Time-out from Positive Reinforcement
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Particles were subsequently made by coacervation with gelatin. Examination of cells by fluorescence microscopy showed the presence of DNA particles in the cytoplasm (Fig. 1, middle).

Since the nuclear DNA obscured the possible presence of particles in the nucleus when the cells were examined after staining with both Feulgen and acridine orange, a third method of following particles was devised. A mouse with sarcoma 180 in the ascitic form was inoculated with tritiated thymidine (total, 1.4×10^6 count/min; specific acitivity, 1.9 c/mmole). After 2 hours the cells were removed from the peritoneal cavity and carefully washed free of extracellular thymidine, and the DNA was extracted by the phenol method. Dialyzed particles (0.5 ml, with a total of 30,000 count/min), prepared by coacervation of protein and DNA labeled with tritiated thymidine, were incubated with the cells, as described above, in the presence of unlabeled thymidine (10 mg/100 ml). This relatively enormous concentration of thymidine was considered sufficient to act as a metabolic trap which would prevent any labeled thymidine, released as a result of membrane degradation of the large nucleic acid molecule, from reaching either the cytoplasm or nucleus. The cells were fixed in a solution of acetic acid and alcohol (1:3) and NTB_2 emulsion used in the preparation of radioautographs. Radioautographs showed the presence of many particles over both the nucleus and cytoplasm (Fig. 1, bottom).

It is generally accepted that when cells are grown in a spread fashion on cover slips, the amount of cytoplasm overlying the nucleus is too thin to contain particles or detectable quantities of labeled thymidine.

It has been reported that fibroblasts in vivo incorporate DNA by phagocytosis (*11*), as do white blood cells in the lupus phenomena (*12*). Determination of whether this has any biological significance and whether true transformation is possible in mammalian systems must await the development of genetic markers similar to those used so successfully with bacteria. An abstract describing our work has previously been published (*13*, *14*).

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19 September 1960

Time-out from Positive Reinforcement

Abstract. When an organism can itself impose extinction during fixed-ratio food reinforcement, the duration of the extinction period is a function of the number of responses required for reinforcement. Typically, the subject imposes extinction at the start of the usual fixed-ratio run.

When a response is reinforced, or rewarded, in the presence of a given stimulus, then that stimulus becomes the occasion for more responses. Another stimulus, in the presence of which no reward is obtainable, may be used as a sort of "time-out" condition. It has been shown that time-out can function either to reward or to punish behavior (*1*). Typically, the time-out condition has been introduced at infrequent intervals and for fixed durations. The subject's tendency to initiate or prolong a period of time-out has not been continuously measured. To overcome this limitation, a procedure has been devised in which the organism may initiate, or terminate, a period of time-out at any time. The procedure makes it possible to discover when an organism will initiate a time-out period and how long it will allow the time-out to continue, as functions of the underlying schedule of reinforcement.

A pigeon, at 80 percent of the weight it maintains when allowed to feed freely, is conditioned to peck a plastic disk through reinforcement with food immediately after each peck. Food is then delivered only after every 50 responses —a so-called fixed-ratio schedule of reinforcement. Simultaneously, a second key, the time-out key, is made continuously available to the subject. A single response on this key changes the color and intensity of the ambient illumination, as well as of the light projected on the two translucent response keys. Under the changed illumination, all responses on the food key are ineffective in producing food. As a result, responding on the food key soon drops to zero. However, a second response on the time-out key restores the original conditions of illumination as well as the possibility of reinforcement. Thus, the organism is free at any time to terminate or to restore the stimulus situation which has been differentially associated with positive re-

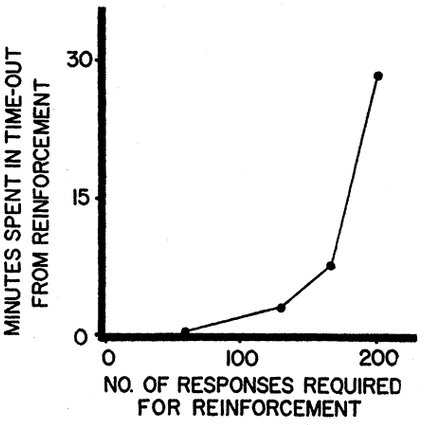

Fig. 1. Self-imposed periods of extinction as a function of the number of responses required during fixed-ratio reinforcement.

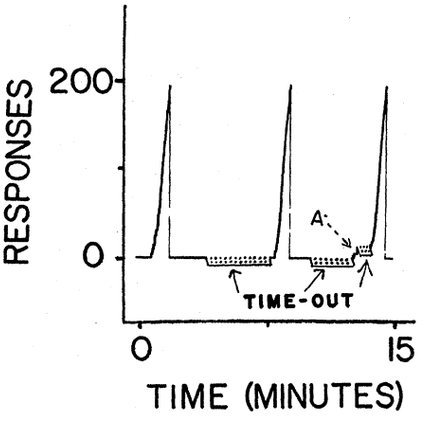

Fig. 2. Cumulative record of responses on a schedule of food reinforcement for every 200th response. The vertical reset line indicates the delivery of the reinforcement. Initiation of extinction is indicated by the downward deflection of the recording pen, and period of extinction, by the dotted area.

inforcement. The procedure may be designated control of extinction (the condition in which reinforcement is not obtainable) by the organism.

Four subjects have given similar results, indicating that the time spent under conditions of extinction is a function of the number of responses required to produce the food reinforcement. Figure 1 shows this relationship for one subject for which the number of responses required per reinforcement was increased from 65 to 200, in daily sessions of 60 minutes each. At low ratios, only a few seconds were spent in time-out. As the ratio was raised, the subject extended the time-out condition for longer periods. At a ratio requirement of 200 responses, the subject spent about 50 percent of the experimental period in time-out. Each point in Fig. 2 is an average for 5 days, but performance was often allowed to stabilize for several weeks.

Figure 2 presents a typical segment of a cumulative response record for one subject. The pattern of responding seen here is characteristic of fixed-ratio food reinforcement: a high rate prevails prior to reinforcement (top of each segment), and a long pause follows before another rapid run begins. The self-imposed periods of time-out are shown as a downward deflection of the recording pen (dotted areas). These occur typically during the long pause preceding the run. Occasionally there is a trickle of responses (as at *A*) before the subject initiates time-out. Once responding is well under way, however, time-out is not produced again until after reinforcement. Time-out is not initiated during the pause immediately following delivery of the food. Thus, time-out is not exclusively associated with lack of responding. Rather, the subject appears to initiate time-out just before making the number of responses required by the schedule.

Why should the pigeon impose a period of extinction upon itself? Accidental contingencies can be ruled out, since responses on the time-out key could not be indirectly reinforced by food, a standard period of several seconds having been interposed between any time-out response and food reinforcement. The change in stimuli was not itself reinforcing, since the pigeon imposed extinction periods regardless of whether an increase or a decrease in illumination was associated with time-out. A plausible explanation is that performance under a schedule of positive reinforcement may at certain stages be aversive in spite of the apparent absence of aversive stimuli (*2*).

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Effect of Psychotropic Drugs on the Uptake of H^3-Norepinephrine by Tissues

Abstract. Reserpine, amphetamine, imipramine, and chlorpromazine markedly reduced the uptake of circulating H^3-norepinephrine by several tissues and elevated the plasma concentration of the H^3-catecholamine.

Many drugs affect the physiological actions of catecholamines, but little is known about their mode of action at a biochemical level. Previous work has shown that the psychotropic drugs reserpine, amphetamine, imipramine, and chlorpromazine increase the rate of disappearance of administered epinephrine and norepinephrine in the body (*1*). These observations prompted a study on the effect of these drugs on the uptake and metabolism of circulating catecholamine hormones in tissues.

Adult male cats, prepared as described previously (*2*), were given 25 μg of H^3-norepinephrine per kilogram (3.44 mc/mg) intravenously. Blood samples were taken periodically and the animals were decapitated 1 hour after the end of the injection. The heart, spleen, adrenal glands, liver, and abdominal wall muscle were immediately removed and assayed for H^3-norepinephrine and its major metabolic product H^3-normetanephrine (*2*). Drugs were given before the administration of H^3-norepinephrine as follows: Reserpine, 3 mg/kg intraperitoneally, 24 and 2 hours; amphetamine, 10 mg/kg, intravenously, 10 minutes; imipramine, 20 mg/kg, intraperitoneally, 3 hours and 1 hour; chlorpromazine, 20 mg/kg, intraperitoneally, 24 hours and 1 hour, and 5 mg/kg, intravenously, 20 minutes. Each drug was given to three cats; seven untreated cats served as controls.

The effect of psychotropic drugs on the tissue concentrations of H^3-norepinephrine is shown in Fig. 1. In those organs where the concentration of administered norepinephrine has been shown to be greatest (heart, spleen, and adrenal gland), treatment with reserpine, amphetamine, imipramine and chlorpromazine caused a profound reduction in the tissue levels of the administered hormone. The concentration of H^3-norepinephrine was reduced in the liver to a lesser extent while the catecholamine levels in the skeletal muscle were unaffected. H^3-normetanephrine concentrations were reduced by one half in heart and spleen after treatment with reserpine, amphetamine, imipramine, and chlorpromazine, but these drugs had little or no effect on the level of the metabolite in other tissues.

Previous treatment with psycho-

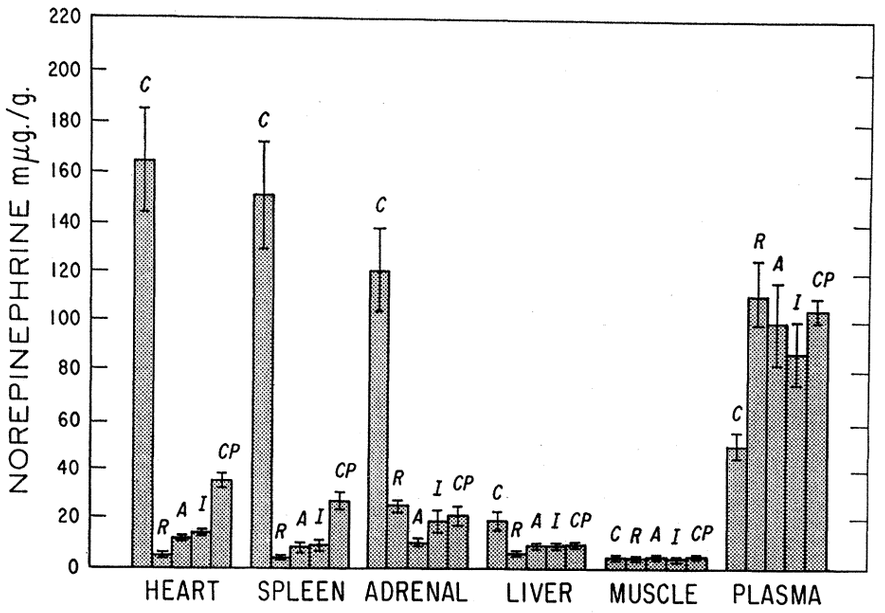

Fig. 1. Effect of psychotropic drugs on the tissue concentration of H^3-norepinephrine. The following drugs were used: reserpine (*R*), amphetamine (*A*), imipramine (*I*), chlorpromazine (*CP*), untreated animals (*C*). The vertical bracketed lines represent the standard error of the mean.