phenomenon probably reflects differences in duration of the active state in different regions along the length of the fiber with the result that portions of the fiber having the longest active state, shorten at the expense of those parts in which the capacity to produce tension declined earlier (*7*).

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Hibernation Induced in Ground Squirrels by Blood Transfusion

Abstract. *Natural mammalian hibernation was continuously maintained under laboratory conditions throughout spring and summer seasons in a colony of thirteen-lined ground squirrels by serial transfusional passage of blood from hibernating animals to active animals. This procedure successfully produced hibernation in animals until late summer, at which time naturally occurring (spontaneous) hibernations occurred in the colony, thus terminating the experiment.*

Mammals which hibernate, whether in field or laboratory, do not ordinarily do so in midsummer months (*1*). There is some variation between species as the bat and the hamster. Hamsters are capable of hibernation, on occasion, under cold, dark, quiet conditions. Ground squirrels and marmots, on the contrary, very seldom hibernate in the midsummer under any conditions. Hibernation was induced in our laboratory animals in the summer, triggered by the transfusion of hibernation blood.

We maintained a colony of approximately 20 thirteen-lined ground squirrels (*Citellus tridecemlineatus*) in a 7°C, dark, quiet room (cold room). None of these animals hibernated between early March and 7 August except the experimental animals described herein.

During the winter of 1967 to 1968, all of the animals in our colony had hibernated. By 6 March 1968, all had returned to an active state except one animal, which continued to hibernate. This donor was in a state of deep hibernation with a low body temperature and very slow respiration. Without arousing this cold animal, we opened the abdominal cavity and drew 3 ml of blood from the dorsal aorta. An anticoagulant was not used in this procedure. Shortly after this exsanguination the animal died (Fig. 1). The blood was kept cold and 1 ml was injected into each of three animals from a 23°C room (warm room) within a few minutes from the time of withdrawal from the hibernator. Blood was introduced directly into the saphenous vein in two cases, and intraperitoneally in the third case. The injected animals were then placed into the cold room. There was no evidence of anaphylactic shock or other adverse reaction to the transfused blood. Three nontransfused animals from the warm room were placed in the cold room as controls, and they remained there through the summer months without going into hibernation. Both animals that had received blood intravenously began to hibernate after 48 hours (Fig. 1). Thereafter they followed a typical hibernating pattern: going into and out of hibernation for varying lengths of time, from a few days to several weeks, until mid-June. Additionally, they displayed other of the characteristics of true hibernation, including the typical head-down balled-up position, lowered body temperature, and greatly decreased respiration. We later obtained blood in the manner described above from these two animals when they were hibernating, and transfused their blood into three more animals from the warm room, that also hibernated when placed in the cold room (Fig. 1). Two animals from the warm room were transfused in a similar way with blood from an active animal and then placed into the cold room as further controls; these did not hibernate. In July, blood of two of the three hibernating animals was transfused into five more active ground squirrels from the warm room, all of which have now hibernated (13 August 1968, Fig. 1). Our colony now consisted of 24 animals, 14 in the cold room and 10 in the warm room. On 7 August two of the control animals (transfused with blood from an active animal) hibernated. Shortly thereafter, other animals in the cold room that had not been transfused began to hibernate. Since the late summer or fall hibernating season had obviously begun, the experiment (valid only as a test for true hibernation in midsummer) came to a close. No data obtained beyond this date could be regarded as significant.

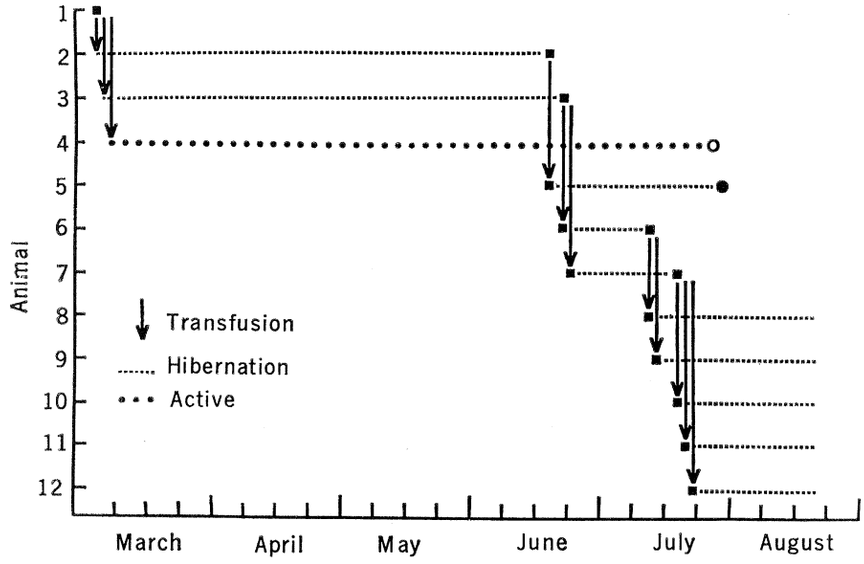

Fig. 1. Transfusions accomplished in spring and summer season (1968) resulting in hibernation of 13-lined ground squirrels (*Citellus tridecemlineatus*). Solid square, hibernating donor; open circle, death (not in hibernation); solid circle, death (in hibernation).

The successful transfusions of blood to induce hibernation includes working in a cold room, so that the donor animal and the instruments used for dissection are refrigerated during the blood withdrawal. The animal must remain in hibernation, so speed is important to avoid a possibility of collecting any "arousal substance" that might be produced during the dissection. It is possible that such a substance could vitiate activity of a "trigger substance." Therefore, total time for dissection and blood withdrawal was never more than 45 seconds.

These results, although based on a very few experiments (Fig. 1), indicate that a "trigger" for natural mammalian hibernation in the ground squirrel is carried in the blood of the hibernating squirrel and can be transferred by transfusion to nonhibernating summer animals from the warm room, causing them to hibernate after their introduction into the cold.

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Facilitation of Brain Self-Stimulation by Central Administration of Norepinephrine

Abstract. *Rats with electrodes implanted in the medial forebrain bundle stimulated their own brains at sharply reduced rates after systemic administration of disulfiram or intraventricular administration of diethyldithiocarbamate. Both drugs inhibit dopamine-β-hydroxylase, the enzyme responsible for the final step in the biosynthesis of norepinephrine. The suppressed behavior was reinstated by intraventricular injections of* l-*norepinephrine, but not by injection of its biologically inactive isomer,* d-*norepinephrine. Intraventricular administration of dopamine and serotonin did not restore self-stimulation. The rewarding effect of medial forebrain bundle stimulation may depend on the availability of norepinephrine as a transmitter, but not on dopamine or serotonin.*

Several lines of evidence support the idea that catecholamines in the central nervous system mediate rewarding or positively reinforcing effects on behavior. This idea was suggested initially by studies of the effects of drugs on self-stimulation of reward areas in the brain (*1*). Drugs that facilitate self-stimulation (for example, amphetamine) release catecholamines rapidly from physiologically active sites. Conversely, drugs that inhibit self-stimulation deplete the brain of catecholamines (reserpine, α-methyl-*p*-tyrosine) or block adrenergic transmission (chlorpromazine). Furthermore, if catecholamines are protected from destruction by inhibitors of monoamine oxidase, or, if the reuptake of catecholamines is retarded by drugs similar to imipramine, the facilitatory action of amphetamine on self-stimulation is increased. On the other hand, if the stores of catecholamines in the brain are depleted by reserpine or α-methyl-*p*-tyrosine, the facilitating effect of amphetamine is decreased.

An anatomical basis for this relation between positive reinforcement and catecholamines is provided by the coincidence of behavioral and histochemical experiments. The behavioral work shows that the most intensely rewarding points in the brain are distributed along the medial forebrain bundle (*2*); the histochemical work (*3*) shows that the medial forebrain bundle is the principal diencephalic pathway of ascending noradrenergic fibers. Recently, these relations were verified by experiments which demonstrate in vivo that rewarding electrical stimulation of the medial forebrain bundle releases norepinephrine and its metabolites into solutions perfused through the hypothalamus and amygdala (*4*).

Taken together, these data suggest that self-stimulation depends on the release of norepinephrine at synapses of the medial forebrain bundle. However, it has not been possible to demonstrate that the rate of self-stimulation may be increased by central administration of norepinephrine. Indeed, such administration suppresses rather than facilitates self-stimulation behavior reinforced by minute injections of chemicals into the hypothalamus (*5*), and generally causes inactivity, sedation, and stupor with increasing doses (*6*).

Our experiments show that self-stimulation can be facilitated by central administration of norepinephrine under certain conditions and that self-stimulation depends more critically on the availability of norepinephrine than it does on that of dopamine or serotonin.

Bipolar platinum electrodes were stereotaxically implanted in the medial forebrain bundles (at the level of the mamillary bodies) of 29 rats anesthetized with pentobarbital; cannulas for injection of solutions were implanted in the lateral ventricle on the opposite side. The design of electrodes and cannulas has been described (*4*). Accuracy of placements was verified histologically at the end of the experiment. The animals were trained to stimulate their own brains by pressing a lever in a Skinner box, according to the technique of Olds and Milner (*7*). Each lever press delivered a 0.15-second train of rectangular pulses 0.2 msec long at 100 pulses per second through an isolation transformer. The current varied between 0.1 and 0.4 ma, and was adjusted in each case to the lowest intensity that maintained a stable rate of self-stimulation.

After several sessions of preliminary training, animals were injected with disulfiram or diethyldithiocarbamate (DEDTC). These inhibitors of dopamine-β-hydroxylase (E.C. 1.14.2.1) block the final step in the biosynthesis of norepinephrine, and thus selectively deplete it (*8*). Animals that were tested with disulfiram were kept on the regular reinforcement schedule. A dose of 200 mg per kilogram of body weight, suspended in 0.3 percent Tween 80 in saline, was injected intraperitoneally 1 hour after the start of the test session. Animals that were given DEDTC were trained to respond on a schedule in which reinforcements were programmed at variable intervals (on the average, once every 10 seconds). Two milligrams of DEDTC were dissolved in 25 μl of Ringer-Locke solution (adjusted to *p*H 7.5) and injected intraventricularly ½ hour after the start of the test. One to three hours after injection of disulfiram, or 15 minutes after injection of DEDTC, various neurohormones as hydrochlorides (*l*-norepinephrine, *dl*-norepinephrine, *d*-norepinephrine, dopamine, and serotonin) were injected into