quite broad, he noted, but the nucleus could possibly be nutating with a period as long as 7.4 days.

On Thursday of the following week the existence, at least, of a longer period got a boost from Belton. Prompted by the light curves of Millis and Schleicher, he had extended his search for periodicity to longer intervals. Sure enough, a 7.4-day period was there, along with the 2.2-day period. Now he favored the rotation plus nutation idea.

The final exchanges on the subject came on Friday, the last day of the Paris meeting. In response to an overview talk on the encounters, Bradford Smith, an astronomer at the University of Arizona and Voyager imaging team leader through encounters with three planets and several dozen satellites, made his position clear. "I want to emphasize something because the word doesn't seem to be getting across. Even if we use the VEGA images alone, it is impossible to get the 7.5-day rotation. It is absolutely ruled out."

Smith's argument was difficult to illustrate for a large audience, but by holding slides against the light at the appropriate orientations, as he did for this reporter, he made an impressive show. It impressed Jean-Loup Bertaux of the National Center for Space Research in Verrières-le-Buisson, France, so much that he dropped his bet against the shorter period that he was about to make with Smith. Bertaux had been the one holdout among those with ready access to spacecraft images.

In his review of ground-based observations of Halley that afternoon, Festou forged ahead in the face of Smith's advice. In another case of data analysis on the road, a colleague of Festou's had spent the previous night compiling all 129 brightness measurements in six data sets spanning the period from September 1984 to February 1985. The 7.4-day period was there but no 2.2-day period, Festou reported.

In the last session, after the second presentation of his talk, Millis, unconvinced that the possibility of a 7.4-day rotation period had been eliminated, made an appeal. "Many of these people were looking for a 2.2-day period. We're now asking for them to look at a broader range of periods and see if it's there." Certainly, the observations in hand merit more thoughtful attention. And the spacecraft images need to be presented in a more visually persuasive format. And observational astronomers must win enough time on enough large telescopes to gather new photometric observations that could settle the argument to their satisfaction. Whether that is possible in competition with stellar astronomers in the post-Halley era remains to be seen. ■ **RICHARD A. KERR**

New Drug Counters Alcohol Intoxication

The experimental drug makes drunk animals sober and may reveal the biochemical basis for alcohol's effects

A few years ago, chemists at the Swiss headquarters of the drug company Hoffmann–La Roche found a remarkable compound that initially sounded almost too good to be true. The compound antagonizes the behavioral effects of alcohol in animals and seems to work at doses of alcohol that produce drunkenness but that are not life-threatening. But now, as investigators examine the full implications of such a drug, there is some question about whether it will be developed at all for clinical use and, if so, by whom.

On page 1243 of this issue of *Science*, Steven Paul and his colleagues at the National Institute of Mental Health report on further studies with this drug, confirming that it makes drunk animals behave as though they were sober and suggesting a biochemical basis for its actions.

The use of the drug, which goes by the name Ro15-4513, is controversial. Although it clearly can be a tool to probe how alcohol produces its behavioral effects, it may not be marketable. After considering the legal and ethical drawbacks of an anti-alcohol drug, Hoffmann–La Roche decided not to develop it for clinical use. On the other hand, several researchers in this country think it could be clinically useful and Paul, for one, hopes to develop it. The idea is to make long-acting derivatives of Ro15-4513 that antagonize alcohol but have no adverse effects. Once it is known that Ro15-4513 blocks the behavioral effects of alcohol, chemists can try to alter its structure slightly to eliminate any undesirable qualities.

"The reason this drug is important is that it is safe," says George Koob of the Scripps Clinic and Research Foundation. Other drugs antagonize alcohol, but they are so dangerous that there can be only a small difference between a dose that prevents drunkenness and a dose that produces convulsions or even death. Ro15-4513, in contrast, is a derivative of the benzodiazepines—drugs such as the Hoffmann–La Roche products Valium and Librium. Benzodiazepines are considered to be much less risky than any previously discovered alcohol antagonist. "You can't kill yourself with an overdose of benzodiazepines," says Koob, who is studying the behavioral effects of Ro15-4513 on rats. He agrees with Paul that a derivative of the drug may be worth developing.

The story of Ro15-4513, begins several years ago when Hoffmann–La Roche chemists synthesized it as a research tool. Their aim was to better understand the receptor for benzodiazepines on brain cells. Ro15-4513 is a photoaffinity label for the benzodiazepine receptor cells and so can serve as a probe of the structure and function of the receptor.

The benzodiazepine receptor is part of the receptor for γ-aminobutyric acid, or GABA—the brain's major inhibitory neurotransmitter. The barbiturate receptor is at another site on the GABA receptor. According to Solomon Snyder of the Johns Hopkins University School of Medicine, "there is a good deal of evidence that alcohol acts on the GABA receptor." In addition to suggestive biochemical evidence linking alcohol, barbiturates, and benzodiazepines to the GABA receptor, there is the clinical observation that the three drugs produce cross-dependence and cross-tolerance. As a consequence, an individual who is addicted to alcohol, for example, and suffers withdrawal symptoms when he does not take the drug can be relieved of his symptoms by taking either benzodiazepines or barbiturates.

Because of this relationship between benzodiazepines, barbiturates, and alcohol, Hoffmann–La Roche investigators routinely test any drug that binds to the benzodiazepine receptor by looking for behavioral effects related to all three drugs. As part of this standard battery of tests, the company investigators looked for effects of Ro15-4513 on animals that received alcohol.

They were astonished to find that it blocked the behavioral effects of alcohol intoxication, according to Willy Haefely of Hoffmann–La Roche in Basel, because other benzodiazepine derivatives do not. "A number of my colleagues were extremely excited," Haefely adds. So they next decided to see whether Ro15-4513 could prevent the lethal effect of very high doses of alcohol. It could not. Ro15-4513 appears to act

only on the brain, preventing the behavioral effects of alcohol but not affecting its metabolism or blood alcohol levels. Alcohol's lethal effects, according to Haefely, are most likely due to nonspecific alterations of cell membranes throughout the body.

At that point, says Haefely, he and his colleagues decided that "the compound has no value. It is useless for treating life-threatening intoxications, and although it could possibly be active in attenuating drunkenness, there are ethical problems." An anti-drunkenness pill, says Haefely, "certainly in the long term would not reduce ethanol consumption but would encourage it." It also could lead to legal problems. "Suppose you go to a restaurant, have a few drinks, take the tablet, and get into your car," he says. "If an accident occurs, you will be considered drunk if your blood level of alcohol is high enough. But there would be tremendous legal complications if you then said, 'Yes, I have a high level of alcohol in my blood, but I took this tablet so I am not drunk.' " Because of these ethical and legal problems, Haefely concludes, the use of a drug like Ro15-4513 "would never be approved by the health authorities."

Nevertheless, Paul and his colleagues at the NIMH, among others, decided to pursue studies with the drug, asking first whether it could help to elucidate alcohol's biochemical effects on the brain. One hypothesis is that alcohol acts on the GABA receptor and, as a consequence, alters the chloride ion channel that is coupled to the receptor. The result is that more chloride ion enters cells.

But alcohol's biochemical effects have been difficult to establish because, Snyder says, "alcohol is such a weak drug. The amount you need for receptor research is grotesquely enormous."

So Paul and his colleagues looked for alcohol-induced effects on chloride ion flux in isolated synaptic vesicles, which contain GABA receptors. They found, first, that relatively low concentrations of alcohol—20 to 80 millimolar—stimulate the uptake of chloride by these vesicles. A person is considered legally drunk when his blood concentration of alcohol reaches 28 millimolar—which usually translates to about three mixed drinks. Because alcohol passes freely through the blood-brain barrier, the amount in the blood reflects the amount in the brain.

In addition, says Paul, lower concentrations of alcohol have an indirect effect on isolated synaptic vesicles. At concentrations of 5 to 10 millimolar —an amount, equivalent to about two drinks, that can affect behavior without causing legal drunkenness—alcohol potentiates GABA's ability to increase chloride ion uptake. Paul believes that this is "the most important effect of alcohol since it is probably responsible for alcohol's tension-reducing, disinhibiting, and antianxiety effects, which may be why the majority of people drink in the first place."

As further confirmation that low concentrations of alcohol have a direct biochemical effect on GABA-mediated chloride ion flux, Raj Ticku of the University of Texas at San Antonio now reports that he finds the same effect in cultured spinal cord neurons.

"We convinced ourselves and others that ethanol stimulates the GABA receptor, at least in vitro," Paul concludes. "We don't think it binds directly, but we think it affects the microenvironment of the receptor by disordering membrane lipids."

Then Paul and his associates tested various drugs that bind to the benzodiazepine receptor to see if they also block alcohol's effects on chloride ion uptake into synaptic vesicles. With one exception, they do not. But the experimental drug Ro15-4513 completely blocks alcohol's ability to stimulate the GABA receptor. Yet it has no effect on the ability of GABA itself or the barbiturates to stimulate the receptor.

Finally, Jacqueline Crawley, Peter Suzdak, and John Glowa of Paul's laboratory tested the Ro15-4513's behavioral effects. They gave rats enough alcohol that they were heavily sedated. Says Suzdak, "The animals hardly move. If you turn them on their backs, they don't turn over. When they lie on their stomachs, their arms and legs flop away from their bodies." But when they inject the rats with Ro15-4513, "within 2 minutes, the animals get up and walk around."

In addition, Paul reports, when they give the animals Ro15-4513 before giving them alcohol, the animals never act intoxicated in the first place. Finally, the drug by itself appears to have no ill effects on the animals.

Paul envisions a Ro15-4513, or some other drug like it, as a treatment for alcoholics, a way for them to avoid becoming drunk while they learn to live without alcohol. It would be analogous to the opiate receptor antagonists that are used to treat heroin addicts. These opiate antagonists block the brain receptor for heroin and prevent the drug from having any effects. Alcohol addiction, says Paul, "is a complex process that may involve some aspect of learning." An alcohol antagonist may help alcoholics unlearn.

Passed out. *The rat on the left has passed out from alcohol intoxication. The one on the right had the same amount of alcohol, but after it passed out, it was given the experimental drug Ro15-4513. Within 2 minutes, it acted sober.*

Haefely of Hoffmann–La Roche says he doubts such a drug will help alcoholics because they drink in order to get drunk and if they took such a drug beforehand, they could end up drinking so much alcohol to override the drug's effects that they could die from alcohol intoxication.

Of course, if a drug like Ro15-4513 were on the market, there would be nothing to stop people from using it to sober themselves in order to drive home from a party, for example. Whether that would be good, because it could prevent traffic accidents, or bad, because it would encourage drinking, is not entirely clear.

But whether or not Paul and his colleagues develop the drug, it is already of great interest to a variety of researchers. Hoffmann–La Roche gives out experimental drugs at no charge for research purposes, but, after deciding that Ro15-4513 was of no commercial interest to the company, the Hoffmann–La Roche chemists stopped synthesizing it. Then, suddenly, they were inundated with requests and had to start making it again. By now, says Haefely, "we've given out hundreds of grams." ■

GINA KOLATA