or other sensory stimulation. Moreover, the units with clearly demonstrable responses to kinesthetic inputs observed in these studies showed changes in activity during both ramp and ballistic movements.

These findings on the preferential relation of neural activity in the putamen to slow movements may have relevance to the pathophysiology of movement disorders involving the basal ganglia in man. Considerable evidence points to a selective disturbance in slow movements in many of these disorders. Generally speaking, the involuntary movements associated with basal ganglia dysfunction (for example, chorea, athetosis, dystonia) are "slow" in character. Also, in the akinetic syndrome of Parkinsonism the major difficulty appears to be in the initiation of slow movements, such as rising from a chair or bed, turning, walking, and so forth. The initiation of simple rapid movements in Parkinsonism patients appears to be less impaired than one would predict (*7*). Kornhuber (*2*) has suggested that akinesia might result from loss of the ramp-generating mechanisms of the basal ganglia, whereas rigidity, chorea, athetosis, and dystonia might result from various forms of "release" of these same neural mechanisms. The present experiment, indicating that the activity of a large portion of the striatum is preferentially involved in the control of slow movements, is consistent with this view as well as the evidence for involvement of the striatum in the pathogenesis of akinesia as well as rigidity, chorea, athetosis, and dystonia (*1*).

M. R. DeLong
Laboratory of Neurophysiology, National Institute of Mental Health, Bethesda, Maryland 20014

References

1. R. Jung and R. Hassler, in *Handbook of Physiology*, section 1, *Neurophysiology*, H. W. Magoun, Ed. (American Physiological Society, Washington, D.C., 1960), vol. 2, chap. 35, pp. 863–927; D. Denny-Brown, *The Basal Ganglia* (Oxford Univ. Press, London, 1962); J. P. Martin, *The Basal Ganglia and Posture* (Pitman Medical, London, 1967).
2. H. H. Kornhuber, *Kybernetik* **8**, 157 (1971).
3. E. V. Evarts, *J. Neurophysiol.* **29**, 1011 (1966).
4. M. R. DeLong, *ibid.* **34**, 414 (1971).
5. ———, *Brain Res.* **40**, 127 (1972).
6. J. P. Segundo and H. Machne, *J. Neurophysiol.* **19**, 325 (1956); D. Albe-Fessard, C. Rocha-Miranda, E. Oswaldo-Cruz, *Electroencephalogr. Clin. Neurophysiol.* **12**, 649 (1960); E. M. Sedgwick and T. D. Williams, *J. Physiol.* **189**, 281 (1967).
7. P. Butz, W. Kaufmann, M. Wiesendanger, *Z. Neurol.* **198**, 105 (1970).

20 November 1972

Preference Enhancement for Alcohol by Passive Exposure

Abstract. *A large and lasting enhancement of alcohol consumption over control levels is reported after direct infusion of 10 percent alcohol into the stomach of rats for 6 days.*

While it has seemed probable that addiction to alcohol is at least in part due to the development of physiological tolerance to the drug, there have to date been no clear demonstrations that alterations in the blood level of alcohol alone (without concomitant experiential factors of taste and ingestion) were sufficient to produce a lasting enhancement of alcohol preference subsequent to treatment (*1*). Here we report a method capable of producing a lasting enhancement of alcohol preference without concomitant oral stimulation. Not only has the method succeeded in separating out the experiential from the more purely physiological factors in alcohol preference in rats, but it also provides a very fast and convenient way of producing an animal preparation of use in the study of alcohol addiction.

This enhancement of preference has been achieved by prolonged passive infusion of alcohol into the stomach of rats. After recovery from surgical preparation (*2*), the rats were placed in a Bowman restrainer cage (*3*) to adapt for 24 hours. After this initial period each rat was connected to a pump (*4*). Seven rats (Sprague-Dawley, 6 months old) were infused with an alcohol solution (10 percent by volume) at the mean rate of about 45 ml per 24 hours. This infusion continued for 6 days.

All rats were released for 30 minutes per day to enable them to groom themselves and to exercise. Rats were also released if they lost consciousness. They were then allowed to recover outside the apparatus. The rate of infusion was 2.17 ml/hour. Seven control animals were treated similarly except that water was infused instead of the alcohol solution. As these rats never lost consciousness, the amount of water infused averaged about 51 ml. Because of the sedating effect of the alcohol, we believe the stress of the restraint was actually less in the rats infused with alcohol. In contrast with the water-infused controls, it was difficult to elicit a startle reflex in them. Alcohol was never presented to the rats before or during the period of the infusion. At the end of 6 days the infusion was stopped; the animals were then kept in the restraining cage for another 3 days, where they were presented continuously with two nozzles, one providing water and the other a solution of 10 percent alcohol by volume. After 3 days, the rats were placed in ordinary Plexiglas enclosures, still with a continuous choice between the alcohol solution and water. They were maintained in this condition for 14 days. The position of the alcohol tube was randomly changed each day. The rats were given unlimited food throughout the experiment, even during the period of infusion, so that it is difficult to ascribe increases in alcohol consumption to a simple enhancement of caloric need.

The food was Simonsen's White Diet, and enriched nutriment used in breeding. Further, while both alcohol-infused and water-infused rats lost weight during their confinement in the restraining cage, the difference in weight loss between them is not significant ($F = 1.32$, $P > .25$). Water infusion leads to an 8.1 percent weight loss

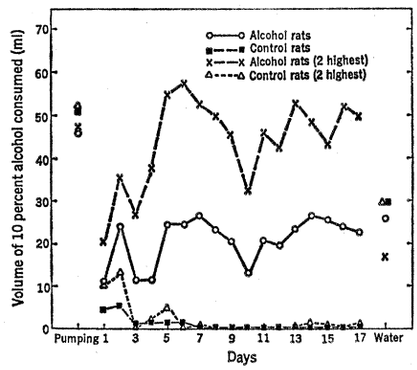

Fig. 1. During the period marked "Pumping" the rats were subjected to a passive infusion of fluid into the stomach; the control rats were pumped with water while the experimental animals were pumped with an alcohol solution (10 percent by volume). Pumping was then stopped and both groups were given a choice between water and the alcohol solution while on unlimited food. The points above "Water" indicate the average intake of water for each group over the whole period.

(initial mean weight 409 g), and alcohol infusion to a weight loss of 11.9 percent (initial mean weight 390 g).

The mean amount of alcohol solution drunk over the 14 days by the two groups shows a very large difference (Fig. 1). The group treated with alcohol drank an average 22.22 ml, whereas the group infused with water drank 0.78 ml ($F = 9.24$, $P < .02$ in a repeated measures analysis of variance). When specific comparisons are made within the design of the repeated measures analysis of variance (*5*) between the alcohol rats and the largest drinker in the control group, five rats are significantly different from the largest control ($P < .01$) and two are not significantly different ($P > .05$). There was no significant change in alcohol consumption during the 14 days of observation (repeated measures analysis of variance, $F = 1.19$, $P > .05$). Two of the alcohol drinkers drank 45.9 ml of 10 percent alcohol per day (averaged over 14 days). They had been infused with 45.9 ml per day of the same solution initially.

There is large individual variation among rats in susceptibility to our treatment, which may be related to the difference in the rate at which tolerance to alcohol develops in various individuals. That tolerance to alcohol is apparent on gross observation. While the infusion of 50 ml of 10 percent alcohol initially produces ataxia and sluggishness, with an occasional lapse into unconsciousness, the rats that drink this amount volitionally after they have been treated cannot be distinguished from normal rats in terms of their gait and alertness. We have observed two rats for 11 weeks and, while their daily alcohol intake has averaged 29.8 and 32 ml, respectively, without any sign of diminution, their general health continues to be excellent and their appearance is quite normal. We have also attempted to see if alcohol intake can be diminished by withholding alcohol for a number of days. Five rats, whose average 5-day intake was 31.1 ml before a "drying-out" period of 5 days, averaged 29.9 ml for 5 days after alcohol was again presented. This diminution is not significant ($F = 0.24$, $P \gg .05$ in a repeated measures analysis of variance). Marked restlessness (increased motor activity) was observed during the period of alcohol withdrawal.

The experiment described here, besides showing that alcohol "addiction" (at least in the psychological sense) can be produced without orosensory exposure to the drug, demonstrates a convenient and speedy method for the study of alcohol addiction with a view to its possible pharmacological control.

J. A. DEUTSCH
H. S. KOOPMANS
Department of Psychology, University of California, San Diego, La Jolla 92037

References and Notes

1. R. D. Myers and W. H. Veale, *The Biology of Alcoholism*, B. Kissin and H. Begleiter, Eds. (Plenum, New York, 1972), vol. 2.
2. The gastric cannulas were made from Silastic tubing [inner diameter 0.040 inch (1.016 mm); outer diameter 0.085 inch (2.159 mm)]. A piece of Marlex mesh was attached to the tube about 1/3 inch (0.85 cm) from one end with RTV Silastic glue. A knob of glue was placed between the mesh and the end of the tube. After a midline incision was made the stomach was gently lifted from the peritoneal cavity. A small hole was made in a relatively unvascularized portion of the fundus of the stomach. The tube was inserted through the hole in the stomach until the mesh was flush with the stomach wall. A loop of 5-0 silk thread tied the tissue around the tube. Two anchor stitches were made from the mesh to the stomach wall. The other end of the tube was threaded through the peritoneal muscle near the stomach's normal resting position and under the skin to the back of the neck. Another small piece of Marlex mesh was put around the tube and placed under the skin at the point at which the tube exits. The rats were allowed to recover for at least 5 days. Peritonitis rarely occurred.
3. The Bowman restraining cage is made by connecting stainless steel rods between two Plexiglas endpieces. The rat is enclosed and supported by the rods. The rat cannot move forward or backward but can twist around so that he lies on his back. The cage and a full description are available from Nuclear Supply and Service Co., Washington, D.C.
4. The pump was a ten-veined Buchler Dekastaltic pump.
5. B. J. Weiner, *Statistical Principles in Experimental Design* (McGraw-Hill, New York, 1962), p. 85.
6. This work was supported by grant MH 20996-01 from the Public Health Service. We would like to thank P. Branson and B. J. Shebo for their technical assistance and P. Roll for providing computer programs for the statistics.

30 October 1972; revised 26 December 1972

Camptothecin Blocks Memory of Conditioned Avoidance in the Goldfish

Abstract. *Intracranial injection of 10 to 75 micrograms of camptothecin, a plant alkaloid that blocks RNA synthesis in eucaryotic cells, blocks incorporation of tritiated uridine into RNA in the goldfish brain. Injection of 10 to 50 micrograms of the drug within 1.5 hours of training results in greatly diminished memory, tested 1 week later. Injection of the drug 5 or 24 hours after training produces no measurable effect on retention of the learned response.*

When actinomycin D, an inhibitor of RNA synthesis, is injected intracranially into the pericranial fluid of goldfish immediately after training, retention of a conditioned response is diminished (*1*). While an amnestic effect of intracerebrally injected actinomycin has since been claimed in rodents (*2*) and in chicks (*3*), such injections of the drug into the brain substance can produce morphological (*4*) and physiological (*5*) changes. It also has been reported that actinomycin produces behavioral effects not attributable to a block of memory (*6*). Although the goldfish experiments indicate that intracranially injected actinomycin specifically affected memory formation, the recent availability of a less toxic and more reversible inhibitor of RNA synthesis prompted this further investigation on the putative relation of RNA synthesis and memory in the fish. Camptothecin is a plant alkaloid (*7*) known to possess anticancer activity (*8*) and to inhibit synthesis of high molecular weight nucleic acids (*9*, *10*). In HeLa cell cultures, it inhibits nonmitochondrial nucleic acid synthesis: synthesis of heterogeneous nuclear RNA and of 45*S* nucleolar RNA is blocked as is the appearance of 28*S* and 18*S* ribosomal RNA in the cytoplasm. While the inhibition of synthesis includes messenger-like RNA and DNA, synthesis of 5*S* RNA is not affected by the drug. The DNA isolated from camptothecin-treated cells is of significantly lower molecular weight than control DNA (*10*), but direct addition of the drug to isolated DNA has no effect. Whatever the mode of action of the drug, its effects are rapidly reversed within minutes after removal of camptothecin from a cell culture medium.

We measured the labeling of brain RNA in common goldfish (*Carassius auratus*, 8.5 to 12 g body weight, obtained in weekly shipments from Ozark Fisheries) at various times after the intracranial injection of 50 μg of sodium camptothecin (*11*) dissolved in 10 μl of 0.15*M* NaCl, followed after various intervals by a similar intracranial injection of 15 μc of [5-