and actinomycin C, as well as local radiation to the graft which was repeated on the 7th and 10th days after transplantation. Clinical findings and laboratory data suggest that the rejection was reversed.

Additional evidence of graft function includes repeated normal renograms over the transplant without evidence of function of the patient's own kidneys and concentration of activity in the transplant by renal scanning. Intravenous urography demonstrated function of both transplanted kidneys on the 10th day after transplantation.

These cases illustrate that immediate function of the heterografts was satisfactory. Findings in the second case suggest that early rejection may be reversed by currently available immunosuppressive measures. The question of long-term function remains, of course, unanswered.

Note added in proof. The patient described in case 2 was readmitted with pneumonia on 20 December 1963. Despite treatment with antibiotics and reduction in dose levels of immunosuppressive drugs he showed progressive pulmonary infection and hypokalemia. He died on 6 January 1964. Autopsy showed acute bronchopneumonia in the right lower lobe, acute tracheobronchitis, and resolving abscess in the right middle lobe. Sections of the transplanted kidneys showed no evidence of rejection. The findings of acute tubular necrosis were interpreted as consistent with the state of shock, necessitating vasopressors for 36 hours before death; the transplant showed no cellular infiltrate and no changes in the blood vessels. Three patients treated subsequently by a similar method during the past month show satisfactory function of heterografts.

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20 November 1963

Intracranial Reward Delay and the Acquisition Rate of a Brightness Discrimination

Abstract. *An application of the techniques of intracranial self-stimulation to the study of delayed reward indicates that the rate of discrimination learning for stimulation of the hypothalamus is a decreasing function of the delay interval. The resulting delay-of-reward gradient does not appear to differ appreciably from other such gradients based on food reward.*

The demonstration that electrical stimulation of the brain can serve as an effective reward (*1*) has provided a new basis on which to approach the study of many reinforcement phenomena. Numerous investigators have, in fact, used these stimulation techniques to good advantage to study such factors as the brain structures involved in reward effects (*2*), the influence of various drive states on these central reward structures (*3*), and a variety of other related problems. Still another potentially useful application might be in studying the temporal parameters of reward and their relation to learning. Precise control of the duration of reinforcement or of the delay between the occurrence of a response and its reward is frequently complicated when food or water is the reward, since such factors are, in part, contingent upon the animal's behavior. In contrast, the techniques of electrical stimulation permit direct experimental control of such parameters and the use of a wider range of intervals than is normally possible with conventional reinforcers.

Evidence presently available indicates that brain stimulation is an effective reward in a learning situation. Rats will, for example, learn a multiple maze for such stimulation (*4*), and more recent evidence suggests that stimulation of certain areas of the hypothalamus is at least as effective a reward as food for the learning of a brightness discrimination (*5*). In the work reported here, this line of investigation was extended to study the rate of learning among groups reinforced by stimulation when there are differences in the stimulation along a temporal dimension. Delay of reward (stimulation of the hypothalamus) was the parameter chosen.

Male Sprague-Dawley rats were prepared for this experiment by permanent implantation of bipolar electrodes ("chronic electrodes") aimed at the same area of the posterior hypothalamus in all the animals. Subsequent histological examination of the brains of a sample of 12 of the 48 experimental animals revealed that the majority of these electrodes terminated in the dorsomedial and posterior hypothalamic nuclei, the remainder being distributed in the more lateral region of the hypothalamus or more posteriorly in the supramammillary area. Stimulation was provided by a biphasic rectangular waveform, with the parameters held constant throughout the experiment at the following values: peak current, 2 ma; frequency, 85 pulses per second; pulse duration, 0.175 msec; train duration, 0.5 second. Prior work with stimulation of essentially these same areas of the hypothalamus has indicated that effective reward is provided by these stimulus conditions (*6*).

The experimental compartment was a rectangular box containing two response bars; in the pretraining phase of the experiment the box was divided into two boxes, each with one bar, by the addition of a center panel. Under this latter condition each subject was first trained to press for stimulation on one or the other of the bars. A training session followed in which each response extinguished the house lights for a 10-second period and eliminated the opportunity for reinforcement until the lights came on again. Of each group of six animals completing 100 such trials on both sides of the box, one

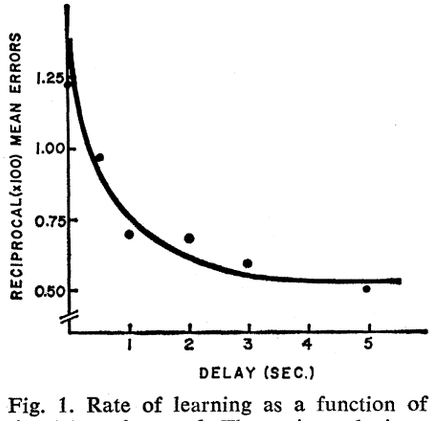

Fig. 1. Rate of learning as a function of the delay of reward. The reciprocal, times 100, of the mean number of errors in 500 trials is plotted against the delay interval. The curve has been visually fitted to the data points.

was assigned at random to each of the following six delay conditions: 0.0, 0.5, 1.0, 2.0, 3.0, and 5.0 seconds. This procedure was repeated until eight animals in all had been assigned to each delay-of-reward condition.

In the learning phase of the experiment the center panel was removed from the box to produce a two-bar discrimination situation. The task of the subject was to choose between the two bars, over one of which there was a light (the "discriminative" light). A response on either bar immediately extinguished both the discriminative light and the house lights for a 10-second interval. A response on the lighted bar resulted in delivery of the stimulation after an interval determined by the delay condition to which the animal had been assigned. The side of the box on which the positive stimulus of illumination appeared was varied according to a prearranged order, and each correct response advanced this sequence. With this procedure, a subject was given 500 trials; for the most part these were given in two sessions—300 trials in the first and 200 in the second. In a few cases, especially under the longer delay conditions, an animal would stop responding for 15 minutes or more. When this occurred, training was terminated for that day and continued on the next, for as many daily sessions as were necessary to complete 500 trials.

The reciprocal of the mean number of errors made by each group in the 500 trials was plotted against the delay condition to produce the delay-of-reward gradient shown in Fig. 1. Statistical analysis of these data showed that the differences between the error scores for the six groups were reliable ($p < .001$). Examination of the acquisition curves (not shown) revealed that the first three groups—those subjected to 0.0-, 0.5-, and 1.0-second reward delay—attained a terminal performance level between 90 and 100 percent correct. The curves for the other three groups were still rising at the end of the 500 trials, and it is possible that they would have reached this same performance level had training continued. It is worth noting, however, that an increasing number of animals in the groups where delay was longer failed to show clear evidence of learning over the 500 trials, and three of the animals subjected to 5-second delay responded at what was close to a chance level throughout the experiment. It may be, therefore, that for a visual discrimination the 5-second delay is close to the limit for learning in the rat, as was suggested in an earlier study (*7*).

Much of our present knowledge concerning the relation of delayed reward to the rate of learning in rats is based upon the work of Grice (*7*), who used a food reward. While the work reported here resembles this earlier study in the choice of a visual discrimination task, the two do differ, both with respect to the reinforcing stimulus employed and in the use of a two-bar rather than a two-alley testing situation. In spite of these differences, comparison shows the two sets of data to be remarkably similar. It is possible, of course, that a closer examination of the relation between delayed reward and learning may reveal differences in the responses for food reward and for stimulation reward, perhaps at very short delays where, with food stimuli, the response time of the systems mediating reward may introduce a certain delay that central stimulation eliminates. On the other hand, the close similarity of the present data to those of Grice argues strongly for the essential comparability of food and stimulation as rewards for learning. This, together with the observation that group comparisons of experimental treatments are feasible in spite of the expected variation between subjects in electrode placement, offers considerable encouragement for applying these brain-stimulation techniques to studying the relation between reward and learning.

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Vinblastine Sulfate Treatment of Hodgkin's Disease during a Pregnancy

Ferm has reported [*Science* **141**, 426 (2 August 1963)] that embryocidal and teratogenic effects follow the treatment of pregnant golden hamsters with vinblastine sulfate (VLB) or vincristine sulfate (VCR). In view of this it is perhaps of interest to report the case of a patient with Hodgkin's disease who was treated throughout pregnancy with VLB, before we were acquainted with Ferm's findings.

Prior to pregnancy the woman had been treated with VLB intravenously, but it had become impossible to give further injections when her veins became inaccessible. Fortunately, oral VLB maintained the remission. Treatment with oral VLB commenced 15 August 1962, and has been continued without interruption since then. During most of this time the dosage has been one 5-mg tablet by mouth on each of five consecutive days each week.

For two reasons we believe that the patient absorbed the orally administered VLB. (i) The number of leukocytes per cubic millimeter was reduced on 14 September 1962 to 2300, on 19 October 1962 to 3900, and on 8 March 1963 to 3300. After each leukopenic episode the dosage of VLB tablets was temporarily reduced to permit the leukocyte count to return to normal. (ii) Prior to pregnancy, only 3 weeks after intravenous VLB dosage had been temporarily discontinued, the patient had an acute relapse, with signs of generalized Hodgkin's disease. If the oral preparation had not been absorbed systemically, we would therefore have expected another relapse. Further, we had previously not merely maintained but actually induced remission with oral VLB in other patients suffering from Hodgkin's disease.

On 15 July 1963, after 11 months of oral VLB treatment, the patient spontaneously gave birth to a full-term, normal male infant weighing 3570 g (7 lb 14 oz). Physical examinations of the infant have failed to reveal any abnormalities. As this is written he is 3 months old and thriving.

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