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What Really Causes FAS?

To the Editor:

When Jones and Smith ('73) labeled a pattern of anomalies they observed in a group of children born to alcoholic women as "fetal alcohol syndrome" (FAS), their label, as much as their discovery, brought this birth defect to international attention. Although alcohol was involved, the facts, as Jones and Smith reported them, indicated that it was not simply alcohol, but its abuse, that was responsible for the calamity (Jones et al., '73). In retrospect, the fact that the syndrome was associated with maternal "alcoholism" rather than "alcohol" ought to have been strongly emphasized in the label, if for no other reason than clarity.

Because of the inference attached to the "alcohol" in the label, many physicians and researchers continue to labor under the misguided idea that even exposure to small amounts of alcohol during gestation can not only cause brain damage to a fetus, but even the full-blown syndrome. For example, a study surveying physicians in Michigan found that a third of the more than 500 obstetricians, pediatricians, and general practitioners who responded to a questionnaire believed that "fetal alcohol syndrome" could result from consumption of as little as one (not an "average" of one) drink a day during pregnancy (Abel and Kruger, '98).

Since FAS, by definition, only occurs among women who are "alcoholics," the term "fetal alcohol syndrome" trivializes the real impact of alcoholism during pregnancy by implying that any amount of "alcohol," rather than "alcoholism," is causative. The same argument applies to individual anomalies which are often referred to as "fetal alcohol effects" (FAE), "alcohol-related birth defects" (ARBD), or more recently, "partial FAS."

The intended meaning of "partial FAS," FAE, or ARBD has also been obfuscated because of the ambiguity associated with the unmodified "alcohol" in these terms. While these terms refer to the expression of only some of the characteristics of FAS, the severity of expression for those characteristics is equal to that seen in FAS. This means that instead of exhibiting growth retardation, facial anomalies, and cognitive disturbances, someone with "partial FAS" has only one or two aspects of this tripartite condition. It does not mean that any one of these conditions is less severe than if this same individual had the same condition as part of the entire syndrome; the degree of damage to an individual organ resulting from alcohol abuse during pregnancy is the same whether it occurs in isolation or as part of the syndrome. It follows, then, that it is maternal alcohol abuse, especially alcoholism, which is responsible for the abnormalities associated with "partial FAS," just as alcohol abuse is the sine qua non for FAS.

Taken to its extreme, the contention that individual components of the syndrome do not necessarily arise from alcohol abuse, but are instead the potential outcome of any amount of drinking, means that there is no "safe level" of drinking during pregnancy. A corollary to this argument is that components designated as partial FAS may be expressed so mildly they may not be discernible in any single individual, but may be evident in population studies. The implication is that anyone whose mother drank any amount of alcohol during her pregnancy may give birth to a child who has "partial FAS" to a certain extent.

However, the concept of a monotonic dose-response relationship for the effects of alcohol is empirically untenable; alcohol's effects are biphasic, not linear (Abel, '98a). Linearity only begins to be observable once a particular threshold is exceeded, e.g., in excess of an "average" of six drinks per day (Ernhart et al., '87) (this "average," as discussed momentarily, may reflect as much as consumption of a gallon of wine a drinking day), with no effect attributable to consumption below this level.

Although statistically significant associations in epidemiological studies have often been found between relatively low levels of drinking, which are often labeled "moderate," and some perinatal outcome (Abel, '98a), more than 20 years of research into this possible relationship indicate that "these statistical associations are typically weak and the estimated average effects are usually small... (and) have little clinical significance for individual children" (Stratton et al., '96). A detailed review of this research can be found in Abel ('98a).

The reason low levels of consumption have sometimes been linked to some adverse perinatal outcomes is that these low levels refer to some "average" number of drinks per day. However, in reality, all the drinking entering into the "average" occurs on 1 or 2 days of the week, so that the *consumption per drinking day* is far greater than what is implied by the "average." More often than not, none of the abnormal children in the

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alcohol-exposed group had a mother who actually drank the average number of drinks on any one day.

For example, while the statistical threshold defining the number of drinks causing harm in the study of Jacobson et al. ('93) was an *average* of 0.5 ounces of alcohol (1 drink) a day, these authors comment that "this (was) almost never the usual intake; instead it (was) more like a median of six drinks per occasion for women who drank above this threshold." Ernhart ('91) likewise points out that while one of the mothers in her study met the criterion for drinking less than an *average* of a half drink a day, her drinking amounted to consumption of 4– 5 cans of beer during the day, and an equal amount during the evening, every Friday, Saturday, and Sunday, and six drinks of beer every other day during the rest of the week, for the first 3 months of her pregnancy.

In another study a mean decrease of 6.7 points on performance IQs in a group of 7-year-old children was attributed to the impact of "moderate" drinking, but 25% of the "moderate" drinkers had consumed five or more drinks a day during mid-pregnancy, and at least one of the "moderate" drinkers had consumed over 50 drinks a day (Streissguth et al., '89)!

Although indices such as "average drinks per day" are supposedly only a way of summarizing drinking behavior, this practicality is usually lost sight of when these studies are referred to by others. For example, in a study published by the Centers for Disease Control (CDC) ('87), "heavy" drinking was defined as "regularly having an *average* of two or more drinks every day," but in the editorial comment that followed this article, the text omits the "average": "the cut-off defined by 'two or more drinks per day' appears to identify a level of exposure..."

The undeniable fact is that pregnancies complicated by alcohol abuse, not simply alcohol, possess the greatest danger to the unborn child; the effects of so-called "moderate" drinking are not the result of one or even two drinks a day, but an "average" of one or two drinks, which in reality is seven or 14 drinks on a drinking day during the week.

The conclusion that very high levels of alcohol consumption are what places the unborn child at risk has considerable convergent support from the experimental literature using animal models. For example, the 4 g/kg/day dose, typical of experiments studying the effects of alcohol in "animal models" of FAS (Abel, '98a), is the human equivalent of 18 drinks per day in an adult male. The 12 g/kg/day of alcohol consumed by animals in the form of liquid diet is the equivalent of 54 drinks a day (Abel, '98a). These doses in animals typically result in blood alcohol levels (BAL) well over 150 mg% (Abel, '84).

A BAL of 150 mg% is the level a 140-pound male would attain if he drank seven and a half drinks over a 3-hr period. Allowing for gender differences, this level would be associated with consumption of about six drinks if consumed during the same period by a woman (Frezza et al., '90). Such BALs are far above those considered the legal level of intoxication in any part of the world that has such criteria for intoxication and fall far short of the concept of "moderate." The relevance of these statistics to humans would be clearer if, in addition to citing the grams per kilogram of alcohol given to, or ingested by animals, researchers would provide a rough human equivalent in terms of drinks, preferably based on peak BAL levels of exposure. Furthermore, in many of these animal studies, these levels are maintained over several days and are therefore the counterpart of chronic drinking throughout the day over almost the entire course of gestation, as described by Ernhart ('91) or result from bathing cells in alcohol for long periods of time, (e.g., Ramanathan et al., '96). Experimental strategy necessitates testing animals with such high doses of alcohol to recreate the conditions that give rise to anomalies like those associated with FAS, but such studies in animals should acknowledge that these doses are far removed from what would normally be encountered in the general population of human consumers. As important as our animal model studies are for understanding the biological effects of prenatal alcohol (abuse) exposure, we must not lose sight of the fact that our animal models reflect extreme levels of exposure.

While there are problems operationally defining "alcohol abuse" and "alcoholism," conceptually, both are typically defined in terms of consequences, and embody the idea of drinking at a level that affects one's own health or welfare, or that poses harm to the developing embryo or fetus. In contrast to the reasonably accurate descriptions clinicians or researchers would likely formulate if asked to characterize the health status of an "alcohol abuser," those same clinicians and researchers would be hard-pressed for a similar description of a "moderate" drinker. Whatever impression they might formulate, it would certainly not include any of the health problems associated with alcohol abuse such as cirrhosis and malnutrition.

If we are to prevent FAS, we must identify those women who are truly at risk, and target our prevention efforts at them (Abel, '98b). To do this, we need to be much more specific in our definitions, especially with respect to "moderate" drinking and "alcohol abuse:" we need to define drinking behavior in terms of drinks per drinking occasion, not in terms of "averages," an artifact that has caused misunderstanding of the syndrome as to its etiology even among physicians.

We must also be aware that consumption of alcohol alone, no matter how high, does not necessarily result in the birth of a child with FAS (Abel, '98a,b). On the other hand, there is virtual certainty that this will happen if the mother has previously given birth to a child with FAS and she drinks during her subsequent pregnancy (Abel, '88). Women who have given birth to children with FAS are not merely a variation of the general population of drinkers: they are the group that defines the risk for FAS, and our research and our prevention efforts need to be targeted at them.

We should not obfuscate the levels of alcohol consumption that cause fetal damage. Characterizing the drinking behavior associated with this problem in terms of "average drinks" per day or week distorts its etiology. This problem needs to be considered in terms of the broader context of alcoholism: the emphasis should be on the alcoholic who is also pregnant, rather than on the pregnant woman who (never) becomes an alcoholic during pregnancy. At the very least, a change in the name of this disorder that reflects its etiology, e.g., "fetal alcohol abuse syndrome," would have the heuristic effect of focusing our thinking on the problem and not the artifact (Abel, '98a).

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