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17. Strains USA 1 to 17 were received from Drs. H. Kim and C. Brandt, Children's National Medical Center, Washington, D.C.; Bang 1 to 6 from Dr. M. Merson, Cholera Research Laboratory, Dacca, Bangledesh; Guate 1 to 10 from Drs. J. Urrutia and L. Mata, INCAP, Guatemala; NCDV 1 to 3 from Dr. C. Mebus, University of Nebraska; UK-1 and H-1 from Drs. T. Flewett and G. Woode, Berkshire, England; P-1 from Dr. J. Lecce, North Carolina State University; SA-11 and O from Dr. H. Malherbe, San Antonio, Texas; EDIM virus from Drs. J. D. Parker and H. J. Collins, Microbiological Associates, Bethesda, Md. The EDIM antiserums prepared by Microbiological Associates under a contract with the Virus Cancer Program of the National Cancer Institute were prepared by oral inoculation of 3-day-old suckling mice; followed by two separate intraperitoneal inoculations, the second with Freund's incomplete adjuvant; followed by two separate intramuscular inoculations.
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Neuroleptic-Induced "Anhedonia" in Rats: Pimozide Blocks Reward Quality of Food

Abstract. *The dopamine receptor blocker pimozide attenuated lever-pressing and running for food reward in hungry rats. In each case the characteristic behavior of pimozide-treated rats was the same as that of undrugged rats when reward was simply withheld. Drug-induced performance difficulties were ruled out by the presence of periods of normal responding in drug-treated animals. Pimozide appears to selectively blunt the rewarding impact of food and other hedonic stimuli.*

Neuroleptics both alleviate the symptoms of schizophrenia and cause symptoms resembling those of parkinsonism (*1*). Animal studies have not yet suggested important hypotheses for understanding these effects in man, in part because there can be no very adequate model for schizophrenia in lower animals. However, the finding that neuroleptics alter the rewarding quality of intravenous amphetamine injections and intracranial electrical stimulation in rats (*2*) may have implications for understanding complex human behavior. If neuroleptics also block the reward value of natural rewards, this fact may be important for understanding aspects of schizophrenia and parkinsonism. The dysphoria of parkinsonism may reflect a loss of sensitivity to normally rewarding stimuli which parallels the similar loss induced by neuroleptics. The affective abnormalities of schizophrenia may reflect an oversensitivity to such stimuli, which is reversed by neuroleptics. We now report that the neuroleptic pimozide blocks the rewarding (*3*) quality of food for hungry rats, at doses that do not cause incapacitating sedation or motor side effects (*4*).

In the first experiment, four groups of six to eight rats each were tested daily in 45-minute lever-pressing sessions; each lever-press caused delivery of one 45-mg food pellet. Testing occurred 16 to 20 hours after the animals' daily 2-hour period of free food access. When stable lever-pressing for food was established (2 to 3 weeks), the groups were tested in various treatment conditions as follows:

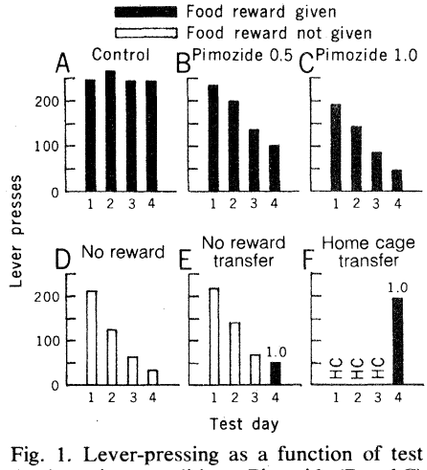

Fig. 1. Lever-pressing as a function of test day in various conditions. Pimozide (B and C) caused animals that received food pellets for lever-pressing to behave like undrugged animals that received no food for responding (D). The control conditions in (E) and (F) are explained in the text. Drug dosage is given as milligrams per kilogram.

one group was tested without reward (the pellet dispenser was not loaded); two groups were tested with normal reward 4 hours after pimozide treatment (0.5 or 1.0 mg per kilogram of body weight); and a control group received normal reward 4 hours after injection with the drug vehicle (*5*).

All groups responded vigorously at the start of the test sessions and slowed to only token responding after 45 minutes of testing. There were no significant differences in the total number of responses or in rates of responding at various times in the sessions (*6*). The fact that pimozide-treated animals responded as often as did the normally rewarded control group shows that there was no significant impairment of normal lever-pressing capacity by these doses of pimozide. However, these initial data do not make clear whether pimozide had any effect on reward function. The pimozide-treated animals, like the nonrewarded animals, might have responded out of habit and not because of food's normal rewarding or response-sustaining quality. It was not possible to say from this experiment whether pimozide-treated animals more closely resembled nonrewarded or normally rewarded animals.

In order to more clearly differentiate the behavior of nonrewarded, normally rewarded, and pimozide-treated rats, additional groups were tested in a second experiment with a repeated-test paradigm; these new groups were tested four times in treatment conditions, with two normally rewarded retraining days between tests.

Performance of nonrewarded animals became progressively less vigorous in this experiment; on the fourth test a mean of less than 30 responses was made whereas more than 200 were made on the first day and in the normally rewarded control condition (Fig. 1, D and A). Animals tested repeatedly with pimozide showed a similar decrease in number of responses per session (Fig. 1, B and C). Thus animals treated with pimozide, like nonrewarded animals, became discriminable from normally rewarded control animals by the fourth test day even though they were not so initially (*7*). The difference between pimozide-treated and control animals was greatest in the high dose condition.

The progressively reduced responding seen in successive pimozide tests cannot be attributed to cumulative drug effects, but must reflect some learning experience in the pimozide tests. This is clear from the performance of two additional groups. One group was given the first three pimozide injections (1.0 mg/kg) in

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the home cage but not tested; the fourth pimozide injection was given in the test situation (the first test for these animals). Thus this group had a different setting for its drug experience, but in all other respects had the same pharmacological history as the animals given four successive pimozide tests. Unlike the successive pimozide test condition, however, this condition produced normal responding on day 4 (Fig. 1F), indistinguishable from that of animals tested with this dose of pimozide on day 1. Thus it was not cumulative pharmacological effects of pimozide that accounted for the minimal day 4 performance in groups with repeated pimozide testing; rather it was a cumulative experiential effect—an effect specific to the consequences of pimozide injections when given in the lever-pressing situation.

Another group of animals was given three tests in the nondrugged, nonrewarded condition, and was given pimozide and normal reward for the first time on day 4. Performance of these animals on day 4 was similar to that of animals that had been treated with drug before the three previous tests (Fig. 1, C and E). Thus pimozide-treated animals showed minimal response perseveration (resistance to extinction) if they had prior testing either with pimozide or without reward. Again, it was not simply the animals' pharmacological history which predicted performance levels on the fourth test day; nonreward experience attenuated subsequent performance with pimozide but pimozide experience in another setting (home cage) had no such effect.

A history of testing with normal reward and pimozide was the apparent equivalent to drug-free testing without reward. Since the animals were capable of responding but did not, it would seem that pimozide blocks the normal response-sustaining feedback property of food reward (*8*).

If this conclusion were valid, it could be demonstrated in a discrete-trial paradigm. Since the reward quality of food is not encountered by the animal until after a response is made, any consequence of an alteration of this quality should be reflected only in performance that follows initial responding, and not in performance which precedes it. In order to facilitate trial-by-trial analysis we tested four additional groups of six rats each in a 2-m straight-alley runway. Ability to initiate voluntary movement and to organize complex motor acts was inferred from measurements of response latency (time to leave the start box) and running speed on each of eight discrete trials per day. Running was rewarded by one 45-mg food pellet on each trial. After running speeds were consistent for three consecutive days one group was tested without reward (no food in goal box) while the other three groups were tested with normal reward after treatment with pimozide (0.5 or 1.0 mg/kg) or injection vehicle (*5*).

Again, performance on initial trials on the first test day did not differ between groups. Throughout the first test day latency and running times of pimozide-treated animals were similar to those of vehicle-treated rats; running time of nonrewarded rats increased on later trials (Fig. 2). All animals were given a retraining session and were retested under the same treatment conditions 1 week after the first test. On test 2 the performance of pimozide-treated animals and of nonrewarded animals progressively slowed, while the performance of vehicle-treated, normally rewarded animals remained stable (*9*). Response decrements were seen with both doses of pimozide, with greater decrements in the higher dose condition. Neither dose of pimozide produced decrements as severe as those seen with no reward.

Again, performance in pimozide-treated animals resembled performance in nondrugged, nonrewarded animals. Initial performance was normal in both cases, but just as an empty food hopper failed to sustain responding in the nonrewarded animals, so did food fail to sustain responding in the pimozide-treated animals. Pimozide-treated animals responded normally before the first taste of food; thus the sensory stimuli in the runway were normally effective, and the animals did not suffer from a general sensory neglect syndrome. Some aspect or consequence of the sensory properties of food, however, was not normally effective in these animals. Thus in the case of the natural reward of food for hungry animals, as in the case of the laboratory rewards of intracranial stimulation and intravenous amphetamine injections (*2*), pimozide blocks the rewarding effectiveness of the normally rewarding event, and it does so at doses that do not impair response capacity.

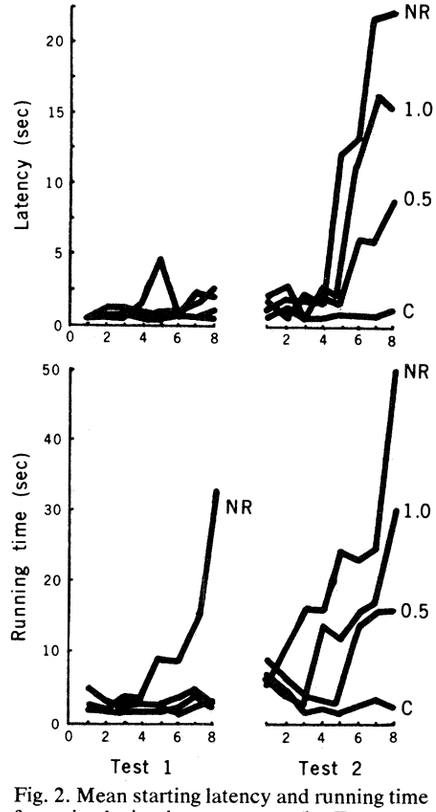

Fig. 2. Mean starting latency and running time for animals in the runway task. Treatment conditions are indicated by letters (*C*, control; *NR*, nonreward) or pimozide dose; see (*9*) for statistical analysis.

Our data suggest that there is a critical dopaminergic link in the neural circuitry that mediates the control of behavior by positive rewards (*10*). This dopaminergic link and its postsynaptic consequences must be synaptically activated by the taste and smell of food if food is to act as a reward for hungry animals. This link must be electrophysiologically or neurochemically activated, respectively, if intracranial stimulation or intravenous amphetamine are to act as rewards (*2*). If the system is blocked pharmacologically, the rewarding impact of these hedonic stimuli is blocked, even though animals are still guided by other sensory stimuli in the environment. Our animals pick up, handle, and eat food with normal facility; thus it is not all sensory aspects of food that lose their impact under pimozide treatment. Rather, pimozide selectively blocks only those properties which give food reward value for hungry animals. In introspective language we would say that neuroleptics appear to take the pleasure out of normally rewarding brain stimulation, take the euphoria out of normally rewarding amphetamine, and take the "goodness" out of normally rewarding food.

These animal studies may provide a useful model for some of the affective aspects of abnormal dopamine function. Degeneration of dopamine-containing cells in parkinsonism is accompanied by profound depression, and L-dopa therapy can cause elation to the point of mania (*11*). Our data suggest that the mood of the parkinsonian patient may derive more from the functional state of a dopaminergic reward substrate than from the patient's cognitive response to the disease and prognosis. The affective

abnormalities in schizophrenia may also be linked to abnormal function in the reward substrate (*12*). If so, our data would suggest that it is a hyperactive dopaminergic reward substrate that typifies the schizophrenic patient and is returned to a normal range of function by neuroleptic treatment (*13*).

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3. The rewarding quality of food is defined as the quality that causes trained animals to continue to perform their learned response and causes untrained animals to learn such responses. We take no position here on issues stemming from attempts to more precisely analyze reward phenomena; for present purposes our usage of "reward" subsumes all of the qualities variously designated as "reinforcement," "incentive," and "priming" in the specialist literature.
4. Neuroleptic drugs block or attenuate lever-pressing habits for a variety of rewards in animals (*2, 14, 15*). Since neuroleptics block central dopamine release and receptors (*16*), this has suggested the possibility that central dopaminergic systems play a critical role in mediation of reward phenomena (*2*). On the other hand, since neuroleptics cause parkinsonian side effects in man, and since Parkinson's disease involves a difficulty in initiation of voluntary movements, it has been suggested that neuroleptics attenuate lever-pressing habits because of some nonselective action on motor mechanisms (*14*).
5. The normally rewarded control group was treated in the same manner as the pimozide groups except that vehicle (tartaric acid) was injected instead of drug.
6. No statistically significant differences between groups were revealed by analysis of variance ($F_{3,26} = 0.26$, not significant).
7. Three-way analysis of variance (treatments by trials by subjects) revealed a significant treatment effect ($F_{3,28} = 12.1$, $P < .001$), a significant trial effect ($F_{3,84} = 49.1$, $P < .001$), and a significant treatment by trials interaction ($F_{9,84} = 5.9$, $P < .001$). The interaction reflected the fact that while there were no significant differences between groups on the first test trial, the nonreward group ($t_{14} = 4.32$, $P < .01$), the 1.0 mg/kg group ($t_{14} = 4.34$, $P < .01$), and the 0.5 mg/kg group ($t_{14} = 2.96$, $P < .01$) each differed from the control group by the fourth trial.
8. Data from Fig. 1E rule out two additional artifactual explanations of data from Fig. 1, B and C. First, repeated drug-food pairings might produce a conditioned taste aversion that accounts for progressively poorer performance with repeated testing in the pimozide groups. In Fig. 1E, however, the same day 4 performance under pimozide was produced in animals that had no prior drug-food pairings; a taste aversion hypothesis cannot account for these data. In a fatigue hypothesis, pimozide would cause abnormal susceptibility to fatigue, and the progressive decrease in responding within sessions would reflect fatigue and not extinction. This hypothesis cannot account for the day 4 performance of Fig. 1E, nor can a hypothesis that drug accumulation causes the performance deficit.
9. Running time data showed a significant trial effect ($F_{7,133} = 6.90$, $P < .001$) and a significant trial by treatment interaction ($F_{21,133} = 2.04$, $P < .001$). For the trial 8 data there were significant differences between control and nonreward scores ($t_{10} = 3.44$, $P < .01$), control and pimozide (1.0 mg/kg) scores ($t_{10} = 2.15$, $P < .01$) but not control and 0.5 mg/kg scores ($t_{10} = 1.29$, not significant). There was considerable variability in latency data, which showed no statistically reliable differences by our tests.
10. We have not seen similar effects of pimozide against opiate reward and thus do not suggest that all positive rewards or hedonic stimuli depend on the integrity of a dopaminergic substrate. Opiates may be unique in their independence of dopamine mechanisms or may represent a class of such rewards; however, further research may implicate brain dopamine in even opiate reward.
11. O. Sacks, *Awakenings* (Duckworth, London, 1973).
12. Several days of treatment with neuroleptic drugs are required before therapeutic effects are seen [P. Lerner, P. Nosé, E. K. Gordon, W. Lovenberg, *Science* **197**, 181 (1977)]. Similarly, in our paradigm pimozide did not reach maximum behavioral effectiveness until the fourth day of testing or later. If schizophrenia involves the abnormal function of a dopaminergic reward substrate, an unlearning process like that caused by repeated pimozide testing might account in part for the delayed onset of neuroleptic therapeutic effects.
13. This runs opposite to earlier speculations linking abnormal reward mechanisms to schizophrenia. Our view is that the reward system is hyperactive or hyperresponsive in schizophrenia, where the earlier view was that a (noradrenergic) reward system might be partially degenerated in schizophrenia [L. Stein and C. D. Wise, *Science* **171**, 1032 (1971)]. Either hyperactivity or hypoactivity of a central reward substrate could explain the observation that while schizophrenics appear to have a normal range of affective responses, these responses are typically inappropriate to the environmental situation [J. D. Page, *Psychopathology* (Aldine, New York, 1971), p. 191].
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17. Supported by the Non-Medical Use of Drugs Directorate and the National Research Council of Canada. We thank Janssen Pharmaceuticals for donating the pimozide; F. E. Bloom, S. L. Foote, and S. J. Henriksen for criticisms of the manuscript; and T. Gray for use of equipment.

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Physiological Basis of Anisometropic Amblyopia

Abstract. *In the visual cortex of kittens that have received their only visual experience while wearing a high-power lens before one eye, most neurons are dominated by input from the normal eye. Moreover, contrast sensitivity and resolving power are lower for stimulation through the originally defocused eye, mimicking psychophysical results from human anisometropic amblyopes.*

Anisometropic amblyopia is a developmental disorder of vision: babies with uncorrected differences in refractive power in the two eyes are often left later in life with defective vision in one eye, which cannot then be rectified optically and which is not caused by any obvious retinal or ocular pathology (*1*).

Brief occlusion of one eye (*2, 3*) even with a translucent diffuser (*4*) causes neurons in the visual cortex of kittens or monkeys (which normally often receive input from both eyes) to become almost totally dominated by the nondeprived eye. Such developmental changes in the ocular dominance of cortical cells are restricted to a postnatal sensitive period (*5*); this phenomenon therefore provides an animal model for the profound amblyopia that occurs if one eye is totally occluded within the first few years of a baby's life (*6*).

It is tempting to think that anisometropic amblyopia is essentially similar in its causes to the amblyopia caused by occlusion. Because the two eyes are not normally capable of adopting different accommodative states, it is assumed that an anisometropic baby sets its accommodative effort to bring images to a sharp focus in one eye, leaving the other retinal image inevitably and habitually blurred. The constant defocus (*7*) in one eye will reduce the contrast (*8*) of its image, especially for high spatial frequencies (*9*); neurons in the visual pathway (particularly those with very small receptive fields of higher resolving power, near the visual axis) should thus be deprived of adequate stimulation through that eye, as suggested by Ikeda and Wright (*10*). We have recorded from cells in the visual cortex of kittens reared with artificial anisometropia and have found changes in ocular dominance and in the spatial resolution of neurons which are similar to certain characteristics of human amblyopia.

Five kittens were reared in a totally dark room except for exposure in a well-lit environment for an hour or two each day, when each animal wore a pair of goggles (*4*) containing a high-power negative spherical lens [−8 diopters for three animals, −12 for the other two (*11–13*)] in front of one eye. Retinoscopic examination showed that the accommodative state of the animals was appropriate for the eye with no lens in front of it and did not differ between the two eyes. The kittens soon grew accustomed to the goggles and would run, jump, and play with each other with no evidence of discomfort. They each received a total of

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