Fetal Alcohol Advisory Debated

Some researchers question the government's advice that pregnant women not drink at all

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has a simple message for women: "For baby's sake . . . and yours, don't drink during pregnancy." But, says NIAAA director John DeLuca, "The message certainly is controversial." For every researcher who endorses the NIAAA position, there seems to be at least one who thinks the advice is ill-considered or unwarranted because it is so absolute. Nonetheless, the NIAAA is preparing a $1.2-million radio and television campaign to publicize the dangers of alcohol abuse, including the advice that any drinking at all during pregnancy can be harmful.

The NIAAA campaign follows on the heels of the first official government warning against even moderate alcohol consumption during pregnancy. This summer, Acting Surgeon General Edward Brandt issued an advisory saying that pregnant women should not only abstain from alcoholic beverages but also should "be aware of the alcoholic content of food and drugs."

The surgeon general and the NIAAA have chosen to follow a slippery slope type of reasoning. High doses of alcohol are bad for fetuses. There is some suspicion that moderate drinking—meaning an average of 1/2 to 1 ounce of absolute alcohol a day—may be harmful. Therefore, they concluded, the best advice is not to drink at all. (One ounce of absolute alcohol is the equivalent of two mixed drinks or 24 ounces of beer or 8 ounces of wine.)

At the heart of the dispute over the no-drinking advice is the perennial question of how safe is safe. What kind of evidence is needed before a substance should be ruled harmful in any amount? Ruth Little, an epidemiologist who is director of the alcoholism and drug abuse program at the University of Washington and who has done research on moderate drinking during pregnancy, asks: "What is the great benefit of drinking at all? That's what people should focus on rather than this frantic search for a safe level." On the other hand, Henry Rosett, a psychiatrist who directs the Fetal Alcohol Education Program at Boston University School of Medicine and who is chairman of the NIAAA's Fetal Alcohol Syndrome Study, says the government is losing credibility by crying wolf. "Doctors won't believe this advisory. They are skeptical of simplistic propaganda."

No one denies that alcohol can cause birth defects if a woman consumes enough of it. The existence of a fetal alcohol syndrome is not in question. According to Robert Sokol, who is co-director of the Perinatal Clinical Research Center at Case Western Reserve University's Cleveland Metropolitan Hospital and who conducted a large prospective study of alcohol and pregnancy, an alcoholic woman has about a 2 percent chance of giving birth to a child with a cluster of defects that include characteristic facial features: a short upturned nose, a small and underdeveloped midface, short eyeslits, and absent or minimal ridges between the nose and mouth. The children also are unusually small, have poor motor development, and are mentally retarded. Both Sokol and Rosett say they know of no reports of a child with fetal alcohol syndrome born to a mother who was not, clearly, a chronic alcoholic. By chronic alcoholic, they mean a woman who has been abusing alcohol for years, who is dependent on alcohol, and who probably drank throughout her pregnancy.

The evidence for effects of moderate drinking on fetuses is not nearly as strong. Although associations between miscarriages and low birth weight babies and women's reports of moderate drinking have been reported, it is impossible to say whether the women who claimed to be "moderate" drinkers, averaging 1/2 to 1 ounce of absolute alcohol a day, are underreporting their consumption. Or, even if they are accurate in their self-reports, they may be women who, on occasion, go on drinking binges. Thus an average of two drinks a day may mean no drinks for 6 days and 14 drinks on the seventh day.

Frederick Glaser, a psychiatrist at the Addition Research Foundation in Toronto, says it is a sticky problem to determine whether drinkers' self-reports are accurate. "It is hard to validate what people tell you. We have some biological markers [of chronic drinking] but the problem is that we don't know enough to say with confidence that they are good markers," Glaser says.

In his advisory, the surgeon general refers to three studies implicating moderate alcohol consumption and adverse pregnancy outcomes. Two of the studies associate drinking with spontaneous abortions; the other associates drinking with lower birth weights.

The two reports associating moderate drinking with spontaneous abortions were published in the 26 July 1980 issue of *Lancet*. One of these reports is a study by S. Harlap of Hebrew University in Jerusalem and P. Shiono of the University of Hawaii of 32,019 pregnant women participating in the Kaiser Foundation Health Plan in northern California. Those women who reported drinking at least once a day were two to three times as likely as nondrinkers to have spontaneous abortions, Harlap and Shiono found. They cautioned, however, that "We are also unable to assess whether there was any significant degree of under-reporting of alcohol use in our population."

Sokol says he is highly suspicious that there was underreporting in Harlap and Shiono's study because too few of the women admitted to drinking heavily. It is generally estimated that at least 8 percent of the women in this country of childbearing age are alcoholics. Yet, Sokol says, "Only 2.9 percent of the 32,000 patients said they drank at least one to two drinks a day." Sokol himself found that women who are alcohol abusers (the 3.5 percent of the drinkers in his study of 2913 Cleveland women who admitted drinking the most) had increased incidences of spontaneous abortions or had low birth weight babies. He says that Harlap and Shiono's "moderate" drinking group actually consists of alcohol abusers because the "moderate" drinkers represent the heaviest drinking 2.9 percent of the sample.

The second report associating moderate drinking and spontaneous abortions was from a study by Jennie Kline, Zena Stein, and their associates at Columbia University that compared the amount of drinking reported by 616 women hospitalized for spontaneous abortions to the

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amount reported by 632 women whose babies were born after at least 28 weeks of pregnancy. Women who had spontaneous abortions were more than twice as likely as the controls to report drinking at least two times a week.

As was pointed out in a *Lancet* editorial accompanying this report, a possible drawback to the Columbia University study is that the differences in drinking habits between the cases and controls may simply reflect other differences between the groups. For example, the women who had aborted were interviewed nearer to the beginning of their pregnancies and so may have been more likely to recall how much they drank. Kline stands by her conclusions but does note that the results of a more recent, unpublished, study by her group does not confirm these initial results. The published study involved women receiving public assistance. Kline and her associates repeated the study with private patients and found no obvious effect of moderate drinking on spontaneous abortions. In neither study, she says, did she find an association between reports of moderate drinking and low birth weights.

Asked to assess her results, Kline said, "I don't know for a fact that there is an effect with drinking twice a week. Alcohol histories are notoriously difficult to obtain and the women may all be underestimating the amount they drank. Or it may be that that group of women [who reported drinking twice a week] includes those who on occasion drink a lot of alcohol."

The surgeon general's evidence that moderate drinking is associated with low birth weight is from a study by Ruth Little, published in the *American Journal of Public Health* [**67**, 1157 (1977)]. She studied 263 members of a group health cooperative and found that those who reported drinking two drinks a day had babies weighing an average of 160 grams (about 1/3 pound) less than babies of women who reported drinking less. "I interviewed most of those women myself," says Little. "They probably underestimated their drinking but they were not alcohol abusers, in my clinical judgment."

Another way to get at the question of whether moderate drinking during pregnancy is harmful is to look at animal models. Ernest Abel of the Research Institute on Alcoholism, in Buffalo, explains that "the animal work duplicates almost everything we see in humans." Pregnant rats, for example, that are intoxicated each day to a level of 150 milligrams of alcohol per kilogram of body weight (the equivalent in humans is 3 ounces of absolute alcohol for a 150-pound person) during the period of their lives corresponding to adolescence in humans. The peak intoxication level for the mice was 120 to 150 milligrams of alcohol per deciliter of blood (mg/dl); legal intoxication is defined in most states as 100 mg/dl.

Alcohol: The Ultimate Birth Control Drug

The fetal alcohol syndrome is just one facet of the effect of alcohol on the human reproductive system. Other aspects of alcohol's damage are much less controversial and much better documented. Altogether, alcohol has a devastating effect on human reproductivity.

Recently, for example, Robert A. Anderson, Jr., of the University of Illinois Medical Center reported that the drinking of alcohol during adolescence may delay the onset of sexual maturity. He told a meeting of the Federation of American Societies for Experimental Biology in Atlanta that he fed alcohol to male mice during the period of their lives corresponding to

Holly Bishop

adolescence in humans. The peak intoxication level for the mice was 120 to 150 milligrams of alcohol per deciliter of blood (mg/dl); legal intoxication is defined in most states as 100 mg/dl.

Anderson examined the mice at the time when they would normally become sexually mature, 29 days after birth, and observed that they had smaller reproductive organs than the controls, that their sperm showed a higher incidence of abnormalities, and that the sperm was less effective at impregnating females. After 14 more days, however, the alcohol-fed mice had reached the same levels of sexual maturity as the control group and all measures of fertility were approximately the same. In humans, Anderson says, this would be equivalent to delaying sexual maturity from the age of 16 or 17 to about 19. Similar studies have not yet been conducted in female animals, in part because of the difficulties of controlling hormonal cycles. David Van Thiel and his colleagues at the University of Pittsburgh School of Medicine have shown, however, that somewhat higher levels of alcohol in female rats prevent ovulation.

Van Thiel has been one of the principal investigators of the effects of alcohol on sexual function. In recent years, he and others have shown that drinking a pint or more of hard liquor per day for 5 to 8 years can produce impotency, sterility, and feminization in men and premature menopause in women. Several studies have shown that alcohol damages the hypothalamus and the pituitary [*Gastroenterology* **81**, 594 (1981)]. The hypothalamus secretes gonadotropin-releasing hormone, which in turn stimulates the pituitary to secrete both follicle-stimulating hormone and luteinizing hormone. These stimulate the testes to produce sperm and testosterone, respectively.

By its effects on the hypothalamus and pituitary, alcohol thus reduces sperm counts, which makes men sterile, and reduces the amount of testosterone in the blood, which may lower their sex drive and make them impotent. Investigators have also observed an increased production of estrogen-like compounds in the peripheral cells of alcoholic men. The combination of increased estrogen activity and decreased testosterone produces changes in secondary sex characteristics.

But effects on the hypothalamus and the pituitary are not the only sexual manifestations of alcohol abuse in men and may not even be the most important. Van Thiel recently reported [*Metabolism* **30**, 537 (1981)] that ethanol is toxic for Leydig cells, which produce testosterone and sperm. In isolated perfused rat testicles (a technique which eliminates the effects of external hormones), ethanol reduced the production of testosterone at concentrations ranging from 25 to 300 mg/dl; the reduction in testosterone was dose-related and averaged about 35 percent at 100 mg/dl.

The Pittsburgh group also observed that the size of the smooth endoplasmic reticulum and the overall size of the Leydig cells were reduced, but that mitochondria were "dramatically bigger." Acetaldehyde, which is the first product of ethanol metabolism, was toxic to the cells at much lower concentrations. In experiments in animals and isolated cells, Van Thiel's group also found that ethanol inhibits the enzyme system 3β-hydroxy-Δ^5-steroid dehydrogenase/3-oxosteroid-Δ^{4-5}-isomerase and that acetaldehyde inhibits 17α-hydroxy-progesterone aldolase. All three enzymes are

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lute alcohol in an hour) have fetal wastage and offspring with decreased body weights, growth retardation, and behavioral aberrations resembling hyperactivity and learning disorders. However, says Abel, with animals there are definite threshold effects. When pregnant animals are intoxicated each day to a level less than 100 milligrams of alcohol per kilogram of body weight, there is no apparent effect on their offspring. When they are intoxicated to a level of 100 to 150 milligrams of alcohol per kilogram, their offspring weigh less at birth but later catch up in weight.

Why, then, in light of the equivocal evidence that anything other than heavy drinking during pregnancy is harmful, did the NIAAA decide to recommend no drinking at all? "The key science behind the decision is based on the fact that at the moment we don't know a safe level of drinking," says NIAAA director DeLuca. Yet, a number of scientists ask who the NIAAA's message is going to help. Says Sokol, "The 95 percent of women who probably will not experience any effect from their drinking have been warned. The 5 percent whom we know may have adversely affected infants are not helped by the advice. That is the group that really needs study and treatment." Says Kline, "Neither the birth weight finding nor the spontaneous abortion finding is so secure that women should feel guilty if they take a drink. As scientists, I don't think any of us believe that a little bit of alcohol causes these effects."—GINA BARI KOLATA

No Gap Here in the Fossil Record

Fluctuations in the history of an African lake have trapped the detailed steps in species evolution

Peter Williamson, a paleontologist at the Museum of Comparative Zoology, Harvard University, has just reported the first detailed documented evolution of one species into another, as revealed by the fossil record.* This new evidence, which comes from a series of fossil mollusk species near Lake Turkana in northern Kenya, has important bearings on the current discussion of the mechanisms that shape the pattern of evolutionary change.

The floodplain and delta deposits near the lake are extensive and clearly stratified. They therefore offer a rare opportunity to follow the periodic morphological changes in fossil species over relatively short periods. Added to this, the lake basin is virtually a closed system so that ecological and evolutionary events are to some degree self-contained. Anthony Hallam, a paleontologist at the University of Birmingham, England, describes the material available there as "the nearest thing you could get to an evolutionary experiment."

Williamson examined 3300 fossils from 13 different species of the lake snails, through a depth of 400 meters of sediment. Using selected morphological criteria, he traced the changes in these species over several million years. "The most immediate impression is the tremendous morphological stasis," says Williamson. "Some species still live in the lake today looking exactly as they did several million years ago," he observed in an interview with *Science*.

The most interesting observation comes at two points in geological history when the lake level dropped sharply. When this happened, all the species that Williamson studied underwent a brief period of change, at the end of which time clearly identifiable progeny species were established. By brief here is meant something between 5,000 and 50,000 years. "Compared with the millions of years during which we see complete morphological stasis for these organisms, 50,000 years is a brief period in which a new species arises," says Williamson. In his *Nature* paper Williamson writes that the pattern he sees "conforms to the punctuated equilibrium model" of evolutionary change.

The significance of the coincidence of the rise of new species with major regressions in the lake is, says Williamson, that the organisms "in the basin are likely to have been both isolated and under [environmental] stress." This is consistent with Ernst Mayr's classic 1954 paper on speciation, which Williamson paraphrases in the following way: "Mayr's model considers that homeostatic mechanisms and gene flow prohibit significant evolutionary change in large panmictic species populations, but in small, stressed, geographically isolated populations, homeostatic mechanisms break down during 'genetic revolution' and rapid evolution may ensue."

Paleontologists have known for a long time that new species appear to come into the fossil record abruptly, with no intermediates between the parental and progeny forms being apparent. There are two explanations for this. First, as Mayr suggests, new species arise in small peripheral populations and their apparently sudden occurrence in the fossil record coincides with their reinvasion of the ancestral range. Second, the transition period is very short compared with the time resolution that obtains in much of the fossil record, and the "instant" of speciation may therefore be missed.

In the case that Williamson describes the instant is not missed: it is documented with intermediates along the path from the old species to the new ones. "Williamson finds what we all find, but his data are so much better," comments Hallam.

At least as important as a record of intermediate forms, says Williamson, is a demonstration that, during the transition, the morphological variation of the species increases markedly. "For most of a species' lifetime, the genetic variation in individuals is to some extent buffered in embryological development so that the adult phenotype is relatively constant," he says. "When the population is isolated and under stress, buffering breaks down, and the phenotypic variance rises dramatically. It settles down again later, as a new species is established."

When the lake rose again it was no longer cut off from other lake systems in the continent, and the ancestral species returned to Turkana from elsewhere. This transgression of the lake coincides with an abrupt disappearance of the new species from the fossil record. "Mayr considers this pattern of events to be the common fate of new species in geographical isolates," says Williamson.

Williamson concludes his paper by suggesting that "speciation is a qualitatively different phenomenon from gradual, intraspecific microevolutionary

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