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How Operant Conditioning Can Contribute to Behavioral Toxicology

by Victor G. Laties*

Operant conditioning can contribute to the development of behavioral toxicology in many ways. Its techniques are useful in training animals in the various behaviors the toxicologist may wish to study. They make possible the sophisticated assessment of sensory functioning. Operant conditioners excel at using schedules of intermittent reinforcement to create the type of stable animal performance needed in studying substances that produce effects only after prolonged exposure. Schedule-controlled behavior also helps elucidate the precise behavioral mechanisms involved in toxicity. In the early assessment of toxic substances a judiciously chosen sample of schedule-controlled performances may provide the best estimate whether the integrity of complex operant behavior remains unchanged. The development of improved behavioral techniques and computer technology promises to bring down the cost of such assessment.

The six papers that follow demonstrate how animal behaviorists can contribute to the study of toxic substances. Stebbins and Rudy (1), Evans (2), and Wood (3) discuss methods used to study audition, vision, and olfaction, respectively. Thompson and Moerschbaeher (4) present one approach to the study of how animals learn. Annau (5) summarizes work on the use of reinforcing brain stimulation in toxicology. Dews (6) describes a method for assaying behavioral effects in mice that have been taught to perform on a pair of simple reinforcement schedules. By and large, the methodology underlying their experimental work is derived from an area within psychology called operant conditioning. The practitioners of the art, operant conditioners, particularly emphasize the study of learned as opposed to reflex or innate behavior. They have a healthy respect for the great power that the immediate outcome of behavior has in determining the subsequent frequency of similar behavior. Outcomes that strengthen behavior—increase its frequency—are called reinforcers. Operant conditioners make their contributions to fields such as pharmacology, physiology, and toxicology by exploiting the principle of reinforcement in a myriad of wondrous ways (7-11). Some of these will be touched on here during brief discussions of four broad areas: (1) the pro-

duction of behavior; (2) measurement of sensitivity to environmental stimulation; (3) schedules of reinforcement; (4) assessment of behavioral toxicity. The general principles of operant conditioning cannot be discussed here but many excellent introductions are available (7, 8). Shorter introductions, written for those particularly interested in behavioral pharmacology, have also appeared (9-11).

Production of Behavior

A great strength of operant conditioners lies in their ability to manufacture behavior to specifications manipulating the way an animal's responses pay off. The general rule is that behavior of a specified form can be molded by reinforcing instances that more and more closely approximate the behavior we wish eventually to produce (12). Naturally, due respect must be paid to the biological capabilities and limitations of the animal (13-15). By employing this principle, operant conditioners can, for example, teach animals to respond rapidly or slowly (16), to exert great or small amounts of force (17-19), to hold down a lever for a specified length of time (20), to pause for a specified time before responding (21, 22) or to emit a specified number of responses before doing something else (23-25). In short, it is possible to shape the temporal and intensive aspects of the animal's responding in creative ways to produce many fascinating and useful types of behavior. A good description of more esoteric

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behaviors that animals have been taught with these methods appears in Lubow (26).

Suppose, for example, the toxicologist is interested in how a chemical affects the ability of an animal to engage in repetitive strenuous physical activity. One alternative is a treadmill on which the animal is forced to run in order to keep from being tumbled against the end of the box or from being shocked. But suppose one wishes to avoid the physiological effects of tumbling or shocking. Or suppose the toxicologist would simply rather use positive reinforcement. Davis et al. (27), taught squirrel monkeys to run up and down a 3-m vertical pole, pressing levers at both ends in order to earn food pellets. They found that the monkeys would work steadily on this task for a 45-min period, ascending and descending about three times per minute. This is a lot of work; the monkey climbed about 400 m. The experimenters chose a reinforcement schedule producing a steady, rather slow rate of performance. But they could just as easily have produced a much higher or much lower rate. The point is that they induced work by a small monkey at a pace called for by the particular problem facing them without subjecting the animal to stressful coercion.

Measurement of Sensitivity to Environmental Stimulation

Operant conditioners can also teach animals to respond differentially to various physical dimensions of their environment. They do so by reinforcing one response in the presence of a particular stimulus and another response in its absence. The stimulus then comes to control responding and this can be used to answer questions about the special senses, that is, what the animals see, hear, smell, etc. Most toxicologists are unacquainted with the full flowering of this technology. A few years ago, Herbert Stokinger, writing of the limitations of animal behavioral toxicology, (28), said: "Resorting to animal experimentation instead of man eliminates one whole area of response, namely the organoleptic or sensory response, the entire area of subjective effects of irritation, headache, nausea, dizziness, and the like; animals simply can't communicate these finer sensibilities."

Stokinger was reflecting an opinion also held by Claude Bernard over 100 years ago (29): "... experimental study of sense organs . . . must be made on man . . . because animals cannot directly account to us for the sensations which they experience." But much progress has been made over the past century, and an excellent account of the development of what has come to be known as "animal psychophysics" can be found in Stebbins' in-

troductory chapter in his book of that title (30). Stokinger is much too pessimistic. We can teach animals to "talk," as it were, telling us whether or not they can see or hear or smell whatever we present. And, by varying our stimuli appropriately, we can measure how well they sense their environment (31, 32). We can establish the minimum detectable energy level—the absolute threshold. We can also establish how easily animals detect small increments or decrements—the difference limen. This field is just maturing; three of the contributions to this symposium discuss approaches to the measurement of sensory phenomena (1–3).

Even more challenging than the measurement of the special senses is the measurement of an animal's reaction to internal stimulation. How can we study, to quote Stokinger again, "... the entire area of subjective effects of irritation, headache, nausea, dizziness, and the like; . . .?" (28). Here, Stokinger's doubts are more relevant, for little work has been done to put such study on firm scientific footing. Interoceptive events, however, can serve as discriminative stimuli; the slight inflation of a balloon in the small intestine, for example, can so function (33). An animal can also be taught to react according to which drug it has just been given (34, 35). It should be possible to show how an animal is reacting to an unknown drug or toxic substance by first training it to react to agents with known effects. It might, for instance, be possible first to make exposure to an appropriate level of a known headache-inducing substance or procedure a discriminative stimulus for responding on one lever. Responding on a second lever would be appropriate when a control substance has been given. If the animal then responds on the first lever when presented with a test substance, we may be justified in suspecting that its head aches. This type of study of private events is rare, but the theoretical basis of such study is available (36).

The problem of measuring the strength of irritating substances can be approached in a similar fashion but also may be studied through the use of avoidance or escape conditioning if the substances are sufficiently aversive. Wood (3) expands upon the latter theme.

Schedules of Reinforcement

Operant conditioners excel at producing the stable animal behavior that typically is maintained when reinforcers are available only intermittently. On such schedules, characteristic patterns of responding emerge that are quite specific to the contingencies of reinforcement (16, 37–40). These schedule-controlled operant baselines are stable,

not only within single experimental sessions but also from day to day and even from month to month. With many substances, such as carbon monoxide (41) the focus of interest lies in following the development of toxicity during a short exposure period. With others, such as methylmercury (42) the questions of concern arise from chronic actions. In both cases, stable behavioral baselines aid in acquiring useful time-effect data.

Schedule-controlled performances are also useful in the quest for the behavioral mechanisms of action, that is, just which aspects of behavior are most relevant to how a substance produces its effects (10, 11, 43-48). Does it modify the way discriminative stimuli modulate the performance (24, 25, 49-51)? Does it change the strength of the reinforcer (52)? Does it exert its effect by changing some aspect of the motor performance itself (18)? To what extent does the effect depend upon the underlying response rate (53)? Careful parametric studies of a variety of schedule performances have made crucial contributions to the science of behavioral pharmacology. Rather little of this type of work has yet been done in behavioral toxicology.

Reinforcement schedules have not yet contributed much to the study of toxic effects on the acquisition of new behavior, the phenomenon called "learning." There can be as many ways of studying learning as there are ways of confronting organisms with changed reinforcement contingencies and then watching them adapt to the new contingencies (54). Many such methods have been devised, but most have not proved useful when a single subject must be used over and over again, as when one wishes to study the slow development of a learning disability during exposure to a poison. Thompson and Moerschbaecher (4) describe a method based on work by Boren and Devine (55) in which the subject relearns a new sequence of responses each day. Although it has been used in pharmacological research, so far only one group in behavioral toxicology has used this promising approach (56).

Schedules can also help the worker interested in how different reinforcers reveal toxicity. Over 20 years ago, Olds and Milner (57) showed that a rat would press a lever that produced electrical stimulation of the septum. This phenomenon has been the subject of thousands of studies (58). Only recently have toxicologists begun to use it. Annau and his colleagues have examined the effect of carbon monoxide and trichlorethylene (5). Brain stimulation as a reinforcer has a potentially important feature not yet fully exploited. Although type of reinforcer usually has not proved very important in determining the effects of drugs (11, 59), it may be more important with toxic chemicals. Many sub-

stances interfere with appetite or produce weight loss when given chronically. Studies comparing toxic effects on performance baselines supported by different reinforcers would be valuable in establishing the role of the reinforcer itself in determining the nature of the toxicity.

A toxic substance can itself serve as a reinforcer when delivered according to a schedule. Wood (3) describes work with toluene, a solvent that sometimes serves as the vehicle for the ingestion of more toxic compounds such as those which appear in household aerosol products. Toluene is also important to toxicologists because of its abuse by sniffers and its widespread use in industry. Many chemicals are capable of sustaining behavior, but most work has been done on drugs that are taken orally, such as alcohol, or intravenously, such as morphine (60). Inhaled substances only recently attracted the attention of scientists who were interested in substance abuse and wished to study their reinforcing properties in animals (61-64). Probably the most important toxic substance man inhales voluntarily is tobacco smoke. Cigarettes produce acidic smoke that does not yield its nicotine readily to the mucous membranes of the mouth (65). However, the nicotine is readily absorbed if the smoker inhales the smoke into the lungs. Not surprisingly, cigarette smokers do this and thereby give themselves increased amounts of carbon monoxide and of other tobacco constituents such as tars. Thus, deep inhalation, reinforced by nicotine, leads to exposure to toxic substances that may have more important consequences than the nicotine itself. Ironically, reductions in nicotine content may lead to increases in inhalation of these substances as the person attempts to maintain a constant intake of nicotine (66).

The stability of schedule-controlled operant performance can be valuable in reducing the variability of sensory or physiological measures; anyone wanting to make repeated determinations in the awake animal would be well advised to consider the advantages offered by these straightforward methods. It is possible, for example, to teach a monkey to gaze steadily at a spot of light while a spectral sensitivity curve is determined (67). Another example is given by Stebbins and Rudy (1) in their contribution to this symposium; they describe how a suitably trained monkey patiently presents auditory stimuli to itself.

Reinforcement schedules have served in pharmacology as ways of generating sustained functional changes that could then be studied after drug administration. Hypertension, for example, can be induced in rats (68) and monkeys (19, 69, 70). These methods will undoubtedly prove equally important in toxicology.

Assessment of Behavioral Toxicity

The role of operant conditioning during early toxicity screening contrasts sharply with its role in the development of basic information in behavioral toxicology. Operant conditioners often will not test a compound until considerable data have been accumulated on simple reflexes and unlearned behavior (71, 72). At the very least, the kind of information gathered in the course of routine toxicity testing will be available; some will have been recorded during the determination of acute lethality or during subchronic ingestion studies. Massive behavioral effects will have been detected. Toxicologists interested in the assessment of hazard will not always need sophisticated information about the behavioral effects of a substance. Something akin to Lincoln Moses's *Principle of the Blunt Ax* applies here: "If the ax chopped down the tree, it was sharp enough." Moses (73) was pointing out that under some circumstances a simple statistical test might demonstrate the reliability of a difference; a complicated analysis would then be a waste of time. Similarly, the industrial toxicologist will not be interested in subtle behavioral effects of a carcinogen.

However, operant conditioners will contribute to relatively early toxicity assessment by examining important compounds that have shown no untoward effects in the initial screening tests. Ideally, to establish an unchallengeable "no observed effects level" it would be necessary to gather information about every type of behavior that an animal can display. Since that is obviously not possible, we must settle for a judiciously chosen sample. To start, a combination of schedule-controlled behaviors could be used (71). Indeed, a very common first look at the effects of pharmacological agents on complex learned behavior involves the use of a multiple schedule consisting of fixed interval and fixed ratio components. Very different variables are important in controlling performance on these two schedules. With the interval schedule, reinforcement is mainly on the basis of time; with the ratio, it is on the basis of number of responses (16, 37-40). The two schedules differ greatly in sensitivity to drugs (74), and it is this difference that probably accounts for the popularity of this particular combination in behavioral pharmacology. This multiple schedule also has some history of use in toxicology (6, 75-79). With such schedules, each individual schedule is controlled by its own distinctive stimulus, usually a light or tone, and the animal alternates between the two schedules of reinforcement, spending only a few minutes working on one before the signal evoking the other appears. In this way the experimenter gathers time-effect data on two types of behavior almost simultaneously. In

studying substances that need days or even weeks of exposure before an effect appears, the animal is asked to perform for a short period each day and changes in performance in both components are monitored. But there is nothing sacrosanct about this particular combination of schedules and it would be unfortunate indeed for behavioral toxicology if regulatory agencies or mere custom came to dictate the use of a small subset of the large number of potentially useful methods that can be developed using schedules of reinforcement. As Dews says in his contribution to this symposium, "Rules of testing promulgated today have an infinitesimal chance of specifying methods that are optimal, and the required use of less good methods will consume the resources that should be going into the development of better ones" (6).

We should note that one of the most commonly used preparations in Soviet behavioral toxicology resembles a multiple schedule (80). In the Kotljarevskij chamber, the rat opens the door to the food container with its head. It is taught to do this after a bell has rung or while a light is on, but not while a buzzer is sounding. Rate of response is not taken as the primary datum and degree of automation is much less than is typical in operant conditioning work in this country, but the interest is in operant behavior, and the performance is put under strong stimulus control. Very little work is done in Soviet toxicology on what is known here as respondent or classical conditioning (80).

For many toxic substances, the first laboratory work in behavioral toxicology will come after an environmental disaster alerts the scientific community to the compound's general effects. Witness, for instance, the recent spate of activity with methylmercury after the poisoning incidents in Japan and Iraq (42). Operant conditioning methods will then prove essential in answering specific questions that arise from clinical findings.

The cost and efficiency of behavioral methods concern some toxicologists who contemplate the burgeoning growth of behavioral toxicology. The argument is sometimes made that operant methods, in particular, are too expensive. This argument should diminish in importance over the next few years. Continued development of behavioral methodology will make it easier to produce reliable performance baselines; these should, in turn, be even more sensitive to small amounts of toxic substances. Any decrease in variability should lead to a decrease in the number of animals needed to establish credible results and cost should come down. Perhaps emphasis on refinement of methods is the most expeditious path to take in view of the argument that there may be limits to the increase in sensitivity yielded by increased numbers of animals (6). The continued development of computer

technology will make it easier to control the experimental environments and collect the data for behavioral experiments (81, 82). A dozen animals, each working in its own operant chamber, can be monitored simultaneously with a mini-computer. Programming is in a relatively simple language, with the data collected in such a form as to be readily analyzed (83, 84). Thus, the efficiency of operant procedures should increase with time.

This trend would be hastened if more effort went into methodological studies in behavioral toxicology. Most workers including operant conditioners, concentrate on substances and choose methods from the literature, using what others have used before them. Perhaps this is inevitable in a field under great pressure to deliver quick answers. But time and money must also be devoted to developing more sensitive methods and refining those now in use. This assumes extra importance given the present state of disastrous underfunding of basic research on animal behavior. We are now living off our intellectual capital and those interested in the health of behavioral toxicology should recognize that fact. The refinement of current methods would be aided greatly by analysis of behavioral situations to discover which aspects of behavior are most sensitive to particular toxic substances. This type of parametric study is now rare even in behavioral pharmacology. It usually is not feasible to spend much time in such work before starting to study a substance. Nor is it usually possible to study each of several levels of the behavioral variable at each of several exposure levels of a substance. A modest positive step would be to try always to incorporate into each study two values of any behavioral variable—two different fixed ratio sizes, two levels of shock intensity, and so forth. In this way, some knowledge of the importance of parameter value would come out of the work. And, while data from only two values would be unsatisfactory for establishing a definitive relationship, two values would at least point the next investigator in the right direction. For instance, if greater sensitivity to toxic insult occurred at the lower shock intensity, the next study could move even lower. In this way, more sensitive test procedures would evolve out of normal laboratory behavior.

Of course, the same general idea applies to investigators using other approaches. If all of us contributed in this fashion to the search for the interactions between parameter value and sensitivity, useful early assessment methods would be developed more expeditiously than is now the case. Work of this sort would cost a bit more but would be likely to pay good dividends in enhanced future productivity. Operant conditioners, whose training usually

stresses this type of close experimental analysis of behavior, will certainly contribute their fair share to the rapidly growing field of behavioral toxicology.

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REFERENCES

1. Stebbins, W. C., and Rudy, M. C. Behavioral ototoxicology. *Environ. Health Perspect.* 26: 43 (1978).
2. Evans, H. L. Behavioral assessment of visual toxicity. *Environ. Health Perspect.* 26: 53 (1978).
3. Wood, R. W. Stimulus properties of inhaled substances. *Environ. Health Perspect.* 26: 69 (1978).
4. Thompson, D. M., and Moerschbaecher, J. M. Operant methodology in the study of learning. *Environ. Health Perspect.* 26: 77 (1978).
5. Annau, Z. Electrical self-stimulation of the brain: a model for the behavioral evaluation of toxic agents. *Environ. Health Perspect.* 26: 59 (1978).
6. Dews, P. B. Epistemology of screening for behavioral toxicity. *Environ. Health Perspect.* 26: 37 (1978).
7. Catania, A. C., Ed. *Contemporary Research in Operant Behavior*. Scott, Foresman and Co., Glenview, Ill., 1968.
8. Reynolds, G. S. *A Primer of Operant Conditioning*. Scott, Foresman and Co., Glenview, Ill., 1968.
9. Thompson, T., and Schuster, C. R. *Behavioral Pharmacology*. Prentice-Hall, Inc., Englewood Cliffs, N. J., 1968.
10. Iversen, S. D., and Iversen, L. L. *Behavioral Pharmacology*. Oxford University Press, New York, 1975.
11. Kelleher, R. T., and Morse, W. H. Determinants of the specificity of behavioral effects of drugs. *Ergeb. Physiol. Biol. Chem. Exp. Pharmacol.* 60: 1 (1968).
12. Skinner, B. F. *The Behavior of Organisms: An Experimental Analysis*. Appleton-Century-Crofts, New York, 1938.
13. Skinner, B. F. The phylogeny and ontogeny of behavior. *Science*, 153: 1205 (1966); reprinted in *Contingencies of Reinforcement: a Theoretical Analysis*, B. F. Skinner. Appleton-Century-Crofts, New York, 1969, Chapt. 7.
14. Seligman, M. E. P., and Hager, J. L., Eds. *Biological Boundaries of Learning*. Appleton-Century-Crofts, New York, 1972.
15. Shettleworth, S. Constraints on learning. In: *Advances in the Study of Behavior*, Vol. 4, D. S. Lehrman, R. A. Hinde, and E. Shaw, Eds., Academic Press, New York, 1972.
16. Ferster, C. B., and Skinner, B. F. *Schedules of Reinforcement*. Appleton-Century-Crofts, New York, 1957.
17. Notterman, J. M., and Mintz, D. E. *Dynamics of Response*. Wiley, New York, 1965.
18. Falk, J. L. Drug effects on discriminative motor control. *Physiology and Behavior* 4: 421 (1969).
19. Dews, P. B., and Herd, J. A. Behavioral activities and cardiovascular function: effects of hexamethonium on cardiovascular changes during strong sustained static work in rhesus monkeys. *J. Pharmacol. Exptl. Therap.* 189: 12 (1974).

20. McMillan, D. E., and Patton, R. A. Differentiation of a precise timing response. *J. Exptl. Anal. Behav.* 8: 219 (1965).
21. Sidman, M. Technique for assessing the effects of drugs on timing behavior. *Science* 122: 925 (1955).
22. Weiss, B., and Laties, V. G. Reinforcement schedule generated by an on-line digital computer. *Science* 148: 658 (1965).
23. Mechner, F. Probability relations within response sequences under ratio reinforcement. *J. Exptl. Anal. Behav.* 1: 109 (1958).
24. Laties, V. G. The modification of drug effects on behavior by external discriminative stimuli. *J. Pharmacol. Exptl. Therap.* 183: 1 (1972).
25. Laties, V. G. The role of discriminative stimuli in modulating drug action. *Fed. Proc.* 34: 1880 (1975).
26. Lubow, R. E. *The War Animals*. Doubleday, New York, 1977.
27. Davis, T. R. A., Kensler, C. J., and Dews, P. B. Comparison of behavioral effects of nicotine, *d*-amphetamine, caffeine and dimethylheptyl tetrahydrocannabinol in squirrel monkeys. *Psychopharmacologia* 32: 51 (1973).
28. Stokinger, H. E. Behavioral toxicology in the development of threshold limit values. In: *Behavioral Toxicology*, C. Xintaras, B. L. Johnson, and I. deGroot, Eds., U. S. Government Printing Office, Washington, D. C., 1974, pp. 18-19.
29. Bernard, C. *An Introduction to the Study of Experimental Medicine*, H. C. Greene, (transl.), MacMillan, New York, 1927, p. 125.
30. Stebbins, W. C. Principles of animal psychophysics. In: *Animal Psychophysics: The Design and Conduct of Sensory Experiments*, W. C. Stebbins, Ed., Appleton-Century-Crofts, New York, 1970.
31. Stebbins, W. C., Ed. *Animal Psychophysics: The Design and Conduct of Sensory Experiments*, Appleton-Century-Crofts, New York, 1970.
32. Appel, J. B., and Dykstra, L. A. Drugs, discrimination, and signal detection theory. In: *Advances in Behavioral Pharmacology*, Vol. 1, T. Thompson and P. B. Dews, Eds., Academic Press, New York, 1977.
33. Slucki, H., Adam, G., and Porter, R. W. Operant discrimination of an interoceptive stimulus in rhesus monkeys. *J. Exptl. Anal. Behav.* 8: 405 (1965).
34. Schuster, C. R., and Balster, R. L. The discriminative stimulus properties of drugs. In: *Advances in Behavioral Pharmacology*, Vol. 1, T. Thompson and P. B. Dews, Eds., Academic Press, New York, 1977.
35. Ho, B. T., Richards, D. W. III, and Chute, D. L., Eds., *Drug Discrimination and State Dependent Learning*. Academic Press, New York, 1978.
36. Skinner, B. F. *Science and Human Behavior*, Macmillan, New York, (1953), Chapt. 17.
37. Morse, W. H. Intermittent reinforcement. In: *Operant Behavior: Areas of Research and Application*, W. K. Honig, Ed., Appleton-Century-Crofts, New York, 1966, Chapt. 3.
38. Dews, P. B., and DeWeese, J. Schedules of reinforcement. In: *Handbook of Psychopharmacology*, Vol. 7: Principles of Behavioral Pharmacology, L. L. Iversen, S. D. Iversen, and S. H. Snyder, Eds., Plenum Press, New York, 1977.
39. Schoenfeld, W. N., Ed. *The Theory of Reinforcement Schedules*, Appleton-Century-Crofts, New York, 1970.
40. Zeiler, M. D. Schedules of reinforcement: the controlling variables. In: *Handbook of Operant Behavior*, W. K. Honig and J. E. R. Staddon, Eds., Prentice-Hall, Englewood Cliffs, N. J., 1977.
41. Laties, V. G. Behavioral effects. In: *Carbon Monoxide*, National Academy of Sciences, Washington, D. C., 1977, pp. 127-151.
42. Evans, H. L., Laties, V. G., and Weiss, B. Behavioral effects of mercury and methylmercury. *Fed. Proc.* 34: 1858 (1975).
43. Thompson, T., and Boren, J. J. Operant behavioral pharmacology. In: *Handbook of Operant Behavior*, W. K. Honig and J. E. R. Staddon, Eds., Prentice-Hall, Englewood Cliffs, N. J., 1977.
44. Laties, V. G., and Weiss, B. Behavioral mechanisms of drug action. In: *Drugs and the Brain*, P. Black, Ed., Johns Hopkins Press, Baltimore, 1969, p. 115.
45. Dews, P. B. Analysis of effects of psychopharmacological agents in behavioral terms. *Fed. Proc.* 17: 1024 (1958).
46. Harvey, J. A., Ed. *Behavioral Analysis of Drug Action: Research and Commentary*, Scott, Foresman and Co., Glenview, Ill., 1971.
47. Weiss, B., and Laties, V. G., Eds. *Behavioral Pharmacology: The Current Status*, Plenum Press, New York, 1976.
48. Morse, W. H., and Kelleher, R. T. Schedules as fundamental determinants of behavior. In: *The Theory of Reinforcement Schedules*, W. N. Schoenfeld, Ed., Appleton-Century-Crofts, New York, 1970, p. 139.
49. Laties, V. G., and Weiss, B. Influence of drugs on behavior controlled by internal and external stimuli. *J. Pharmacol. Exptl. Therap.* 152: 388 (1966).
50. McKearney, J. W. Rate-dependent effects of drugs: modification by discriminative stimuli of the effects of amobarbital on schedule-controlled behavior. *J. Exptl. Anal. Behav.* 14: 167 (1970).
51. Dews, P. B. Studies on behavior: II. The effects of pentobarbital, methamphetamine and scopolamine on performances in pigeons involving discriminations. *J. Pharmacol. Exptl. Therap.* 115: 380 (1955).
52. Stein, L. Self-stimulation of the brain and the central stimulant action of amphetamine. *Fed. Proc.* 23: 836 (1964).
53. Dews, P. B., and Wenger, G. R. Rate-dependency of the behavioral effects of amphetamine. In: *Advances in Behavioral Pharmacology*, Vol. 1, T. Thompson and P. B. Dews, Eds. Academic Press, New York, 1977.
54. Sidman, M. *Tactics of Scientific Research*, Basic Books, New York, 1960.
55. Boren, J. J., and Devine, D. D. The repeated acquisition of behavioral chains. *J. Exptl. Anal. Behav.* 11: 651 (1968).
56. Leander, J. D., McMillan, D. E., and Barlow, T. S. Chronic mercuric chloride: behavioral effects in pigeons. *Environ. Res.* 14: 424 (1977).
57. Olds, J., and Milner, P. Positive reinforcement produced by electrical stimulation of septal area and other regions of the rat brain. *J. Comp. Physiol. Psychol.* 47: 419 (1954).
58. Mogenson, G., and Cioe, J. Central reinforcement, a bridge between brain function and behavior. In: *Handbook of Operant Behavior*, W. K. Honig and J. E. R. Staddon, Eds., Prentice-Hall, Englewood Cliffs, N. J., 1977.
59. Morse, W. H., McKearney, J. W., and Kellerher, R. T. Control of behavior by noxious stimuli. In: *Handbook of Psychopharmacology*, Vol. 7, Principles of Behavioral Pharmacology, L. L. Iversen, S. D. Iversen, and S. H. Snyder, Eds., Plenum Press, New York, 1977.
60. Cotton, M. deV., Ed., *Symposium on control of drug-taking behavior by schedules of reinforcement*. *Pharmacol. Revs.* 27: 287 (1975).
61. Yanagita, T., et al. Voluntary inhalation of volatile anesthetics and organic solvents by monkeys. *Japan. J. Clin. Pharmacol.* 1: 13 (1970).
62. Wood, R. W., Grubman, J., and Weiss, B. Nitrous oxide self-administration by the squirrel monkey. *J. Pharmacol. Exptl. Therap.* 202: 491 (1977).
63. Jarvik, M. E. Tobacco smoking in monkeys. *Ann. N. Y. Acad. Sci.* 142: 280 (1967).
64. Rucker, W. L. An analysis of the cigarette puffing response in woolley monkeys. Unpublished doctoral dissertation, University of Rochester, 1970.
65. Russell, M. A. H. Tobacco smoking and nicotine depen-

- dence. In: *Research Advances in Alcohol and Drug Problems*, Vol. 3, R. J. Gibbins, Ed., Wiley, New York, 1976.
66. Schachter, S. Studies of the interaction of psychological and pharmacological determinants of smoking. I. Nicotine regulation in heavy and light smokers. *J. Exptl. Psychol: Gen.* 106: 5 (1977).
 67. Crawford, M. L. J. Behavioral control of visual fixation of the rhesus monkey. *J. Exptl. Anal. Behav.* 25: 113 (1976).
 68. Falk, J. L., Tang, M., and Forman, S. Schedule-induced chronic hypertension. *Psychosom. Med.* 39: 252 (1977).
 69. Brady, J. V., Anderson, D. E., and Harris, A. H. Behavior and the cardiovascular system in experimental animals. In: *Neural and Psychological Mechanisms in Cardiovascular Disease*, A. Zanchetti, Ed., Casa Editrice, Il Ponte, Milano, Italy, 1972.
 70. Kelleher, R. T., Morse, W. H., and Herd, J. A. Effects of drugs on schedule-controlled behavior and cardiovascular function in the squirrel monkey. In: *Behavioral Toxicology*, B. Weiss and V. G. Laties, Eds., Plenum Press, New York, 1975.
 71. Laties, V. G., et al. Behavioral toxicity tests. In: *Principles and Procedures for Evaluating the Toxicity of Household Substances*; National Academy of Sciences, Washington, D. C. 1977, Chapt. 8, pp. 111-118.
 72. Weiss, B., et al. Effects on behavior, In: *Principles for Evaluating Chemicals in the Environment*, National Academy of Sciences, Washington, D. C., 1975, Chapt. 11, p. 62.
 73. Moses, L. E. Quoted in: *Biostatistics, An Introductory Text*, A. Goldstein, MacMillan, New York, 1964, p. 62.
 74. Dews, P. B. Studies on behavior: I. Differential sensitivity to pentobarbital of pecking performance in pigeons depending on the schedule of reward. *J. Pharmacol. Exptl. Therap.* 113: 393 (1955).
 75. Levine, T. E. Effects of carbon disulfide and FLA-63 on operant behavior in pigeons. *J. Pharmacol. Exptl. Therap.* 199: 669 (1976).
 76. Wenger, G. R., and Dews, P. B. The effects of phencyclidine, ketamin, *d*-amphetamine and pentobarbital on schedule-controlled behavior in the mouse. *J. Pharmacol. Exptl. Therap.* 196: 616 (1976).
 77. Anger, W. K., and Lynch, D. W. The effect of methyl *n*-butyl ketone on response rates of rats performing on a multiple schedule of reinforcement. *Environ. Res.* 14: 204 (1977).
 78. Armstrong, R. D., et al. Behavioral changes in the pigeon following inhalation of mercury vapor. *Am. Ind. Hyg. Assoc. J.* 24: 366 (1963).
 79. Barthalmus, G. T., et al. Chronic effects of lead on schedule-controlled pigeon behavior. *Toxicol. Appl. Pharmacol.* 42: 271 (1977).
 80. Pavlenko, S. M. Methods for the study of the central nervous system in toxicological tests. In: *Methods Used in the USSR for Establishing Biologically Safe Levels of Toxic Substances*. World Health Organization, Geneva, 1975, p. 86.
 81. Weiss, B. *Digital Computers in the Behavioral Laboratory*, Appleton-Century-Crofts, New York, 1973.
 82. Wood, R. W., Sette, W. F., and Weiss, B. Interfacing the experimenter to the computer: languages for psychologists. *Am. Psychologist* 30: 230 (1975).
 83. Snapper, A. G., et al. Time-sharing in a small computer based on a behavioral notation system. In: *Digital Computers in the Behavioral Laboratory*, B. Weiss, Ed., Appleton-Century-Crofts, New York, 1973.
 84. Snapper, A. G., et al. *The Sked Software System (Manual 2) OS/8 and Time Share SKED*, State Systems, Inc., P. O. Box 2215, Kalamazoo, Mich., 1976.