weight or poor maternal weight gain during pregnancy), and/or by smoking (1,10,60). Mothers of FAS children can also suffer from many alcohol-related illnesses including alcohol withdrawal, gastritis, gastric ulcers, infections, cirrhosis, and pancreatitis (1,60). Although none of these conditions has been associated directly with FAS, women who suffer from ill health during pregnancy have children characterized by low birth weight, poor health, physical anomalies, developmental delays, and behavioral disorders, more often than mothers who experience no health problem during pregnancy (206, 274).

Undernutrition is a provocative factor for FAS because the nutrient pool necessary for supporting fetal growth and maintaining maternal health is less than optimal (79). Heavy alcohol consumption itself is one cause of both primary and secondary malnutrition (162). Primary malnutrition occurs because alcohol has a high energy content and replaces other energy sources in the diet. In so doing, alcohol can reduce nutrient availability to both mother and fetus. Secondary malnutrition occurs as a result of alcohol-induced gastrointestinal dysfunction, which includes inhibition of nutrient absorption from the gut, inhibition of placental transport of nutrients essential to fetal growth and metabolic activity, and impairment of energy-dependent mechanisms in nutrient utilization (88-92,121,122, see also below), further reducing nutrient bioavailability to the fetus. Finally, nutrient delivery to the fetus is also reduced because alcohol impairs placental blood flow (20,86,191,251,323).

Perhaps the most significant finding from over 15 years of research with whole animal models of ARBDs is that alcohol exposure does not have teratogenic actions independent of either gross nutritional factors or of outright maternal toxicity (cf. 88,149,309,310). Although procedures such as pair-feeding provide equivalent caloric or sometimes equivalent specific nutrients for alcohol and control groups (e.g., 311,315), alcohol-treated animals invariably weigh less than animals allowed ad lib access to food (110). This means the alcohol-treated groups in any study with liquid or other diets, are always both alcohol treated and undernourished (149).

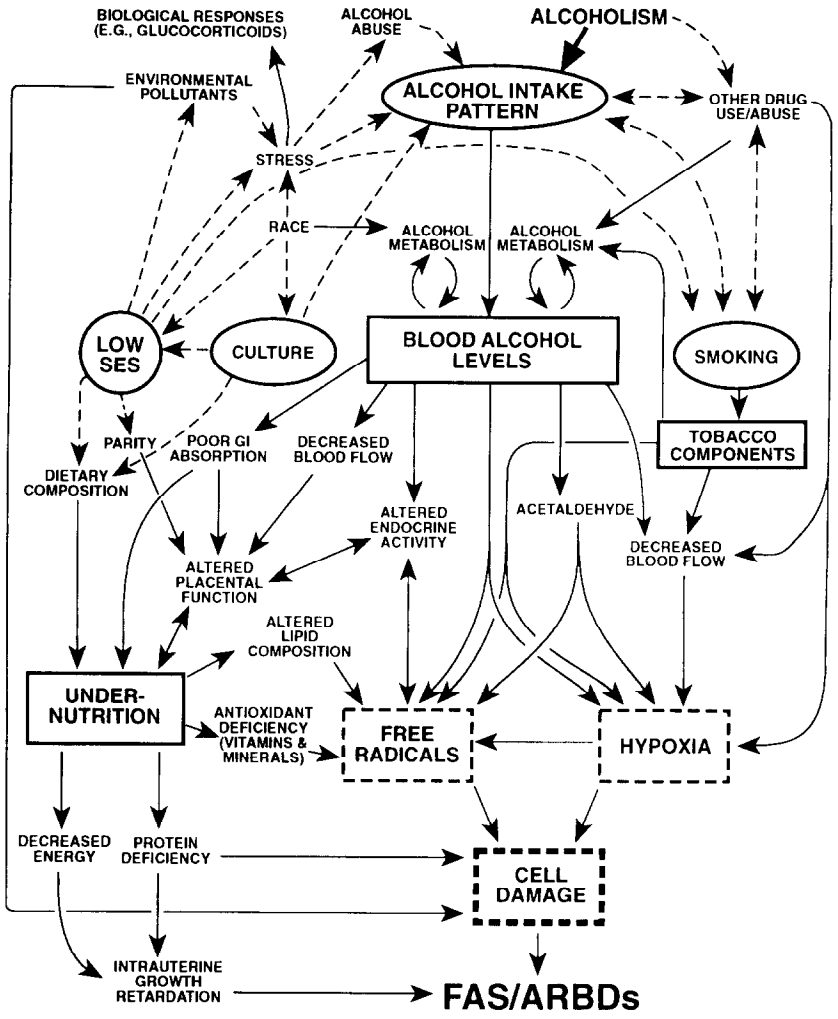

FIG. 1. Schematic summary of some of the relationships among permissive and provocative maternal risk factors, and among mechanisms underlying Alcohol-Related Birth Defects (ARBDs), including Fetal Alcohol Syndrome (FAS). Sociobehavioral Permissive Factors (inside the circles), include alcohol intake pattern, low socioeconomic status (low SES), particular aspects of culture, and smoking behavior. Permissive factors are highly correlated among themselves and increase risk for FAS/ARBDs by establishing an environment for, and/or predisposing fetuses to alcohol's direct cellular teratogenic effects by exacerbating the provocative risk factors. The key biological Provocative Factors (inside the solid squares) are peak blood alcohol levels (BALs), undernutrition and tobacco smoke constituents. Similar to the relationship between alcohol drinking pattern (permissive factor) and BALs (provocative factor), smoking is essentially both a permissive and a provocative risk factor because cigarette smoking is highly correlated with alcohol abuse and poor nutrition (permissive factor), and because tobacco smoke (provocative factor) exacerbates the effects of alcohol and directly impacts fetal development. The several pathways by which the permissive and provocative risk factors act on the maternal/placental/fetal unit are shown: The dotted-line arrows (- - - - >) show recognized, sometimes bidirectional associations among various environmental, demographic, and behavioral variables. For example, low SES is highly correlated with high parity, smoking behavior and stress. The solid-line arrows (———>) indicate biological relationships and physiological pathways. For example, binge drinking (alcohol intake pattern) increases peak BALs which in turn leads to decreased blood flow, altered placental function, undernutrition, etc. The key teratogenic mechanisms of FAS operate via hypoxia and free-radical damage (dashed squares) to converge on the necessary proximal cause of FAS, cell damage. The effects of cell damage on developing fetuses include altered cellular proliferation, differentiation, migration and/or apoptosis, as well as the regulation and timing of these events in all organ systems. Cell damage occurs because of disrupted membrane integrity (membrane order or fluidity), increased Ca^{++} influx, toxic levels of glutamate release, mitochondrial damage, as well as altered intracellular signal transduction, nuclear transcription, and gene expression. In addition to contributing to cell damage via various nutrient deficiencies, undernutrition also directly contributes to intrauterine growth retardation, a cardinal feature of FAS/ARBDs.

Any differences between these groups and nonalcohol-treated controls may be due to the interactive effects of alcohol plus undernutrition (173,309,310). The fact that anomalies occur to a greater extent in alcohol-exposed animals than in pair-fed controls does not eliminate the likelihood of a nutritional contribution but only indicates that undernutrition per se cannot account for ARBDs.

In vitro studies, likewise, do not eliminate the potential role of nutritional factors because the artificial media may not contain dietary substances, e.g., vitamins, whose effects may attenuate alcohol's biological effects on embryos (68). The same potential for interactions between alcohol and nutrient availability exist in cultured cells and whole animals. Disproving the provocative influences of undernutrition in ARBDs would require demonstrating specific ARBDs when alcohol-treated dams maintain the same body weight and the same functional nutrient status as untreated animals given ad lib access to food. This has never been, and probably cannot be shown. Other approaches assessing the role of nutrition have shown an exacerbation of alcohol's toxic and teratogenic effects in animals by diets low in important nutrients, e.g., protein or antioxidants (173,309,310,311,315, and see below). In addition, even when alcohol dosages are equivalent, undernourishment results in significantly slower rates of alcohol metabolism and as much as three- to four-fold increases in BALs (180,265,298).

Environmental pollutants. Low SES is associated with living in the inner city (130,200,217,254), which is an independent risk factor for poor pregnancy outcome, in part, because of increased exposure to environmental pollutants. Whereas many pollutants could be cited (169), we briefly mention only lead from industry and paint because considerably more is known about the effects of lead exposure on development.

The threshold level for CNS damage from lead for children was recently lowered to 10 μg/dl with increasing damage associated with increased exposures (17,83,85,195,205,259). Many of the effects of prenatal alcohol exposure, e.g., intrauterine growth retardation (IUGR) and CNS dysfunction, are also associated with prenatal lead exposure (17,83,195,205,259). Because alcohol consumption can increase blood lead levels (66,85,105,106), the likelihood of fetal damage from a synergism between alcohol and lead exposure is greater among infants born to alcoholics living in the inner city.

Parity. High parity, another correlate of poverty (130,200, 217,254), can be a provocative factor for FAS and ARBDs because of the obvious relationships between age and history of alcoholism. The longer a woman drinks heavily, the more severe her potential medical complications (25). Later-born children are more prone to FAS (7,63,137,165) because they can be exposed to higher BALs in utero than their older siblings, due to tolerance-related increases maternal alcohol intake and the greater severity of maternal alcohol-related medical problems interacting with continued alcohol exposure (149,172,247). Finally, uterine and placental collagen and elastin content also increases with parity, decreasing blood flow to the conceptus, contributing to fetal hypoxia (234,318), and thereby further exacerbating the impact of alcohol.

Psychological/physical stress. Psychological stress or physical abuse is a prominent correlate of poverty (21,130, 200,217,254) that may increase vulnerability to FAS. Stress can act directly in itself by affecting maternal physiology and health and by potentiating the biological potency of alcohol, as well as indirectly as a contributing factor in the initiation and maintenance of alcohol consumption by pregnant women (e.g., 40). Whether by cause or effect, victims of violence during pregnancy are also more likely to be heavy drinkers (21).

Maternal stress (marital discord, overcrowding, attitudes about pregnancy, etc.) contributes to increased rates of spontaneous abortions (252), obstetric complications (157), increased rates of low birth weight (81), and to childhood disorders such as bed-wetting, distractibility, sleep disturbances, disorders in reading ability, and cognitive impairment (e.g., 206). Unequivocal instances of behavioral effects in children due to maternal stress during pregnancy are difficult to demonstrate because of the confounding of pre- and postnatal conditions. However, such relationships have been amply documented in animal studies. Consequences of prenatal stress include decreased immune function (266), increased corticosterone responsivity (284), hyperactivity (23,307), and cognitive dysfunction (307), all of which are also concomitants of in utero alcohol exposure (e.g., 4,9,237,275,287,311).

Stress can interfere with maternal nutrient absorption, can activate the maternal hypothalamic-pituitary-adrenal axis, and may contribute independently to many of the individual anomalies associated with FAS/ARBDs, e.g., low birth weight, malformations, behavioral dysfunction, etc. (34,81, 196,274,301). Stress-related hormones such as corticosterone may also be involved in some ARBDs because maternal adrenalectomy attenuates the growth retarding and immunosuppressive effects of prenatal alcohol exposure (228,292). Prenatal stress has been demonstrated specifically to interact with prenatal alcohol to lower birth weight in rats (178) and brain development in mice (305).

Ethnicity's influences on provocative risk factors. Ethnicity and culture are influenced by SES and in turn can influence patterns of alcohol consumption and diet. As noted previously, infants of women in cultures where alcohol is consumed regularly at meals are found to be at less risk for FAS than those in cultures where drinking behavior is periodic (e.g., concentrated on weekends) or where alcohol abuse is characterized by bingeing. Culturally related differences in diet can also influence the risk for FAS/ARBDs when particular diets provide (or do not provide) nutrients (e.g., caffeine, saturated fats, or vitamins), capable of exacerbating (or attenuating) alcohol's effects. We provide examples for this hypothesis below.

Tobacco and other drugs. Alcohol's toxic effects on the developing human fetus are augmented substantially among women who inhale tobacco smoke. We included smoking behavior as a permissive factor (see above) because it is highly correlated with both poverty and alcohol consumption (42, 45,84,130,141,159,170,200,203,216,217,254,281,297,321). Ingredients in tobacco smoke comprise a provocative factor for FAS because, like alcohol, some of these ingredients e.g., nicotine and carbon monoxide, directly reduce blood flow and oxygen content (3), and decrease both overall nutrient availability and levels of specific nutrients whose absence may either retard growth (90) or promote teratogenesis through free radical formation (see below). Smoking also increases blood lead levels (66,85,105,106), creating an additional risk factor from that toxin as well.

Other drugs associated with alcohol abuse are also potential risk factors contributing to alcohol's impact on the fetus. For instance, marijuana, cocaine, and caffeine are all significantly correlated with alcohol consumption during pregnancy (27,42,59,101,141). Like tobacco smoke, marijuana smoke can also increase maternal blood levels of carbon monoxide. Increased blood levels of carbon monoxide or exposure to the many ingredients in marijuana smoke, e.g., tetrahydrocan-

nabinols, may negatively affect fetal outcome (5,70,96,140) or may interact with alcohol to potentiate its effects on the fetus (6).

Reports of the impact of prenatal cocaine exposure in humans and animals are inconsistent (cf. 135), as are studies examining interactions between prenatal alcohol and cocaine (53,59,226). Yet there are aspects of cocaine pharmacology that are potentially important for mechanisms of alcohol teratogenesis (135,140). For example, cocaine-related anorexia could compromise maternal nutrition (135). Cocaine causes uterine artery vasoconstriction, decreases oxyhemoglobin saturation, and exacerbates underlying hypoxic conditions (308). Maternal administration of cocaine to pregnant sheep produces a significant and dose-dependent decrease in total uterine blood flow. Maximal reductions of 24%, 34%, and 47% occur within 5 min after IV injection of 0.5, 1.0, and 2.0 mg/kg of cocaine, respectively. This decrease in uterine blood flow is associated with a significant reduction in fetal blood oxygen levels and a significant increase in fetal heart rate. When cocaine is administered directly to the fetus, there is no significant change in fetal blood oxygen and increases in heart rate are not dose-related and are smaller than what occurs after maternal cocaine administration (319). Because these effects on fetal oxygenation occur only when cocaine is administered to the mother, the fetal changes must be a consequence of the reduction in uterine blood flow. The mechanism of action for this effect may involve cocaine's well-characterized inhibition of presynaptic catecholamine uptake, leading to vasoconstriction and subsequently to decreased uterine blood flow (135,140).

Like smoking, caffeine use is also commonly associated with alcohol intake (27,42,59,101,141). Epidemiological studies have linked caffeine use to lower birth weight in people (18,78) and caffeine has an additive effect with prenatal alcohol in reducing birth weight in rats (108). Caffeine exacerbates alcohol's effects on the fetus (108,123), possibly by reducing folate and/or zinc levels (164,324,325). These essential micronutrients are also profoundly affected by heavy alcohol consumption (79,147,148,164,213; see below). Folate is critical to normal fetal development and folate deficiency may thus be compounded by heavy drinking and caffeine consumption.

We next describe how these various biological changes due to tobacco smoke, undernutrition, or other provocative factors, can exacerbate mechanisms of alcohol-induced teratogenesis, in particular, hypoxia and free-radical damage.

INTERFACE BETWEEN PROVOCATIVE AND PERMISSIVE RISK FACTORS AND MECHANISMS OF ALCOHOL TERATOGENESIS

Ultimately, all alcohol-related perturbations of the embryo/fetus involve cell damage in the form of altered cellular growth, differentiation, proliferation, migration, and/or regulation. These changes operate at several interacting biological levels, not all of which can be detailed here. There are several issues in identifying the key mechanism(s) of FAS. First, the absence of a single alcohol-related pathognomonic effect, coupled with the wide-ranging array of anomalies occurring in conjunction with FAS/ARBDs, suggests alcohol may be operating at different biological levels and/or on different cell types to produce specific outcomes. Second, the apparently ubiquitous effects of alcohol suggest alcohol may be acting on some general process common to all cells to produce FAS/ARBDs.

From our perspective, any viable mechanistic hypothesis for FAS must account for the greater impact of alcohol associated with the permissive influences of high alcohol intake, low SES, cultural correlates, and smoking behavior. A viable mechanistic hypothesis must also allow for a reasonable integration of the provocative biological influences associated with these permissive factors. Based on these criteria and our evaluation of the literature, we propose that the most parsimonious explanation for the growth retardation, CNS disturbance, and characteristic teratogenic effects of alcohol on the embryo/fetus is that FAS arises from a combination of alcohol-induced fetal hypoxia and alcohol-induced free radical formation. We contend that the combination of these two factors can accommodate all of the other previously proposed mechanistic explanations for FAS (e.g., 2,41,145,186,212,225,253), as well as integrate roles for the various permissive and provocative factors that we and others have identified.

Hypoxia

Hypoxia is believed to be the most common cause of all cellular damage (62,177). There is considerable evidence implicating hypoxia's involvement in FAS, although a specific role for alcohol-induced ischemia and hypoxemia in FAS remains to be proven. Oxygen delivery to the fetus is linearly related to umbilical blood flow (139) and ischemia of umbilical vessels can occur even at relatively low BALs (e.g., 10 mg/dl) (20). Low levels of alcohol exposure constrict human umbilical cord arteries (251). Very high BALs, such as those associated with bingeing, can disrupt or completely collapse umbilical vasculature (191,323). This may explain alcohol's abortifacient effects in primates (19,54,256), and cerebral infarcts in mouse fetuses following maternal alcohol administration (51,154,227). Not only does alcohol decrease blood flow through the placenta and to the fetus, the oxygen content of this blood is also reduced (hypoxemia) because considerable oxygen is removed during hepatic metabolism of alcohol by the mother (138, 162,290).

One sensitive behavioral index of fetal hypoxia is suppression of regular fetal "breathing-like" movements which occur reliably in both humans and animals following maternal intake of even small amounts of alcohol (94,160,179,207). Blood lactate concentrations and/or the lactate-pyruvate ratio, the standard clinical markers for hypoxia, are both elevated by prenatal alcohol exposure (33,100,231,261). Although a fetus can adapt somewhat to this hypoxia by more efficient oxygen extraction and by diverting blood flow to organs essential for short-term survival (especially brain), there are limits to such adaptations (190,209,258).

In addition to increased lactate production and the lactate-pyruvate ratio, acute hypoxia initiates a cascade of cellular events beginning with inhibition of oxidative phosphorylation leading to decreased ATP production, increased reliance on glycolysis as a source of ATP, impaired Na^+-K^+-ATPase function in cell membranes, and decreased intracellular pH (62,177). Impairment of membrane Na^+-K^+-ATPase activity results in an increase in intracellular levels of Na^+, and a greater movement of water into the cell. This causes cellular and mitochondrial swelling, disruption of the endoplasmic reticulum, detachment of ribosomes, and leads to impaired cellular function (62,177). Many of these hypoxia-related effects have now been documented specifically in connection with prenatal alcohol exposure, including decreased production of ATP, impairment of Na^+-K^+-ATPase, increased lactate levels, mitochondrial swelling and inhibition of protein synthesis (76,88,89,91,92,121,122). As a result of alcohol-induced hypoxia, Na^+-K^+ stimulated ATP-ase activity in the placenta is inhibited, resulting in decreased active transport of essential

amino acids (92,190,209,256). Impairment of cellular metabolic activity may also undermine nutrient utilization (88, 91,121).

Alcohol's regionally specific impact on the developing brain may also be related to hypoxia (186). The hippocampus and cerebellum are especially sensitive to both hypoxia and in utero alcohol exposure (77,95,313). Although the dentate gyrus in the hippocampus can be affected profoundly by perinatal alcohol exposure (313), it is much less sensitive to such insult than the CA1 region (77,95,313). The hippocampus may be especially vulnerable to hypoxia because it is richly vascularized and densely populated with excitatory amino acid neurotransmitters such as glutamate and aspartate (77,95,255). These neurotransmitters are released extracellularly in high concentrations during both hypoxia and fetal alcohol exposure, which can put developing neurons at risk for excitotoxic damage. Release of glutamate can also precipitate destruction of organelle membranes (77,95,186,313).

Free-Radical Oxidative Stress

The anomalies associated with FAS may also arise from excess generation of short-lived reactive oxygenated free radicals such as superoxide anion (0_2^-), singlet oxygen ($^1O_2$), hydroxyl radical (OH^-), and hydrogen peroxide (H_2O_2) (36, 67,74,199). In contrast to most molecules which contain paired electrons, free radicals are molecules with one or more unpaired electrons. These molecules are highly unstable and reactive, becoming more stable by either removing an electron from or donating their unpaired electrons to other molecules. Because these reactions initiate a chain of responses, free radicals can be highly damaging to cells (36,67,74,199). Free oxygen radicals are constantly produced in the course of normal metabolism in respiring cells when electrons shuttling along the respiratory chain in mitochondria "leak" from their electron carriers and are taken up by oxygen (93).

Radicals are normally scavenged by endogenous antioxidative enzymes such as superoxide dismutase, glutathione peroxidase and catalase, and by nonenzymatic antioxidants such as ascorbic acid (Vitamin C), α-tocopherol (Vitamin E), and reduced glutathione (36,67,74,199). Cell damage from alcohol could arise from increased production of reactive oxygen radicals or decreased levels of endogenous cellular defense protectants (114,230), altering the balance of pro-oxidant and antioxidant systems. Any alteration in favor of the former causes oxidative stress (199).

Oxidative stress is damaging to cells because reactive oxygen radicals disrupt cellular integrity. The substrates for these disruptive effects include lipids, proteins, receptors, chromosomes, etc. Of these different disruptive effects, lipid peroxidation has received considerable attention.

Lipid peroxidation occurs when normally stable lipids are disrupted. This disruption can result in these lipids becoming free radicals themselves. For instance, hydroxyl radicals (OH^-) may remove a hydrogen atom (H^+) from unsaturated fatty acids in cell membranes. This in turn can initiate a chain reaction of free radical formation that attacks cell membranes until these radical species are finally neutralized. During the chain reaction, membrane decomposition occurs, manifested by changes in membrane fluidity and "leakiness," changes in membrane fatty acid levels and phospholipid and glycolipid composition, and decreases in activity of membrane-bound enzymes such as calcium-ATPase and Na^+-K^+-K^+-ATPase as well as structural deformations ("blebs"), all of which have been observed in offspring exposed prenatally to alcohol (24,44,45,107,192,229,300). Gangliosides, one of many of the lipids in cell membranes are of special interest because their exogenous administration reduces alcohol's intoxicating effects and normalizes the effects of an alcohol challenge on offspring prenatally exposed to alcohol (132,133).

Alcohol-related cellular damage due to oxygen radicals can also occur independently of ischemia or hypoxemia, as evidenced by the damage seen in embryos exposed to alcohol in culture (43,56,219). In vitro studies have shown that neural crest cells, which are devoid of superoxide dismutase, are particularly sensitive to alcohol exposure (68). This sensitivity could account for both the facial and visceral (e.g., cardiac) malformations characteristic of, or associated with FAS, because craniofacial and visceral structures derive from neural crest cells (68). A causal role for oxygen radicals in these malformations is indicated by the attenuated neural crest cell death that occurs when superoxide dismutase or antioxidants such as vitamin E or selenium are added to the culture medium (68). Fetal cells, in general, may be more sensitive to oxidative stress because they possess lower levels of these enzymes and antioxidants (68). The CNS may be more vulnerable than other organs to alcohol exposure because of its high rate of metabolism, dependence on uninterrupted blood flow, high content of polyunsaturated fatty acids, and relatively low levels of free-radical scavenging enzymes and antioxidants (see below).

Some of the free radical scavenging enzymatic defense mechanisms require micronutrients such as zinc and manganese (superoxide dismutase), selenium (glutathione peroxidase), riboflavin (glutathione reductase), niacin and tryptophan (NADH/NADPH), β-carotene, and vitamins E and C. Primary antioxidants, such as vitamin E, prevent or markedly attenuate lipid peroxidation by acting as electron donors, thereby transforming free radicals into more stable materials. Free radical scavengers, such as vitamin C or β-carotene, quench or trap superoxide, hydroxyl, and singlet oxygen radicals and thereby inhibit their activities. Secondary antioxidants, e.g., chelating agents, attenuate toxic reactions by removing cofactors such as iron, thereby delaying oxidation rates rather than breaking the radical chain reaction. Antioxidant enzymes, such as superoxide dismutase also convert highly reactive oxygen radicals, e.g., hydrogen peroxide, to more stable species. Iron is of particular importance because of its high brain content and because in its free state, iron can catalyze generation of the highly damaging hydroxyl radical (65). Alcohol abuse is associated with increases in cellular iron content (171), although the mechanism for this siderosis is unknown. The involvement of iron in free radical formation means that alcohol-induced siderosis will increase the potential for cellular damage (36,67,74,199), especially in the brain which undergoes lipid peroxidation very rapidly (199).

Deficiencies in antioxidant nutrients, especially vitamin E and vitamin C, can potentiate alcohol's toxic effects throughout the body. In addition to enhancing membrane stability, vitamin E reduces membrane peroxidation by trapping free radicals (97). Vitamin E supplementation, however, has mixed effects on the fetal response to alcohol. Vitamin E deficiency plus alcohol may have a synergistic impact on the rat embryo/fetus. Dietary vitamin E supplementation, however, does not attenuate alcohol's impact on fetal body or cerebral weight, even though vitamin E supplementation reduces lipid peroxidation (286). Certain CNS regions, e.g., hippocampus and cerebellum, may be particularly susceptible to alcohol's teratogenic effects because they have very low membrane concentrations of vitamin E relative to other brain areas (97,158,182).

Zinc deficiency, one outcome of chronic alcoholism, has also been implicated as a mechanism of alcohol's teratogenic effects (79,147,148,242,285). Zinc is an essential trace mineral critical to cell duplication and protein synthesis, and is a co-factor in enzymes involved in free radical defense mechanisms, such as superoxide dismutase. There is evidence from animal models that zinc deficiency and prenatal alcohol exposure interact synergistically to reduce birth weight and brain weight (79,148,242,285). High maternal caffeine intake can also reduce zinc and thereby decrease efficacy of superoxide dismutase (238), particularly in combination with alcohol (cf. 108). Prenatal caffeine exposure may therefore potentiate alcohol's effects by exacerbating zinc deficiency (324,325). However, zinc supplementation of nutritionally adequate diets has had only modest effects in attenuating alcohol's growth retarding effects (79,148,242,285).

A Role for Altered Prostaglandins in Hypoxia- and Free-Radical-Induced Alcohol Damage

Prostaglandins (PGs) are members of a ubiquitous family of fatty acids (eicosanoids). The PGs and, in particular, the PGE_2 subfamily has received considerable attention as potential mediators of ARBDs (41,213,225) because PGE_2 levels are increased in maternal and fetal cerebrospinal fluid and blood following maternal alcohol infusion (260,262,263). Whereas exogenous PGs are teratogenic when administered in doses up to 1 million times normal serum levels (98,120,128,163,211), the significance of these findings for ARBDs is unclear.

The normal physiological role of PGs can be an adaptive response to membrane alterations. Specifically, removal of hydrogen atoms from fatty acids in cell membranes during peroxidation can induce membrane-bound phospholipase A_2 to produce arachidonic acid which is then converted by cyclo-oxygenases into intermediate endoperoxides which are, in turn, converted to PGs. Lipid peroxides also stimulate production of thromboxanes, which are potent vasoconstrictors, perhaps increasing ischemia and hypoxia, and ultimately producing more free radicals.

In this situation, one member of the PG family may be cytoprotective for the fetus, especially with respect to attenuating damage due to hypoxia. PGE_2 is a potent vasodilator whose serum levels are increased during ischemia (50,82,250), presumably to restore blood flow and countering the effects of peroxide-stimulated thromboxanes. PGE_2 also attenuates the fetal acidemia that occurs during hypoxia, thereby reducing the potential for cytotoxicity (75,131,188,288). These same cytoprotective effects of PGE_2 may also operate after prenatal alcohol-induced hypoxia and free-radical formation because prenatal alcohol exposure causes decreases in mature fetal ovine breathing movements (179,262) which are accompanied by transient increases in PGE_2 production (260,262,263).

PGE_2 clearly has an essential role in normal fetal development as evidenced by the fact that drugs such as indomethacin, aspirin, and ibuprofen, which inhibit cyclo-oxygenase, can be teratogenic (151,212,280,312). These same drugs attenuate alcohol-related fetal mortality, reduce birth weight, and increase brain hypoplasia and limb and kidney malformations in mouse and chick embryos (210,222,223,224) but not in rats (174). The mechanisms underlying this effect have not been elucidated and may not necessarily involve inhibition of PG synthesis but rather could be due to the thromboxane-inhibiting (304), oxygen radical-scavenging, (36,67,74), or iron-chelating properties of these drugs (146,150,158,182). The iron-chelating effects of aspirin or indomethacin are pertinent because free iron has pro-oxidant functions intimately involved in hydroxyl radical formation (see above), and as noted, chronic alcohol intake can be siderotic (171). Because aspirin and indomethacin both chelate iron (36,67,74,146, 150), this suggests another non-PG pathway by which these drugs may attenuate free radical-induced ARBDs.

Whereas it is not yet possible to attribute alcohol's cytotoxic effects directly to reactive oxygen radicals, or secondarily to PGs, we believe the known cytotoxic effects of oxygen-free radicals argue more strongly for their etiological role in ARBDs compared to PGs. The involvement of free radicals is also consistent with the permissive and provocative risk factors contributing to FAS. PGs are not depicted in Fig. 1, despite their sensitivity to alcohol, hypoxia and free radicals because, on balance, we think PGs are protective rather than provocative.

AN INTEGRATION OF PERMISSIVE AND PROVOCATIVE RISK FACTORS AND MECHANISMS OF ALCOHOL TERATOGENESIS

We propose that key sociobehavioral permissive risk factors—drinking behavior, smoking behavior, low SES, and cultural/ethnicity influences—create provocative biological conditions such as high peak BALs, circulating tobacco constituents, and undernutrition. These provocative factors exacerbate fetal vulnerability to alcohol-related hypoxia and free radical-induced cell damage. We hypothesize these are two of the main mechanisms underlying alcohol's teratogenic effects. This next section provides what we believe are some credible examples of the functional linkages among these three components of our model-permissive risk factors, provocative risk factors, and cellular mechanisms.

Culturally Related Diet, Undernutrition, and Free-Radical-Induced Membrane Damage

The apparently lower incidence/prevalence rates for FAS in England and Italy, compared to Germany and the United States (see above), could be due in part to dietary differences. For example, Italy and Great Britain have about 18% lower per capita intakes of polyunsaturated fatty acids (~13.5 g/day) than do Germany (26.0 g/day) or the United States (~16.3 g/day) (168). Germany, Great Britain, and the United States, on the other hand, have comparable intakes of saturated and monosaturated fatty acids and cholesterol (168). Cell membranes contain saturated and unsaturated fatty acids. Unlike proteins, whose primary structure is determined entirely by the genome, the content of structural lipids is entirely dependent on dietary sources (243,244). There is a close relationship between the lipid content of maternal diets and brain lipid composition in offspring (64,181,244,302,303). In addition, psychological stress is positively correlated with concentrations of lipid peroxidation products in serum of pregnant women (248,252).

Neuronal membrane "fluidity," or disorder, is determined by fatty acid composition. The more unsaturated its fatty acids, the greater the membrane's "fluidity," and the greater the potential susceptibility to alcohol's membrane disorganizing effects (103,167). Whereas long-term dietary intake of saturated fats may be unhealthy as far as maternal cardiovascular fitness is concerned, epidemiological and experimental studies suggest saturated fats can be cytoprotective against alcohol's effects on liver cells (193,194,243).

Dietary saturated fats may also be cytoprotective for fetal development because membranes with a high ratio of saturated to polyunsaturated fatty acid would not only be less susceptible to the "fluidizing" effects of alcohol, they would also be less susceptible to lipid peroxidation (48,322). Because the proportion of saturated to unsaturated fats in the diet is higher in Italians and Britons compared to Americans and

Germans (168), developing fetuses in Italy and England could also have a higher saturated to unsaturated fatty acid cell membrane ratio. If this does indeed reduce susceptibility to the membrane fluidizing and peroxidation effects of prenatal alcohol (300), preserving levels of endogenous antioxidants, this could explain how cultural dietary factors could influence risk for the teratogenic effects of prenatal alcohol exposure.

Smoking Behavior, Tobacco Smoke Effects, Hypoxia, and Free-Radicals

Like alcohol, products in tobacco smoke directly affect fetal development through a combination of hypoxia and free radical activity. Tobacco smoke causes ischemia and fetal hypoxemia (57,115,283), increases maternal and fetal concentrations of free radicals (197,220), liberates pro-oxidant iron from ferritin (29,189), and interferes with maternal/fetal zinc metabolism (156). In the course of scavenging these tobacco-related free radicals, the mother and fetus are also depleted of cellular reserves of antioxidants and zinc (116,117,119,156). Smoking also contributes to primary undernutrition by reducing nutrient intake, such as the antioxidant vitamins A, C, and E, and zinc (116,117,119), and tobacco smoke produces secondary undernutrition by inhibiting absorption of antioxidant vitamins (201,202). As a result of depleted antioxidant reserves and reduced intake of antioxidants, the potential for scavenging alcohol-generated radicals is greatly compromised in smokers. This may account for the additivity or synergism between alcohol and smoking in producing FAS/ARBDs (e.g., 11).

Other Relationships

The model (cf. Fig. 1) allows for similar elaborations of the interactions among sociobehavioral permissive factors (e.g., stress, culture, other drugs, or dietary factors, etc.), biological provocative causes (e.g., altered endocrine activity, placental dysfunction, etc.), and specific mechanisms of cell damage. While not described here, other potential mechanisms (e.g., morphogens) (145) may also warrant consideration in developing the concepts of permissive and provocative factors.

SUMMARY

While the issues are very complex and span many levels of analyses, we believe we have outlined an effective heuristic model for proposing testable hypotheses and theories, and integrating the myriad risk factors that increase fetal vulnerability for FAS. The relationships among the identified external permissive and internal provocative changes, and the contribution of these factors to specific mechanisms through which alcohol is hypothesized to produce its teratogenic effects, are summarized in Fig. 1.

There is no longer any doubt prenatal alcohol exposure can result in FAS and other physical and behavioral ARBDs, although the latter may be difficult to identify on an individual basis. Alcohol is clearly the only known necessary factor for FAS, but it does not appear to be sufficient. At present, it is not possible to predict which individual woman's fetus is at risk for FAS. Clinical, epidemiological, and animal studies have shown that long-term alcohol abuse, particularly repeated binge drinking, is clearly a key etiological factor. However, we believe certain "permissive" factors must also contribute since only a relatively small proportion of children exposed prenatally to alcohol are diagnosed with FAS. We also need to emphasize that alcohol and not these permissive factors, is the single most important factor in the etiology of FAS.

The key permissive factors contributing to FAS are behavioral patterns of alcohol consumption, low SES, ethnicity, and smoking cigarettes. These permissive factors, which are external to the organism, lead to internal biological conditions which we call "provocative" because they provoke cellular changes which enhance alcohol's toxic actions. These internal conditions include high peak blood levels of alcohol, poor nutritional status, increased stress, pollutants, and the products of tobacco smoke, all of which are themselves either toxic and/or lower cellular defenses capable of otherwise resisting alcohol's toxic effects. The biological responses include placental dysfunction, endocrine changes, and other biochemical and/or physiological changes. We hypothesize these permissive and provocative factors interact with alcohol to exacerbate alcohol's hypoxic and oxygen-free radical-induced effects, and that this exacerbation results in FAS.

Finally, the proposed relationships, based on an extensive literature review, integrate a wide body of findings from epidemiological, clinical/case and basic biomedical research in humans and animals. There are also clearly other relationships of importance to be elaborated and important hypotheses yet to be tested. For example, because offspring of women with key permissive factors are at special risk for FAS/ARBDs, would identifying and targeting these women for special counseling to reduce their alcohol intake and smoking improve infant outcome? Also, because population studies indicate that maternal diets high in saturated fats and antioxidants appear to be cytoprotective, would dietary supplementation with these substances improve infant outcome for women who cannot control their drinking?

ACKNOWLEDGEMENTS

Preparation of this article was supported in part by the Fetal Alcohol Research Center grant (P50-AA07606) and a research grant (R01-AA06721) from NIAAA. The valuable secretarial assistance of R. Goodemoot and M. Meredith is gratefully acknowledged.

Note added in proof: We recently found a Figure 3.1 in Sewell, et al. (1993), with some features similar to our Fig. 1. These authors also recognized relationships among low socioeconomic status, diet, *in utero* alcohol, and cognitive ability. See: Sewell, T. E., Price, V. D., Karp, R. J. In: Karp, R. J., eds. *Malnourished Children in the United States: Caught in the Cycle of Poverty*. New York: Springer Publishing Co.: 1993:24-30.

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