Clearly the inactive phase cannot be explained by a general depression of the "ascending reticular system" because ECoG desynchronization (occurring either spontaneously or following stimulation of the reticular formation) was observed in cortex 1 cm or more from the site of depression. This inference is consistent with the finding of Bureš *et al.* (*18*) that in the unanesthetized rat most reticular neurons only increased in rate during SD. (By contrast, the majority of medial thalamic neurons they studied showed only an inactive phase.) Neither synaptic fatigue (for example, transmitter depletion) nor delayed inhibition, caused by the high level of corticofugal discharge, adequately account for the inactive phase, because it was readily observed during cortical cooling without a preceding phase of hyperactivity. The mean rates of discharge attained during SD excitation exceeded those occurring either spontaneously or in response to stimulation of the reticular formation. However, some innervated neurons may be driven at comparable rates for many seconds by peripheral stimulation but return quickly to the control rate of discharge following such stimulation (*19*).

Although reduction of corticothalamic discharge is associated with reduced activity of VP neurons, our experiments do not directly differentiate between reduced direct excitatory drive and reduced inhibition of tonically active inhibitory interneurons (disinhibition). Either mechanism would lead to reduced facilitation of VP neurons. However, because increased inhibition of tonic inhibition probably could not alone account for the very high level of discharge during the excitation phase we conclude that the dominant effect exerted by corticothalamic neurons is synaptic excitation.

Therefore, the relatively small decrease in excitability that was observed during the early part of the inactive phase probably resulted from reduced synaptic facilitation. Our finding that depression of sigmoid gyrus and adjacent cortex leads to reduced VP neuron activity is consistent with anatomical evidence that this region of cortex projects to VP (*17*). The data imply that the response of VP neurons to reticular formation stimulation requires corticothalamic facilitation. Either reticular activation of VP is mediated solely by corticothalamic neurons, or the response requires the summation of corticothalamic with reticulothalamic discharge. Further investigation is required to differentiate between these alternatives.

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9. Ability of neurons to respond to consecutive stimuli at 500 per second is a useful criterion for identifying an antidromic response, even though antidromic impulses sometimes fail to invade the soma-dendrite region of VP neurons because the cortical stimulus train also evokes postsynaptic inhibition (*16*). We did not apply this criterion in this study because such stimulation may also evoke convulsive afterdischarge in the unanesthetized or lightly anesthetized cortex. However, VP neurons responding to stimulation of somatosensory cortex with latencies of 0.5 to 0.9 msec in cats anesthetized with barbiturate rarely fail to follow four minimally suprathreshold stimuli at 500 per second. Use of the latency criterion alone is unlikely to have resulted in our classifying some interneurons as cortically projecting, but may have resulted in our failure to classify some antidromically invaded neurons with slowly conducting axons as cortically projecting.
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Lateral Hypothalamic Stimulation in Satiated Rats: The Rewarding Effects of Self-Induced Drinking

Abstract. *It is well known that thirsty rats will press a lever for water. The purpose of the present experiment was to demonstrate that, when water is freely available, nonthirsty rats will press a lever for thirst. Three satiated rats, bearing permanently implanted electrodes, were trained to press a lever which caused stimulation to be applied to an area of the lateral hypothalamus which induces thirst. The animals were tested with and without water available. Two of the rats pressed the lever to induce thirst only when water was available. Thus, thirst-inducing stimulation was not rewarding by itself, but only in combination with drinking.*

Thirsty laboratory animals readily learn to engage in responses (for example, pressing levers) which are followed by the presentation of water which they drink. The responses are usually said to be motivated by thirst and reinforced by drinking, and the experiment is said to demonstrate the reinforcement principle or law of effect. However, empirically all that can be said is that thirsty animals respond in order to obtain water, while satiated animals do not; that is, the simultaneous presence of thirst and water constitutes a rewarding situation. The empirical "law" is that responses followed by this combination tend to increase in frequency of occurrence. In this case the law is demonstrated by supplying the animal with one member of the combination (thirst) and presenting the second member (water) after the animal presses the lever. However, it is also logically possible to demonstrate this law by interchanging the members of the combination, that is, by supplying the animals with water, and inducing thirst each time the animal presses the lever. The rapid induction of thirst by electrical stimulation of the lateral hypothalamus (*1*) provides a means of testing this possibility.

Five inexperienced albino rats were implanted with two monopolar stainless steel electrodes placed one on each side of the brain in the lateral hypothalamus (Krieg coordinates: 1.0 mm posterior to bregma, 1.4 mm lateral from the midline, and 8.2 mm below the superior surface of the skull). Also an indifferent electrode consisting of an uninsulated stainless steel wire (5 mm

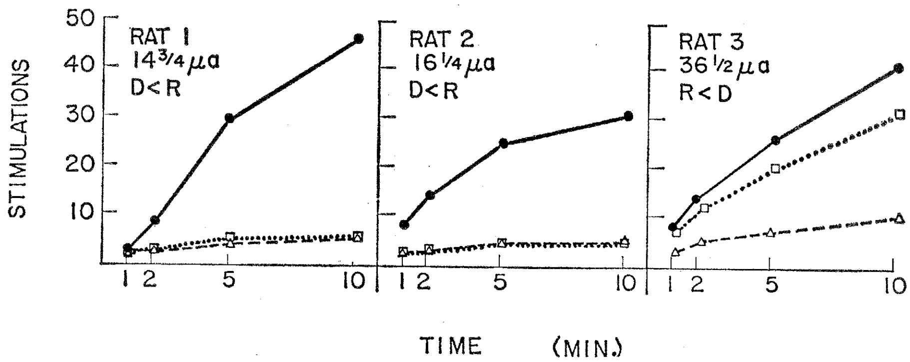

Fig. 1. Median number of thirst-inducing presses on the lever made by each of three satiated rats by the first, second, fifth, and tenth minute of a 10-minute session. Each point on the curves represents the median score for an animal based on 12 sessions. Solid line, both stimulation and water available; dotted line, stimulation available but not water; dashed line, control condition with neither stimulation nor water available.

long) was placed in the brain 3 to 5 mm away from the hypothalamic electrodes. The animals were maintained in cages in which Purina rat food and tap water were available continuously; at no time were they deprived of food or water.

Five days after the electrodes were implanted each hypothalamic electrode was tested separately to see if stimulation of it induced drinking. Sixty-cycle/sec sine-wave current was passed between it and the indifferent electrode at intensities varying from 5 to 50 μa. In two satiated rats stimulation of either hypothalamic electrode induced drinking; in one rat one electrode induced drinking; and in two rats neither electrode was effective. Two weeks after implantation all the electrodes were retested; still only the same five induced drinking in the satiated rat. For each of these electrodes the threshold current for drinking was roughly determined by a method of ascending and descending limits. For each of the two animals in which either electrode was effective, the electrode with the lowest threshold was used in the experiment. The thresholds for the electrodes used were 15.5, 16, and 36 μa (root mean square).

Each rat was given two 10-minute sessions daily in a Skinner box (30 by 13 by 30 cm high); the lever, measuring 10 by 6 cm, was mounted on one of the narrow ends, 2.5 cm above the floor. On each side of the lever a drinking tube projected 1.3 cm into the box and 4 cm above the floor. On one of the daily sessions the tubes contained water, and on the other session they were empty. The order of administration of these sessions alternated from day to day. The sessions were separated by 2 to 3 hours; the animals were replaced in their home cages immediately after each session, with food and water available as usual. Each time the animal pressed the lever it received 5 seconds of intracranial stimulation; the 5-second duration could not be extended by holding down the lever or by pressing it again during the stimulation.

All the rats learned to press the lever within three sessions, and their rates stabilized within 9 days. As of the second day of training the response rate for each animal was much higher when water was available than when it was not available, as previously reported by Mogenson and Morgan (*1*). The median response rates over the last three days of training were 104 when water was available and 72 when it was not; the median numbers of stimulations received were 75 and 42, respectively (both differences significant, $P < .004$ by a sign test).

The day after the response rates stabilized, the current was lowered 0.5 μa daily for each rat until a point was reached at which the rat failed to drink on more than 50 percent of the times that it made itself thirsty. Then the current was raised 0.25 μa daily until persistent drinking was reinstated. The intensity at which this occurred was taken as the "drinking threshold." Using this intensity, we continued testing for 12 days with a slightly modified design: the sessions were separated by 1-hour intervals, and another daily session was introduced in which, with no water available, the animals were tested under extinction conditions, that is, no intracranial stimulation was delivered when the animals pressed the lever. The second of the three daily sessions was always conducted with both water and stimulation available, and the order of administration of the other two conditions (that is, stimulation with no water available, and neither stimulation nor water available) was alternated from day to day. Comparison of the scores obtained on these two types of sessions without water (that is, with and without stimulation for each press on the lever) would indicate whether or not the stimulation alone was rewarding.

In terms of this comparison two different patterns of performance emerged. (i) When no water was available two rats showed the same extinction pattern of responding whether or not they were stimulated when they pressed the lever; neither of these rats was responding at the end of the 10-minute session (Fig. 1, rats one and two). Apparently their drinking thresholds were lower than their reward thresholds (D < R). (ii) The other rat showed the extinction pattern of responding only when neither water nor stimulation was available. In contrast to the other two animals, when stimulation but no water was available rat three pressed the lever throughout the 10-minute test period (Fig. 1). Apparently its reward threshold was lower than its drinking threshold (R < D) (*2*).

The curves for the two D < R rats show that, although they failed to press the lever when stimulation but no water was available, they persistently pressed the lever when both stimulation and water were available. This behavior indicates that the combination of thirst-inducing stimulation and water was rewarding, even though the stimulation itself was not. Although these rats were not thirsty, they apparently pressed the lever in order to become thirsty and drink. In contrast, their rates of responding under the two conditions when no water was available were very low and almost identical, suggesting that thirst induction in the absence of drinking was not in itself rewarding. From the fact that these rats persistently pressed the lever only when each press was followed by drinking, we conclude that self-induced thirst accompanied by drinking is rewarding.

The classical view of motivation maintains that thirst motivates rats to engage in instrumental water-procuring responses. However, the results of the present experiment should cause us to reexamine this theoretical position. In view of these results, it is perhaps no more meaningful to say that thirst motivates rats to press the lever to obtain water than it is to say that water motivates rats to press the lever in order to become thirsty. On the other hand, it is meaningful to say that the availability of the combination of thirst plus water can serve as an incentive to motivate even rats that are not thirsty to engage in responses which produce that combination. Thus if the rat is given the thirst it will press for the water; if given the water it will press for the thirst.

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3. Supported in part by NIH grants MH-31258-02 and MH-13253-01.

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Hemoglobin F and Beta Thalassemia

Kreimer-Birnbaum and Bannerman report on a patient with beta thalassemia (*1*). They injected glycine-2-C^{14} and observed that during subsequent days the specific activity of hemoglobin F in the peripheral blood exceeded that of hemoglobin A. Since this result is opposite to our findings in three patients with beta thalassemia, we would like to ask whether this patient received blood transfusion during the period prior to study. Such an introduction of exogenous Hb A would have lowered its specific activity relative to that of Hb F, and this could thus explain the difference between their result and ours.

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12 April 1967

Our patient with beta thalassemia had received blood transfusions prior to the study, as noted in the clinical description to which we referred (*1*). Transfusions were given at least 30 days and again at 20 days before administration of glycine-2-C^{14}. Gabuzda *et al.* (*2*) are indeed correct in suggesting that exogenous Hb A would have diluted the patient's own Hb A and tended to reduce its specific activity in comparison with Hb F in the earlier part of the study. This is an important point which complicates interpretation, and it may indeed explain the apparent discrepancy between our result and theirs.

After day 50 this dilution would be minimal, and further unpublished data for days 50 to 100 in our patient show that Hb F continued to have a specific activity 1.1 to 1.5 times that of Hb A. During this period, the curves resemble those of Gabuzda *et al.* and their explanation of preferential survival of Hb F is applicable to their curves and ours. We agree that further studies of this kind are needed in β-thalassemia and also in other situations in which there may be heterogeneous metabolism of hemoglobins.

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23 June 1967

The Supernova of 1572

With regard to a recent article by Xi Ze-zong and Po Shu-jen (*1*) that this supernova was observed in China on 8 November, 3 days before Tycho Brahe had done so, the following quotation (*2*) from an observation by Bernard Lindauer (1520–1581), pastor at Winterthur, Switzerland, is interesting.

"On 7 November 1572 a new large bright star has been seen in the sky at Winterthur, equal to the chief (star) of Cassiopeia." The chief star, α Cassiopeia, varies in magnitude from 2.2 to 2.8 with a mean of about 2.4. This would indicate that Lindauer caught the nova on the rise to its maximum magnitude.

A claim by Hageccius from a letter of Paul Fabricius that the nova was already visible at the end of October may have been discounted by Wolf, but, as it seems to have been a slow object, the increase in magnitude might have been somewhat gradual at first. By the time Tycho sighted it, it was as bright as Venus at maximum.

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20 June 1967