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 Kline stands by her conclusions but does note that the results of a more recent, unpublished, study by her group does not confirm these initial results.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 abso-

Alcohol Briefing

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

crucial in the synthesis of testosterone [*Biochem. Pharmacol.* **30**, 1827 (1981)].

Nearly all effects observed by Van Thiel and others are reversible if drinking is moderate or if heavy drinking is stopped before the damage becomes severe. "If you do a little drinking and stop," he says, "you'll probably totally recover. It's like getting in a fistfight—you're not irreparably damaged, but you're bruised. The bruises go away, but if you did that for a living, you'd get pretty smashed up. The body has tremendous ability to recover, but if you don't relent, you can irreparably damage yourself."

A New Name for an Unrecognized Syndrome

Some individuals develop a very severe headache, much like a migraine on both sides of the head, after drinking red wine. This syndrome differs from a conventional hangover in several important respects, says David Goldberg of the University Hospital of South Manchester in England [*Lancet* **1981-I**, 1003 (1981)]. Only two glasses of red wine may be sufficient to produce it. The victim does not wake with the headache, as is the case with a normal hangover, but it develops within an hour of waking. The headache becomes very severe if the victim lies down, but it is relieved to some extent by standing up. "Unfortunately," says Goldberg, who has himself suffered the syndrome three times, "it is impossible to stand up for any length of time, since this exacerbates the nausea. One usually comes to rest at 45°, and time passes very slowly for several hours."

The syndrome is recognized among wine drinkers, says Goldberg, and appears to be associated with "cheap red wine" rather than château bottled vintages. White wine and vin rosé do not produce it.

Because the inexpensive red wines are generally blends, Goldberg speculates that an additive is responsible for the effect. His own experience suggests that wines which produce the effect have a metallic smell, and some other individuals claim that they can identify the offending potations by aroma. As a start toward encouraging research on the phenomenon, Goldberg suggests that the syndrome should have a name. His suggestion: "red head."

To Sleep, Perchance to Gasp . . .

A glass of wine before bedtime has long been an accepted remedy for insomnia. That may still be the case, but new evidence indicates that larger quantities may be counterproductive. A report [*Am. J. Med.* **71**, 240 (1981)] by A. Jay Block and his colleagues at the University of Florida Medical School at Gainesville states that alcohol disrupts breathing during the night and interferes with sleep.

Block and his colleagues studied 20 healthy male volunteers for two nights. The first night, 11 of the men received 100-proof vodka in orange juice (1 milliliter per pound of body weight) and the rest received only orange juice; the second night, the roles were reversed. Both nights, the investigators continually monitored the subjects' respiratory patterns, the amount of oxygen in their blood, and electrical currents in their brains.

The number of episodes of disrupted breathing was significantly greater after alcohol ingestion. A total of 110 episodes of sleep apnea (cessation of breathing for at least 10 seconds) were counted among individuals who had ingested alcohol and only 20 among those who had not. Eighteen of the 20 men had at least one occurrence of disturbed breathing following alcohol consumption, whereas only nine had such a disturbance on the control night. The total number of abnormal respiratory events was 383 after alcohol consumption but only 207 on control nights. The most common event was a sharp drop in oxygen content of the blood. The investigators also found that the increase in frequency and severity of abnormal respiratory events persists for an additional night. "It takes only one night to get drunk," Block says, "but two nights to sleep it off."

Block is now studying the effects of alcohol in lower quantities on asthmatics. He speculates that alcohol's effects on respiration may be related to mortality rates in the whole population. "The same factors that are associated with reduced lifespan are also associated with sleep apnea—male sex, overweight, older age, alcohol ingestion, sleeping pill ingestion. In fact, the prime time to die is about 6 o'clock in the morning, and that's when you have the most REM [rapid eye movement] sleep and the most sleep apnea. All this may be extremely important, not only in people with disease, but also in the general population. And there is a high death rate in alcoholics that has never been adequately explained by auto accidents, liver disease, and so forth. This could be part of it."

A New Way to Reverse the Effects of Antabuse

One treatment that helps alcoholics maintain their motivation for remaining alcohol-free is disulfiram (Antabuse), a deterrent that provokes a severe, occasionally fatal, reaction if the user subsequently ingests ethanol. Some alcoholics do anyway, and physicians have difficulty treating their symptoms—which include a throbbing headache, respiratory difficulties, copious vomiting, tachycardia, and, in severe cases, respiratory depression, cardiovascular collapse, arrhythmias, acute congestive heart failure, and convulsions. Phenothiazines, ascorbic acid, and antihistamines, among other drugs, are used to treat the symptoms of the reaction, but they have no effect on the alcohol-disulfiram interaction itself.

Kai O. Lindros of the University of Helsinki thinks he has found a solution to this problem. He told a conference of the National Alcoholism Forum in New Orleans earlier this summer that 4-methylpyrazole is a specific antidote for the interaction. Lindros says that 4-methylpyrazole inhibits alcohol dehydrogenase, the enzyme responsible for the metabolism of ethanol to acetaldehyde. When acetaldehyde production is slowed, the violent symptoms of the interaction subside. The Finnish physician has used the antidote successfully in healthy male volunteers and in at least one alcoholic. Further safety studies will have to be conducted, however, before the drug could be used on a regular basis.

Thomas H. Maugh II