

13

## Learning and Behavior Change as Neurotoxic Endpoints

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- **The Concurrent Schedule of Reinforcement**
  - **Quantification of Steady-State Performance**
    - Simple Matching
  - **Learning and Behavior Change**
    - Key Elements to the Study of the Role of Consequences in Behavior Change
  - **Quantification of Transitions**
  - **Other Procedures for Studying Behavior in Transition**
  - **Concluding Remarks: Behavioral Mechanisms of Toxicity**
  - **Acknowledgment**
  - **References**
- 

Perhaps the most insidious forms of neurotoxicity are those that disrupt learning. The manifestations in exposed people are not always obvious disturbances, like the profound sensory or motor losses or peripheral neuropathies caused by some neurotoxicants. Subtle, seemingly nonspecific effects can be difficult to spot and once spotted may not be acted on readily (Berney, 1993; Rosner and Markowitz, 1985). Exposure to a variety of substances disrupts learning, or its outcome, even in the absence of gross changes in other health indices.

An impediment to identifying neurotoxicants that disrupt learning processes appears to lie in difficulties in conducting and especially interpreting experiments with nonhuman species that demonstrate such deficits. Most agree that a serious threat is presented by a chemical that causes profound sensory or motor disturbances and that such data should be incorporated into risk assessments. Considerable debate arises, however, when confronted with the sorts of disturbances shown in animals poisoned with lead, a neurotoxicant representative of compounds that produce learning deficits. Concern over lead's neurotoxicity arises largely over its effects on children's scores on IQ tests (Needleman et al., 1979; Weiss, 1988) and, relatedly, its effects on the classroom comportment of exposed children (Needleman et al., 1979). While such

effects might seem impossible to model in nonhuman species, all of the criteria required to identify a compound as a sensory or motor neurotoxicant also apply to lead: behavioral effects are dose related; they are replicated across studies, species, and laboratories; they resemble known and well-characterized effects of behaviorally active drugs; and they appear at about the same blood lead levels in animals at which they appear in humans, even without applying uncertainty factors. These observations have lent considerable support from animal studies to efforts to remove lead from the environment (Cory-Slechta, 1990; Davis et al., 1990, 1993; Rice, 1990).

One difficulty in interpreting the behavioral effects associated with many neurotoxicants seems to lie in the use of schedule-controlled behavior (Cory-Slechta, 1994; Rees and Li, 1994; Wenger, 1994). Here again, lead is a good example. The behavioral procedure most sensitive to lead poisoning, the fixed-interval schedule of reinforcement, is a reinforcement contingency that has no human counterpart, except perhaps under unusual circumstances. Such a specialized laboratory preparation should present little difficulty in a scientific discipline accustomed to the isolated guinea pig ilium or neural membrane, but it does. The fixed-interval schedule is quickly recognized by the behavior analyst or behavioral pharmacologist, however, as a contingency of reinforcement that is of great behavioral interest (Zeiler, 1977), is exquisitely sensitive to behaviorally active drugs, and even shows selective effects to psychomotor stimulants (Branch, 1991; Seiden and Dykstra, 1977). To those familiar with the literature, a disruption by lead in animal studies using schedule-controlled behavior is an unequivocal cause for concern (Cory-Slechta, 1994; Rees and Li, 1994; Wenger, 1994).

The fixed-interval (FI) schedule and other reinforcement schedules recommended for behavioral testing (Sette, 1994; Sette and Levine, 1986) are well suited because of their sensitivity, selectivity, and the expansive literature that can be drawn upon to interpret results. Nevertheless, the mechanisms determining performance under some schedule arrangements are not well understood (Zeiler, 1977), and a full characterization of the neural determinants of FI performance is not likely to appear in the near future.

The identification of behavioral mechanisms and the linking of them to neural mechanisms require the application of procedures that can lead more directly to mechanistic interpretation. A promising candidate for identifying behavioral and neural mechanisms of steady-state behavior, behavior in transition, and toxicant actions is the concurrent schedule of reinforcement. This chapter reviews some of the determinants of concurrent schedule performance, the requirements for the study of behavior in transition, applications, and finally some of the considerations surrounding the identification of behavioral and neural mechanisms of neurotoxicity.

### THE CONCURRENT SCHEDULE OF REINFORCEMENT

A concurrent schedule is an arrangement in which two different reinforcement schedules are in effect simultaneously. The subject can respond on either schedule, and can

switch back and forth, or choose, between the two schedules. The concurrent schedule is a flexible arrangement that can permit the quantitative description of a wide range of behavioral phenomena including choice, reinforcement context, sensitivity to fine differences in reinforcement rates, the transition of behavior from one steady state to another, sensory processes, or motor processes. A mature behavioral literature can provide empirical and theoretical guidance in interpreting behavior under this arrangement and a pharmacological/toxicological literature is developing. It is not the intent here to review all approaches but rather to describe a general procedure. The interested reader can consult several sources for more comprehensive reviews (Davison and McCarthy, 1988; de Villiers, 1977; Mazur, 1991).

Two general variations of concurrent schedules, distinguished according to how the subject selects which schedule is in effect, are commonly used in the laboratory, and others can be useful for specific application. In each procedure, behavior can be allocated to one of two (usually) or more schedules and in each procedure an explicit "changeover" response is required, and measured, to change the schedule in effect. It is worth noting that all behavioral procedures can be thought of as a concurrent schedule in which one response is measured and all others are not, an insight that is developed later.

*The Two-Lever Schedule.* Herrnstein (1961) is generally credited for the arrangement illustrated in Fig. 1, in which the two schedules are programmed to operate independently on separate response devices (usually round disks called keys for pigeons, or levers for mammals). Typically, variable-interval (VI) or random-interval (RI) schedules of reinforcement are arranged to deliver response-dependent reinforcers on the two levers. Under a random-interval 60" (RI 60") schedule, the first response to occur after an average of 60 s results in the delivery of a reinforcer, such as a food pellet for a food-deprived animal. The time to the next reinforcer varies unpredictably (by the subject) from reinforcer to reinforcer. Under a VI 60" schedule the interreinforcer intervals vary but are preprogrammed on a continuous loop.

Most researchers using the two-lever procedure arrange a changeover delay (COD), a refractory period following the change of schedules during which no reinforcers are available. This period, usually 2-4 s or so, is timed from the first response on the alternate lever; that is, it follows a changeover. After the changeover delay has lapsed, any reinforcer that may have been arranged will be delivered after the first response following the COD. The changeover delay decreases the direct reinforcement of switching and enhances the sensitivity of behavior to discrepancies in the reinforcement schedules competing for behavior. It accomplishes this by inhibiting the rapid switching between the two schedules, which tends to result in one-half the behavior allocated to each schedule, and enhances the amount of behavior allocated to the richer schedule. Functionally this is similar to spacing the response devices far apart and imposing a travel requirement.

*The Findley or Changeover Lever Procedure.* Findley (1958) is credited for a variation in which two schedules are programmed independently and continuously on one device (the "schedule" lever or key) and a second device (the "changeover" lever or key) is used to change the schedules. Functionally the schedule operates as

## The Concurrent Schedule of Reinforcement

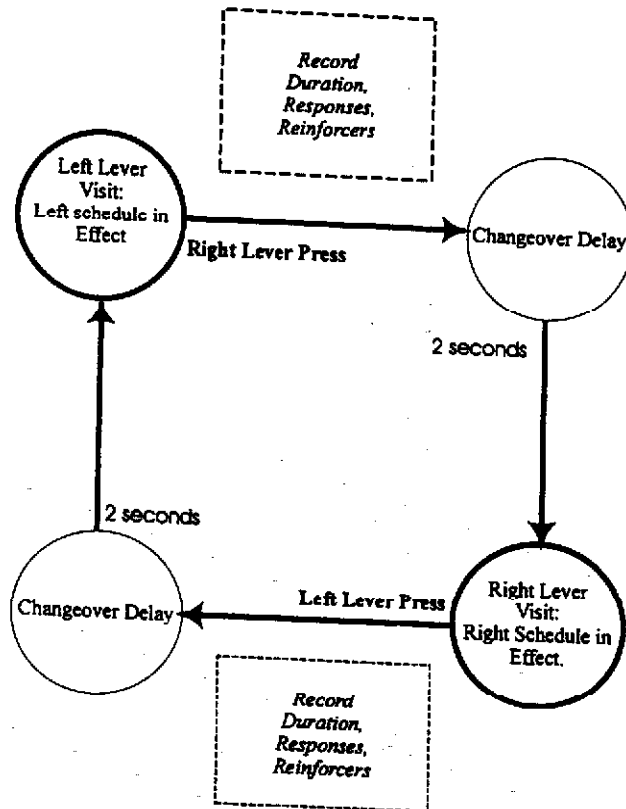


FIG. 1. Schematic of a two-alternative concurrent schedule of reinforcement. A subject might respond on the left lever for a period of time and then change over to the right lever, and then back to the left. Often a refractory period called a changeover delay is imposed after the subject changes response devices. The dependent measures, illustrated in boxes, describe performance. These can be recorded at each changeover or summarized at the end of the session.

illustrated in Fig. 1, but the two response devices are used differently. Responding on the changeover lever results in the presentation of the stimulus associated with the newly active schedule (e.g., a bulb illuminated blue on one schedule becomes illuminated red with the other schedule, for a subject with color vision). One advantage to having a changeover device is that responding on it can be examined as a response in its own right and changeover contingencies can be defined with great specificity (Findley, 1958; Stubbs and Pliskoff, 1969). Any explicit response requirement can be imposed to change the schedule, although care must be taken because a high cost

or complex changeover requirement can interact with the other components of the schedule.

*Modifications.* The VI or RI schedules are primarily time based, and the clock runs on one response alternative while the subject is behaving on the other. Therefore, while the subject is responding on one schedule, a reinforcer can be arranged to follow the next response on the other schedule after the changeover delay has lapsed. If the schedules are response based, for example, concurrent ratio schedules, then there is no advantage to switching from the rich to the lean schedule unless a response on one schedule also increments the response counter on the alternative schedule (MacDonall, 1988). In general, switching is maintained when a reinforcer on one alternative can come due while behavior is occurring on the other alternative.

Even when schedules are arranged independently of one another, one schedule may in fact influence responding under the other schedule (Catania, 1966, 1973; Sidman, 1958). It is also possible for subjects to respond exclusively on one schedule, especially if the discrepancy in reinforcer rates on the two schedules is large (Stubbs and Pliskoff, 1969). Stubbs and Pliskoff offered a modification in which a reinforcer is assigned to one of the two alternatives, with the assignment to one side being more probable than that to the other side. The subject is required to collect a reinforcer on the assigned schedule before another reinforcer is arranged. The behavioral effects are similar to those with the independent schedule arrangements, but the Stubbs/Pliskoff modification can be useful under situations in which the subject may not make explicit contact with each schedule.

*Dependent Variables.* Behavior under a concurrent schedule is a rich lode that can be mined, or in which one can become lost. The following is offered as a guide, but not as the final authority, on independent and dependent measures often used in controlling or describing behavior under concurrent schedules. While an abundance of research on steady-state behavior of normal (no drug or toxicant exposure) animals is available under these schedules, a few data are available on chemical exposure or on transition states. The behavior that spans two steady states, the transition, is of particular interest and receives detailed attention here because these transitions can be used to examine the process of learning directly and quantitatively.

Under a two-lever arrangement, some session time will be spent responding on the left alternative and the remainder on the right. Table 1 shows that either time or number of responses can serve as a measure of behavior. In steady state when there has been no drug or toxicant exposure these two measures, the number of responses and time spent responding, are often closely correlated and provide the same information. Sometimes response biases arise that degrade this relationship. For example, local response rates may be altered in a rate-dependent manner by drugs or toxic substances, or the behavioral adjustments that follow a change in reinforcement contingencies sometimes produce transient biases. Occasionally, a lever bias will appear with responses (e.g., if one lever is slightly easier to operate than the other), but this can usually be eliminated by adjusting the response device. Biases can cloud the description of transitions or steady-state behavior, but the use of time as a dependent variable can circumvent this problem.

TABLE 1. Measures under a concurrent schedule

Measure	Definition	Use
<b>Independent measures</b>		
Programmed reinforcer rate	Overall rate of reinforcement <i>scheduled</i> to be delivered on a response alternative.	Can form the bases for many derived independent measures and for controlling behavior. Independent of the subject's behavior.
Obtained reinforcer rate	Rate of reinforcement actually delivered by a response alternative.	Similar to programmed reinforcer rate, except that it can depend upon the subject's behavior. Used in many behavioral studies conducted in steady state.
Changeover delay	Period of time (usually a few seconds) following a changeover during which reinforcers are not delivered.	Imposition of a changeover contingency enhances the discriminability between the schedule alternatives.
Changeover costs	Contingencies other than a delay imposed on changeovers.	Examples: number of responses, travel requirement, small electric shock.
Reinforcer ratios	Reinforcers obtained on one alternative divided by those on the other (or all other) alternatives. Often log-transformed.	Often used as an independent measure in studies of generalized matching. Presents problems when zero reinforcers are delivered and obtained reinforcer rate is used.
Proportion of reinforcers obtained on an alternative	Reinforcers obtained on one alternative divided by total obtained reinforcers.	Independent measure in "simple" matching and often in studies of behavior in transition. Can handle zero reinforcer rates.
<b>Dependent measures</b>		
Responses on an alternative	Number of responses emitted under a particular schedule alternative.	Forms basis for measuring response allocation, or response rates.
Time spent on an alternative	Time spent on each alternative. <sup>a</sup> The clock begins with the first response on an alternative and ends with the first response on another alternative.	Forms basis for measuring time allocation.
Proportion of responses (or time) on an alternative	Number of responses on one alternative divided by total number of responses.	Used for "simple" matching, hyperbolic descriptions of response rate, and often descriptions of behavior in transition. Can accommodate values of zero.
Response (or time) ratios	Responses (or time) on one alternative divided by responses on the other alternative. This measure forms the basis of the "generalized matching law."	Forms basis of generalized matching in steady state. Does not readily accommodate response rates of zero. Time ratios may be less susceptible to response biases.
Local response rate	Total number of responses on one schedule alternative divided by time spent on that alternative.	Can be used as a measure of overall function, response rate.
Overall response rate	Responses on all alternatives divided by total session time.	Can be used as a general measure of functioning.
Changeovers or visits	Number of switches between schedules.	Measure of sampling of response alternatives. Rate can be influenced independently of other response rates.

<sup>a</sup>When possible, the time spent consuming a reinforcer should be subtracted from time spent responding. Some investigators include changeover times in the calculations, and some do not.

In studies of steady-state behavior, response and reinforcer ratios have been used most often as the dependent variable. In transition states, or after exposure to a high dose of a drug or toxicant, response rates of zero can sometimes occur. In these cases response proportions are called for because ratios cannot handle zeros in the denominator and a log-transform, which is often performed, cannot be performed if the numerator is zero.

*Independent Variables.* Some independent variable must be used to mark the course of the transition. Elapsed time or the number of sessions may be the first choice, but in a sense these measures are arbitrary except that events take place in them. Events that have direct behavioral relevance seem to be best suited as independent variables (Nevin, 1988, 1992), but much work remains to identify the most relevant and sensitive in a toxicological context. Cumulative reinforcers have been used (Newland et al., 1994; 1996), and this has some justification because it is the reinforcer that contacts behavior. It also provides a common, and relevant, metric for comparing conditions across reinforcer rates, whereas session time would be confounded with the different rates. Cumulative visits, or changeovers, can also be useful, and it is not clear at present which is preferable.

Another advantage to using events that directly contact and influence behavior as independent variables is that such a strategy leads directly to an interpretation based upon mechanisms directly relevant to supporting behavior, such as sensitivity to consequences. The large literature on concurrent schedules leads directly to interpretations based upon such sensitivity (see later discussion on quantification). Analyzing transitions based on similar measures permits links to be made more directly to the open literature.

Much of the literature on concurrent schedules of reinforcement emphasizes the allocation of behavior between two response alternatives. It is not widely recognized, however, that the changeover response is an important operant in its own right. The rate at which changeovers occur can be influenced directly by the changeover costs (Findley, 1958; Todorov, 1971) and by the discrepancy in reinforcement rates between the two alternatives (Myerson and Hale, 1988; Tustin and Davidson, 1979). In order for a transition to occur, it is necessary for behavior to make contact with the reinforcement contingencies available, and changing alternatives is a fundamental component of this. Nevertheless, relatively little attention has been devoted to this important variable (but see Machado, 1997).

The visit can also be used to mark transitions. As indicated in Fig. 1, important measures of behavior can be recorded at the end of each visit, permitting the charting of a transition at a finer level of detail than session averages might provide, and enabling the investigator to detect changes on a visit-by-visit basis.

#### QUANTIFICATION OF STEADY-STATE PERFORMANCE

Since the performance of pigeons under concurrent schedules was first examined, a large research effort has been directed at examining steady-state behavior under

concurrent time-based schedules. We briefly describe some of the main outcomes of this research, which can be summarized in a few equations that express some measure of behavior as a function of the consequences of behavior, usually programmed or obtained reinforcement rates. For more comprehensive treatment, the reader is directed to other reviews (Davison and McCarthy, 1988; de Villiers, 1977; Mazur, 1991).

### Simple Matching

Herrnstein (1961) demonstrated a quantitative relationship between response and reinforcer rate in the behavior of pigeons whose behavior was maintained by two concurrent VI schedules (*Conc VI t<sub>1</sub> VI t<sub>2</sub>*) with a COD in effect. The relationship, referred to as *simple* or *strict* matching, expresses the relative proportion of responses allocated to each alternative as a function of the relative proportion of reinforcers acquired under each alternative:

$$\frac{B_1}{(B_1 + B_2)} = \frac{R_1}{(R_1 + R_2)} \quad (1)$$

$B_1$  and  $B_2$  represent behavior (usually response rates or visit durations) on each alternative and  $R_1$  and  $R_2$  are the reinforcers obtained on each alternative. There are no free parameters in this equation.

Equation (1) can be modified to describe a single response under a VI schedule, occurring in a context of all other activities and their associated reinforcers considered collectively (Herrnstein, 1970, 1974). Let  $B_2$  and  $R_2$  represent "other" behavior and reinforcers, respectively. Equation (1) can be rearranged to express response rate,  $B_1$ , as a function of the other terms in Equation (2).

$$B = \frac{kR}{R + r_0} \quad (2)$$

Here,  $B$  and  $R$  are the response and reinforcer rates, respectively, for the target response. There are two free parameters:  $k$  (sometimes called  $R_{\max}$ ), is the asymptotic rate for the target response and is usually interpreted as the maximum response rate possible. The parameter  $r_0$  reflects the efficacy of the programmed reinforcer as compared with other reinforcers available in the context in which behavior occurs (Herrnstein, 1970, 1974; Heyman and Monaghan, 1990). The magnitude of  $r_0$  is the value of the  $x$  axis at which one-half of the maximum response rate takes place. This function begins at the origin (0,0) and curves upward toward an asymptote,  $k$ , with a degree of curvature influenced by the value of  $r_0$ .

Useful in many cases, the expressions contained in Equations (1) and (2) cannot account for the wide range of conditions used to study choice (Baum, 1974; Lobb and Davison, 1975; Myers and Myers, 1977; Staddon, 1964). Often, under concurrent VI schedules, behavioral allocation does not adhere to strict matching expressed in Equation (1), although the fit can be improved somewhat by using time, rather than

response, allocation as the measure of behavior (Lobb and Davison, 1975; Myers and Myers, 1977). In order to handle the diverse data coming from studies of choice, the description of the relationship was modified to describe data in terms of behavior and reinforcer ratios (Baum, 1974). This relationship, referred to as the *generalized matching law*, is described well by Equation (3):

$$\frac{B_1}{B_2} = a \left( \frac{R_1}{R_2} \right)^b \quad (3)$$

where  $B_1/B_2$  is the ratio of behavior (responses, response rate, or time spent on the alternatives) between two alternatives and  $R_1/R_2$  is the ratio of reinforcers obtained or programmed across the two alternatives. The use of obtained rather than programmed reinforcers is addressed in another section below. This expression has two free parameters:  $a$  and  $b$ .

When expressed in log-log coordinates, Equation (3) forms a straight line with slope  $b$  and intercept  $\log a$  and can be fit using linear regression. The value of  $b$  is interpreted as sensitivity to reinforcement, since it expresses the relationship between behavioral allocation and the allocation of reinforcers. A slope  $> 1$ , termed *overmatching*, represents greater sensitivity to reinforcement compared with a slope  $< 1$ , which is termed *undermatching*. The intercept,  $\log a$ , represents bias. If  $a$  is positive then the bias is toward the response alternative expressed in the numerator. A negative bias represents a preference for the denominator. If there is no bias then  $\log(a)$  is zero and the line passes through the origin. In log-log space the origin, (0,0), corresponds to the point  $(10^0, 10^0) = (1, 1)$  in the original coordinates and states that under conditions of no bias, when the two response alternatives produce reinforcers at the same rate (the ratio = 1), behavior is allocated equally between the two alternatives (the ratio = 1). Specifically, if  $\log a = 0$ , then  $a = 1$ .

These relationships, termed the *matching law* (although its status as a "law" is not secure), have provided excellent accounts of behavior using a variety of response classes including key pecking and lever pressing (Davison and McCarthy, 1988; deVilliers, 1977), treadle pressing (McSweeney, 1975), and scanning eye movement rates (Schroeder and Holland, 1969); across species including pigeons and rats (Davison and McCarthy, 1988; deVilliers, 1977), and humans (Horne and Lowe, 1993; Kollins et al., 1997); and across reinforcers such as food (Davison and McCarthy, 1988; deVilliers, 1977) and brain stimulation (Shull and Pliskoff, 1967) and sometimes points (Kollins et al., 1997). It has been applied to psychophysics to separate sensory from biasing influences (Davison and McCarthy, 1988; Nevin, 1981), to behavioral pharmacology (Heyman and Monaghan, 1990) and is beginning to be applied in behavioral toxicology (Newland et al., 1994, 1996; Peele and Crofton, 1987). It has also been extended to as many as eight response alternatives in a radial-arm maze (Elsmore and McBride, 1994).

Squirrel monkeys exposed to high levels of lead or to methylmercury during gestation showed alterations in steady-state performance maintained by concurrent schedules (Newland et al., 1994). The exposed monkeys showed less sensitivity to

reinforcement changes, reflected in a low value of the parameter  $b$  and a greater proclivity to lever bias than control monkeys. Even with very large discrepancies in the reinforcement rate programmed on the two levers, only small changes in response allocation were seen in these monkeys. The effects appeared at relatively high exposure levels (greater than  $40 \mu\text{g}/\text{dl}$  prenatally). The behavior of one of these monkeys is illustrated next.

The hyperbolic Equation (2) has been applied to describe the behavioral effects of pyrethroid pesticides (Peele and Crofton, 1987), neuroleptics, and stimulants (Heyman and Monaghan, 1990). The hyperbolic equation could separate a drug's effects on reinforcer efficacy,  $r_0$ , from its effects on motor performance,  $k$ . Deprivation level influences  $r_0$  with no change in  $k$  and modifications of the response requirement resulted in systematic changes of  $k$  with little effect on  $R_e$  (Heyman, 1983; Heyman and Monaghan, 1987, 1990; Heyman and Seiden, 1985). Low doses of chlorpromazine and pimozide increased  $R_e$  alone (decreased reinforcer efficacy), whereas high doses increased  $R_e$  and decreased  $k$  (decreased reinforcer efficacy of the programmed reinforcer and slowed motor performance). Amphetamine, which acts somewhat opposite to chlorpromazine at monoamine synapses, decreased  $R_e$  at low doses (increased reinforcer efficacy) and increased it at high doses. Amphetamine monotonically increased  $k$  (increased asymptotic response rate).

Peele and Crofton (1987) arranged a multiple schedule of four variable-interval schedules, ranging from VI 10 s to VI 270 s, separated by 20-s periods of no reinforcement in order to determine the effects of cypermethrin and permethrin in rats. They found that low to moderate doses of cypermethrin (less than 30 mg/kg) had little effect on  $k$  but profoundly increased the value of  $R_e$ . The increase in  $R_e$  was maximal at 30 mg/kg, at which point it was roughly 6 times higher than baseline. At the highest dose (60 mg/kg), cypermethrin produced about a 50% decrease in  $k$  while  $R_e$  was only 1.8 times higher than the baseline value. On the other hand, permethrin produced dose-dependent decreases in  $k$  and  $R_e$ , although the effect was less severe for  $R_e$ .

### LEARNING AND BEHAVIOR CHANGE

The behavior of vertebrates is susceptible to important environmental changes that take place rapidly. The behavioral mechanisms supporting behavior change fall under the headings of habituation, sensitization, and respondent and operant conditioning, a collection that can account for a wide range of behavior ranging from the very simple to the impressively complex. This list may not be exhaustive but is sufficiently complete that it includes the plasticity described in virtually all animal behavior and much, if not all, human behavior. There is a wide range of generality across species in the operation of these mechanisms. The list is of general categories of mechanisms; within each category other mechanisms can also apply. For example, with operant behavior, consequences influence behavior, antecedent stimuli guide behavior, and these stimuli interact with one another.

Some key propositions underlie the systematic and reproducible investigation of the behavioral processes involved in learning. The fundamental proposition is that "learning" is not an event that magically occurs but rather reflects orderly processes that can be reproduced, studied, perturbed, and ultimately understood. We refer to *learning* as the change in behavior from one steady-state to another in response to a change in the environment. This broad definition can apply to a wide variety of behavior changes, even to behavior such as reproduction, migration, or foraging patterns that can change over the course of generations through mechanisms such as natural selection, although such slowly changing behavior is not the topic here. That behavior change encompasses time spans ranging from seconds (habituation and respondent conditioning) to generations is instructive because it indicates that there is no single event called "learning" that can show a deficit. A comprehensive understanding of how behavior change can be impaired requires an account of the mechanism by which the behavior change of interest takes place. That is, what kind of change is being examined? What are the mechanisms? And how broad an impairment is it?

#### **Key Elements to the Study of the Role of Consequences in Behavior Change**

The change in behavior from one steady state to another, a transition, has not received the quantitative treatment granted steady-state performance. Under the right conditions such behavior can be brought into the laboratory and analyzed; some of these conditions are specified in this section. The key elements can be linked directly to strategies taken for the study of transitions (Johnston and Pennypacker, 1980; Sidman, 1960). It is necessary to define when a transition begins and ends, to quantify behavior and link it to environmental events, to clearly and unambiguously define independent and dependent variables, to incorporate variability into the account, and, most important, to replicate. By following these guidelines, the analysis of behavior change can reveal mechanisms behind learning and permit refined analyses of toxicant-induced impairments in learning.

The characteristics are illustrated in Figs. 2 and 3, which show the course of several transitions in the behavior of two monkeys and one rat. In these figures, the proportion of responses or time allocated to the left lever (arbitrarily chosen) is shown across many sessions. Also shown is the proportion of reinforcers programmed to be delivered from the left lever, and the proportion actually obtained for responding on the left lever. The transitions for the control monkey and the unexposed rat are strikingly similar despite differences in species, chambers, training history, and other variables. The transitions described in this section required many days to complete and a single experiment requires months. Tactics for describing transitions in a single session are presented next.

*The Beginning and End of a Transition Can Be Identified.* Behavior change can be initiated by a change in the relationships between at least two of the three terms (stimuli, response, or consequence) of the reinforcement contingencies. In Figs. 2

### Representative Transitions

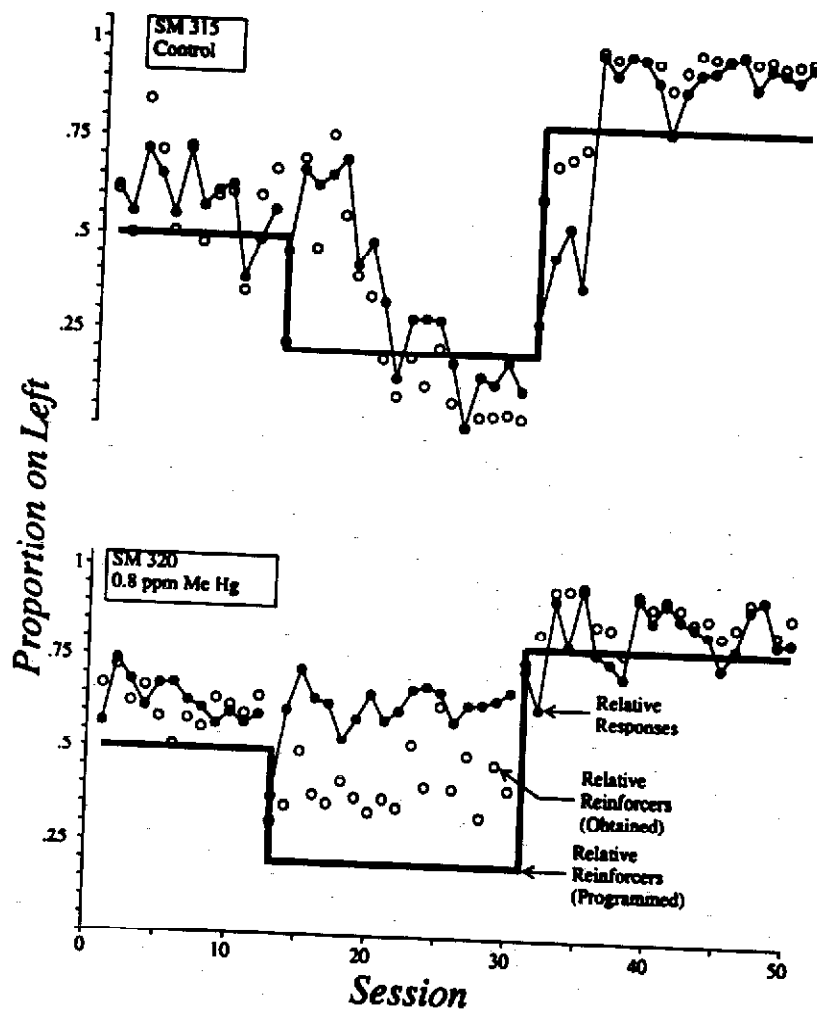


FIG. 2. Representative transitions for a control monkey and one exposed to methylmercury during gestation (adapted from Newland et al., 1994). Symbols represent summaries of performance for individual 30-min sessions. Relative response rate and obtained and programmed reinforcement rates are shown for two transitions. In the top panel the change in behavior and obtained reinforcement rates lagged programmed rates by four sessions. For the exposed monkey, behavior showed little sensitivity to programmed or obtained reinforcement rates in the first transition.

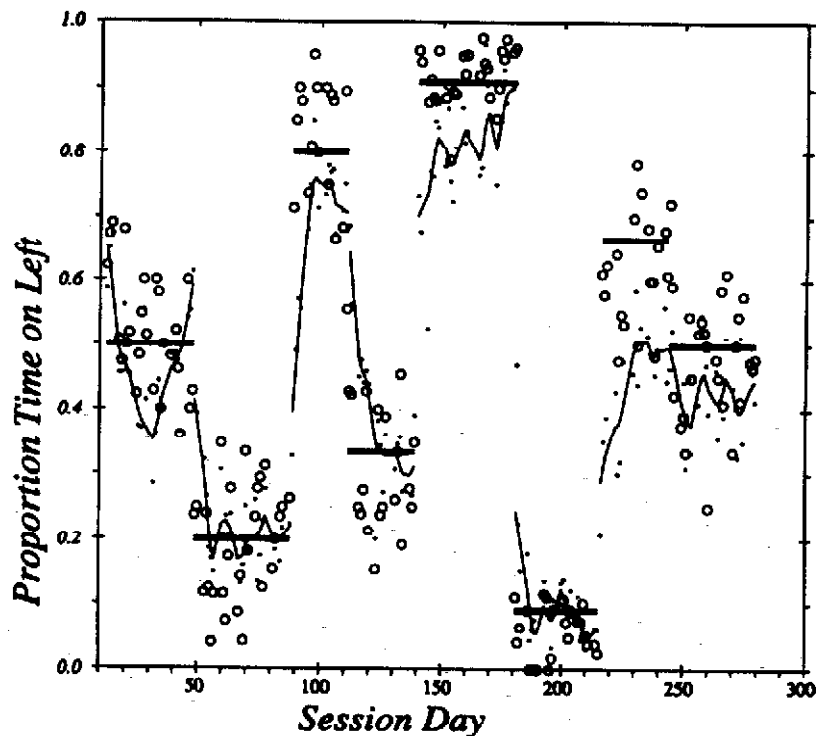
*Representative Time Series*

FIG. 3. Seven transitions for a single rat. Thick horizontal lines and open circles represent relative reinforcement rate programmed and obtained (respectively) on the left lever. Filled points represent relative time on the left lever. The thin line represents a LOWESS smoothing algorithm applied to the relative time on the left lever. Behavior approximately tracked reinforcement rates, but transitions usually required several sessions. Overall, these transitions resemble those seen in the unexposed squirrel monkey in Fig. 2.

and 3 the beginning of a transition is marked by an abrupt change in the thick line, showing a change in the programmed rates of reinforcement. The beginning could be defined as the point at which behavior changes, the point at which programmed contingencies of reinforcement change, or the point at which obtained contingencies change. To characterize the role that neurotoxicants play in learning, the point at which programmed reinforcement contingencies change, illustrated by the horizontal lines, seems to be the proper choice because it makes it possible to determine how effectively subsequent changes in the structure of behavior reflect structure in the environment.

Many basic researchers studying concurrent schedules use obtained reinforcement rates, arguing that it is the obtained rate that actually controls behavior (Davison and McCarthy, 1988; deVilliers, 1977). While this is true, Fig. 2 shows where this approach could result in a poorer independent variable. When using obtained, rather than programmed, reinforcement rates, the "independent" variable (relative reinforcement rates) and dependent variables (relative responding) are not independent of one another because the obtained reinforcement rate depends jointly on programmed rates and behavior. In the control transition in Fig. 2, the obtained reinforcement rate changed a few sessions after programmed reinforcement rates changed. For the mercury-exposed animal, obtained reinforcement rates fell between 50% and the programmed rates, again indicating contamination of the "independent" variable by behavior.

*Transitions Can Be Replicated.* It may seem that interest in studying an unstable process such as learning is incompatible with experimental requirements that a process be reproducible in a laboratory, but there is no incompatibility at all. Figure 3 shows that new steady states and multiple transitions can be achieved repeatedly in a single subject. There are advantages to studying acquisition repeatedly within a single subject, and they draw from the elimination in variability across subjects in such designs. If the goal is to study behavior change, its environmental influences, and perturbation by chemical exposure, then reduction in extraneous variability can only help achieve that goal.

Despite some variability across daily sessions, there is considerable replicability in the general course of the transition. Behavior begins to change shortly after the environmental contingencies change; the change and rate of change are both gradual, and the magnitude of the new asymptote reflects the new contingencies.

*Variability Is Characteristic.* Behavior change follows a trajectory that can be described and reproduced at some level of measurement, but not in every detail. Indeed, an inability to reproduce every detail is due to an important characteristic: there must be variability for behavior to change. Without variability in behavior, it would be impossible for behavior to contact the new contingencies and therefore impossible for those contingencies to select new behavior. Variability increases as behavior changes, a characteristic that is probably fundamental to learning.

It is not evident in the figure, in part because training is not displayed, but variability decreases with experience, a phenomenon sometimes called, probably misleadingly, "learning-to-learn." It sometimes appears with repeated transitions, too. The interpretation might be that this is a form of meta-learning, but a more visible explanation is available. When a subject is placed in a novel setting a variety of activities occur. Some make contact with new reinforcement contingencies and the rest are extinguished. A concrete example illustrates the point. When a rat is first placed in a chamber, it explores the four walls, the floor, the ceiling, any lights and levers available, and the pellet dispenser. When trained to press a particular lever, many of these activities disappear. All these other activities, which are idiosyncratic from rat to rat, contribute to noise in the measurement. Once the rat lever-presses reliably under an intermittent schedule, a change in that schedule occasions a change in behavior, but

unaccompanied by all the extraneous activities, although some may occur. Thus a transition, in which a similar response class is reinforced under a different schedule, can be isolated more readily and determinants of the characteristics of the transition can be examined on a within subject basis, a tactic that has enormous advantages when it can be achieved (Johnston and Pennypacker, 1980; Sidman, 1960).

There is a trade-off in laboratory investigations of behavior change between capturing the sorts of learning that takes place with relatively little contextual support and the behavior change that takes place with considerable support or behavioral history behind it (Latties, 1972; Rees et al., 1985; Thompson, 1975). The former category might be called "difficult" and thereby of interest to neurotoxicologists, but this sort of behavior change is also highly variable because a lot of irrelevant behavior has not been extinguished. The resulting variability can be quite large, making it very difficult to isolate drug or toxicant effects. There is less variability, and perhaps more sensitivity, in behavior with more environmental support or history behind it because in these mature transitions irrelevant behavior has been eliminated.

*Behavioral History Acts in Identifiable Ways.* Behavior under the concurrent schedule represents current and recent consequences of behavior, as is very evident in Fig. 3. The gradual change certainly represents the reinforcement schedule maintaining the previous steady state (Hunter and Davison, 1985) and as such reflects a form of memory.

*Behavior Change Is Quantifiable.* The advantage of having a reproducible, controllable course of behavior change is that it leads to quantification and that, in turn, provides information for those interested in dose-effect relationships and the assessment of risk. A transition must be quantified before mechanisms can be identified or toxicant effects characterized. Practically speaking, the better the quantitative description of the transition, the more fully one can describe dose-related effects of chemical exposure. A simple description such as "trials to criterion" is a minimal requirement, but is inferior to descriptions of the pattern of change, the rate of change, and variability in behavior, because the last set of descriptions points more directly to mechanisms.

*Independent and Dependent Variables Can Be Defined in Behaviorally Relevant Terms.* Measurement is a fundamental element of quantification. The behavior to be changed must be clearly defined. It can be as simple as a lever press, but any behavior susceptible to operant conditioning is a candidate; time spent in an activity or even complex tasks assembled from simpler ones are suitable operants (Newland, 1997). The trajectory of change can be defined when some measure by which change can be compared, a horizontal axis, is identified. The first candidate typically considered is time, as change takes place in time, but this is not always the best. For example, behavior may change more quickly under a rich schedule of reinforcement (one reinforcer for each response, say) than under a leaner schedule, but this conclusion is confounded by the fact that it takes longer for the change in the leaner schedule to contact behavior. Changes in operant behavior occur because of contact with reinforcing contingencies, so the better dependent measure may be the reinforcer itself (Nevin, 1988).

*Mechanisms of Behavior Change and Toxicant Effects Can Be Identified.* By controlling carefully the conditions under which behavior change takes place, it should be possible to identify mechanisms supporting it. Two classes of mechanisms might be sought (Marr, 1990). One reductionistic strategy would entail identifying neural mechanisms of learning such as neurotransmitters or neuroanatomical regions supporting behavior change. Alternatively, strategy aimed at a parsimonious account of behavior change at the level at which it is measured might seek behavioral mechanisms, such as consequences, variability, sensitivity to the primary reinforcers used in animal experiments, or the roles played by behavioral history, memory, or stimulus support. If such mechanisms can be identified, then generalization to other settings, and perhaps even to humans can be accomplished. Identifying mechanisms at both levels is required of a full account of behavior, or toxicant-induced damage.

To summarize this section, the key propositions regarding the study of behavior change are: (1) Consequences determine the steady-state (operant behavior), (2) variability is intrinsic to steady-state behavior and is necessary for change, (3) common mechanisms imply continuity across species, (4) the determinants and mechanisms are identifiable, (5) behavior change is orderly, reproducible, measurable, and quantifiable, and (6) remote and recent history are important influences. Preparations that meet these criteria, as behavior under concurrent schedules of reinforcement does, can lead to the identification of neural or behavioral mechanisms by which transitions take place and by which neurotoxicants impair learning.

### QUANTIFICATION OF TRANSITIONS

In an investigation of the long-term consequences of lead, methylmercury, or mercury vapor exposure during gestation, effects were detectable in behavior during transition states in animals whose behavior resembled controls during steady state (Newland et al., 1994, 1996). The effects were described as retardation in the rate at which the steady state was acquired and were interpreted as reflecting insensitivity to the consequences of behavior. In those experiments it was noted that a logistic equation was well suited to describing the transition state. Parameters describing the transition could be estimated with this equation and used to identify dose-related effects of lead. In this section we examine that contention by showing the fine detail of a transition from one steady state to another under a concurrent schedule of reinforcement, in a single session, and then compare different equations in their ability to describe the course of several transitions.

The overall shape of the transition can be described by fitting an equation, using nonlinear regression, to the data describing the change in behavior. Table 2 lists four equations that might be used to describe transitions, and their characteristics. These equations are illustrated in Fig. 4. Hyperbolic and exponential equations have been used to describe such behavior change in unexposed animals. When averages are taken over relatively long periods, such as 30-min sessions, in animals with no chemical

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TABLE 2. Representative equations for describing behavioral transitions

Name	Equation		Parameters		
	Equation	Description	Term	Description	Graphical interpretation
Exponential	$Y_m(1 - e^{-kx})$	Abrupt beginning, upper asymptote	$Y_m$	Maximum Y	Value of Y after behavior stabilizes.
			$k$	Rate constant	Fractional rate of change/unit time, = 0.69/half-life
Hyperbolic	$\frac{Y_m X}{X + X_{half}}$	Abrupt beginning, upper asymptote	$Y_m$	Maximum Y	Value of Y after behavior stabilizes.
			$X_{half}$	Half maximal X	Value of X when $Y = \frac{1}{2} Y_m$
Logistic	$\frac{Y_m}{1 + e^{k(X_{half} - X)}}$	Symmetric, ogive ( <i>f</i> ) shaped function	$Y_m$	Maximum Y	Value of Y after behavior stabilizes.
			$X_{half}$	Half maximal X	Value of X when $Y = \frac{1}{2} Y_m$ , the inflection point.
			$k$	Rate term	$1/k$ = units of X required to span the middle quarter of the vertical displacement.
Gompertz	$Y_m e^{-e^{k(X_i - X)}}$	Asymmetric, ogive ( <i>f</i> ) shaped function. Rapid rise, slow to asymptote.	$Y_m$	Maximum Y	Value of Y after behavior stabilizes.
			$X_i$	X-inflection	Value of X when $Y = Y_m/e \approx Y_m/2.7$ , the inflection point.
			$k$	Rate term	$1/k$ = units of X required to span $Y_m$ units of vertical change, centered at the inflection point.

exposure these functions fit nicely (Mazur, 1992, 1997). Equations describing an ogive (*f*) shaped function are better suited for cases, such as those seen in some of the exposed monkeys (Newland et al., 1994, 1996), in which behavior did not change until well after the reinforcement contingencies changed. As described here, they also handle the microstructure of behavior change because the onset of behavior change often lags the change in reinforcement contingencies. The specific equations listed were selected because of their shape, the presence of interpretable parameters, and because they arise from difference equations used to describe growth processes in quantitative biology (Edelstein-Keshet, 1988; Murry, 1989). The logistic equation is more tractable and in that sense preferable to the Gompertz. The asymmetry of the Gompertz equation describes transitions that begin rapidly and taper off to the steady-state value more slowly, but in our experience the difference in parameter estimates is usually marginal. In order to make comparisons across conditions, the same equation must be used. The appearance of the equations can be foreboding but the parameters are readily interpretable (Table 2 and Fig. 4). The parameters describe the asymptotes,

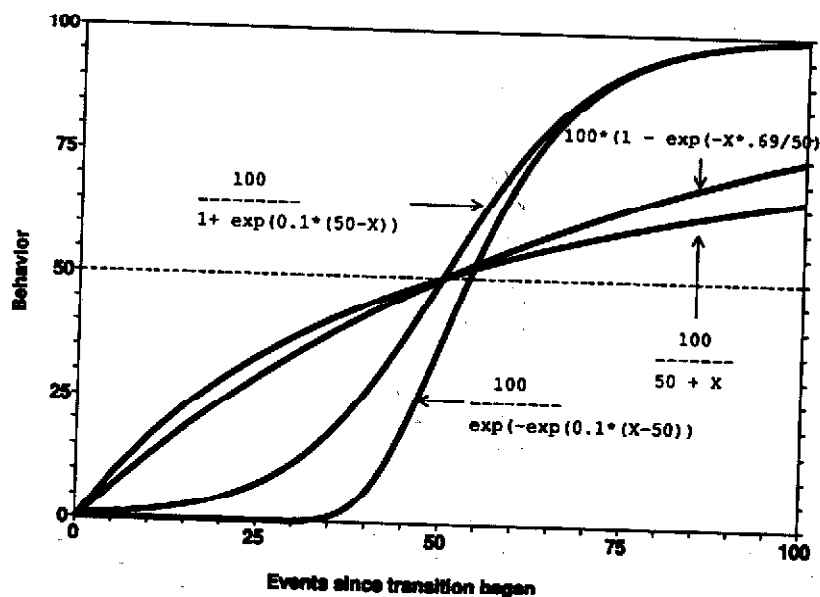


FIG. 4. Curves from Table 2 that might be used to fit behavioral transitions. Two curves (logistic and Gompertz) describing  $f$ -shaped functions and two curves (hyperbolic and exponential) representing functions that rise abruptly beginning at  $X = 0$  are shown. All four curves have an upper asymptote of 100, although the hyperbolic and exponential functions do not come close to this value in the space shown. All but the Gompertz functions have half-maximal values at  $X = 50$ .

a critical point near the middle of a transition, or the rate of change of a transition once it begins.

The study of transitions across multiple sessions, as illustrated in Figs. 2 and 3, is time-consuming. Recently we have examined ways of producing a behavioral transition in a single, 3-h session. Data from such a single-session transition will be used to illustrate the approach to quantifying transitions, even though the multiple-session transitions were used in previously published work (Newland et al., 1994, 1996). The experimental tactic is illustrated in Fig. 5. Briefly, a session begins with a concurrent schedule in which both sides have equal reinforcement rates. Thirty minutes into the session, the contingencies of reinforcement either remain the same or change such that the left or right lever becomes rich; each alternative has a 1/3 chance of occurring. No other stimulus change accompanies the change in reinforcement contingencies so technically this could be called *mixed*  $\{(conc\ RI\ t_1\ RI\ t_2)\ (conc\ RI\ t_3\ RI\ t_4)\}$  (Catania, 1991). If some other stimulus change such as the onset of the light also occurs, then this would be designated a multiple, not mixed, schedule arrangement.

An example of behavior under the mixed concurrent schedule is shown in Fig. 6. The schedule changed at  $X = 0$  from one in which 50% of reinforcers came from the left lever to one in which 90% came from that lever. The data are normalized so that

### Single Session Transition

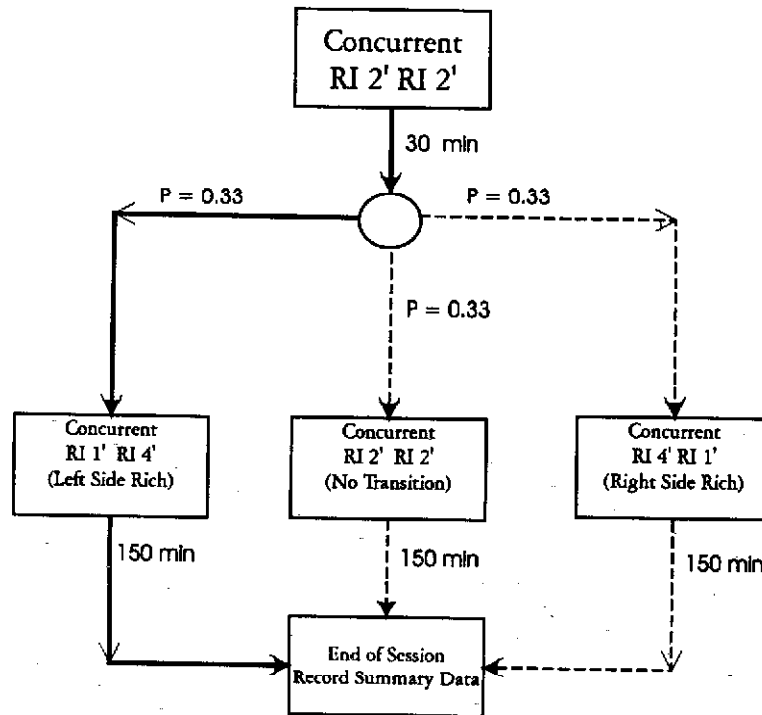


FIG. 5. Experimental procedure for studying transitions in a single session, shown as state notation. Rectangular boxes describe a state and the conditions in place during that state. Text next to a line show the conditions to advance to another state. During the first 30 min a *Concurrent RI 2' RI 2'* schedule is in effect. Then the schedule either does not change or changes such that the left or right side becomes rich. The thick line traces the way in which a session might occur when the transition is to the left.

$Y = 0$  represents the average percentage on the left lever before the schedule changes and  $X = 0$  represents the number of cumulative reinforcers at which the schedule was changed (this normalization helps with the curve fitting routines). Every time the animal changes levers (terminates a visit) the number of reinforcers, responses, and time spent on the lever are recorded. To obtain the data in Fig. 6, every time the animal changed from the left to the right lever, the percent of time spent on the rich lever was calculated for the most recent visit to each lever. This figure shows how this measure changed through the session. There is much variability in visit-to-visit estimates, so a LOWESS smoothing algorithm was applied to clean up the appearance of the data. This smoothing has little influence over the parameter estimates. Visual inspection shows that the proportion of time on the rich lever increased by about 35 percentage

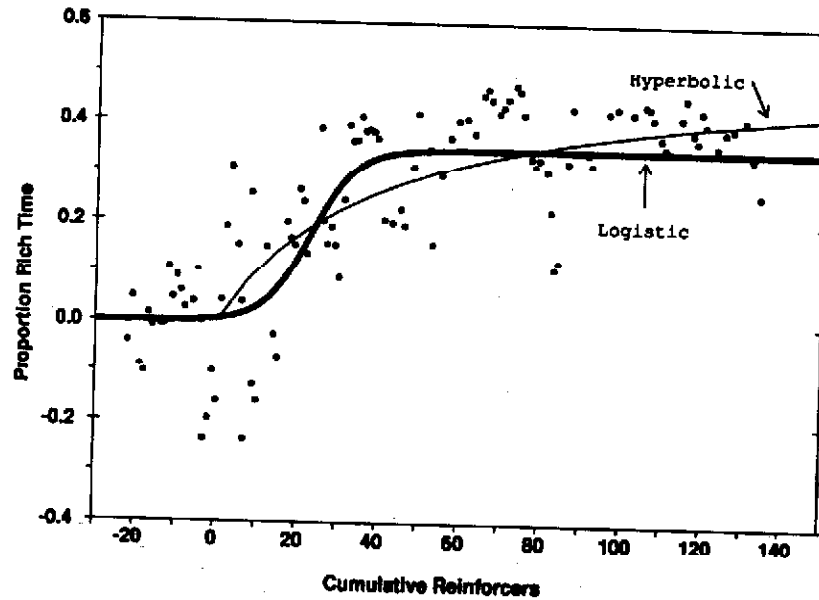


FIG. 6. The result of fitting two curves, a logistic and a hyperbolic curve, to one single-session transition. Every time the subject terminates a left visit the proportion time on the left side is calculated for a left-right dyad. The data have been smoothed using a LOWESS algorithm. The equations are:

$$\begin{aligned} \text{Hyperbolic curve: } Y &= \frac{0.53X}{42 + X} \\ \text{Logistic curve: } Y &= \frac{0.35}{1 + e^{0.18(23-X)}} \end{aligned}$$

points and the transition began about 10 reinforcers after the change in the schedule of reinforcement.

Figure 6 also shows the results of fits of two different equations, a hyperbolic and a logistic function. The logistic equation estimated that the magnitude of the transition was 0.35 (35 percentage points), while the hyperbolic equation produced an estimate of 0.53. The latter estimate exceeds all of the data and seems high. The number of reinforcers required to complete one-half of the transition was estimated to be 23 and 42 reinforcers by the logistic and hyperbolic equations, respectively. The Gompertz equation provided nearly identical parameter estimates to the logistic equation for data shown in Fig. 6 (data not shown). The logistic equation gives an additional parameter that estimated the rate at which the transition changes once it begins. This slope term, 0.18, describes the steepness of the curve at the point identified as  $X_{\text{half}}$ . The value of the slope term,  $k$ , can be estimated by visual inspection. For the logistic equation, estimate the distance along the  $X$  axis required to accomplish the middle fourth of the transition. In the example, one-fourth of the transition =  $0.35/4 \approx 0.09$ . The

estimate of  $k$ , 0.18, indicates that it requires about  $6 \approx 1/k$  reinforcers to span this, the steepest, portion of the curve in the transition shown.

The equations in Table 2 are relatively stable for nonlinear least-squares regression (Ratkowsky, 1989). In our experience, the estimates of the asymptotes and of  $X_{\text{half}}$  or  $X_i$  are reasonably stable; that is, they show small standard errors. Estimates of the slope terms tend to be more unstable. Sometimes the standard error is greater than the estimate, so the estimates have to be examined visually to assure that the value is reasonable and the estimation formulas in Table 2 can help.

Figure 7 describes the fit of these equations to several transitions. While the percent of variance accounted for is a common measure of the quality of fit, this measure performs more poorly in some settings than the standard error of estimate. The percent of variance accounted for is heavily influenced by extreme values in such a way that a fit may appear, visually, to be quite bad for all but one outlying point, but that single point causes the variance accounted for to be relatively high (Parker et al., 1988). The standard error of regression, therefore, is a better measure of the fit. Both measures are shown in Fig. 7. Overall, Fig. 7 shows that the Gompertz and logistic equations are difficult to distinguish from one another. Where one does well, the other does equally well. The hyperbolic and exponential equations generally accounted for a smaller percent of variance and produced larger standard errors than the logistic equation.

*Other Methodological Details.* Some other methodological details are worth noting. Stability in the pretransition baseline, which improves the estimates of the transition, can be improved when (1) the programmed reinforcer ratio on the two levers is 1:1 to balance behavior between the two levers and increases the rate at which switching takes place, (2) the ratio of programmed reinforcers does not deviate significantly from 1:1, and (3) the baseline lasts for at least 20 reinforcers. Criterion 2 can be met by preprogramming the interreinforcer intervals.

#### OTHER PROCEDURES FOR STUDYING BEHAVIOR IN TRANSITION

As stated earlier, learning can involve many types of behavioral events and, accordingly, varied procedures have been used in the laboratory. Some researchers have pointed out that such a complex process requires more than one type of test for adequate evaluation (Miller and Eckerman, 1986; Tilson et al., 1979). While many agree that more than one or two tests are often needed, it has been difficult to reach a consensus about which tests to use, although schedule-controlled behavior ranks high on many lists (Peele and Vincent, 1989). All tests of "schedule-controlled operant behavior" are not equivalent because different tests emphasize different portions of the three-term contingency of reinforcement. To illustrate this point, the repeated acquisition procedure (Cohn and Cory-Slechta, 1994; Cohn et al., 1993; Cohn and MacPhail, 1996; Cohn and Paule, 1995; Paule and Cranmer, 1990; Paule et al., 1990; Paule and McMillan, 1986) can be compared with the concurrent schedule in transition.

## Comparison of Equations

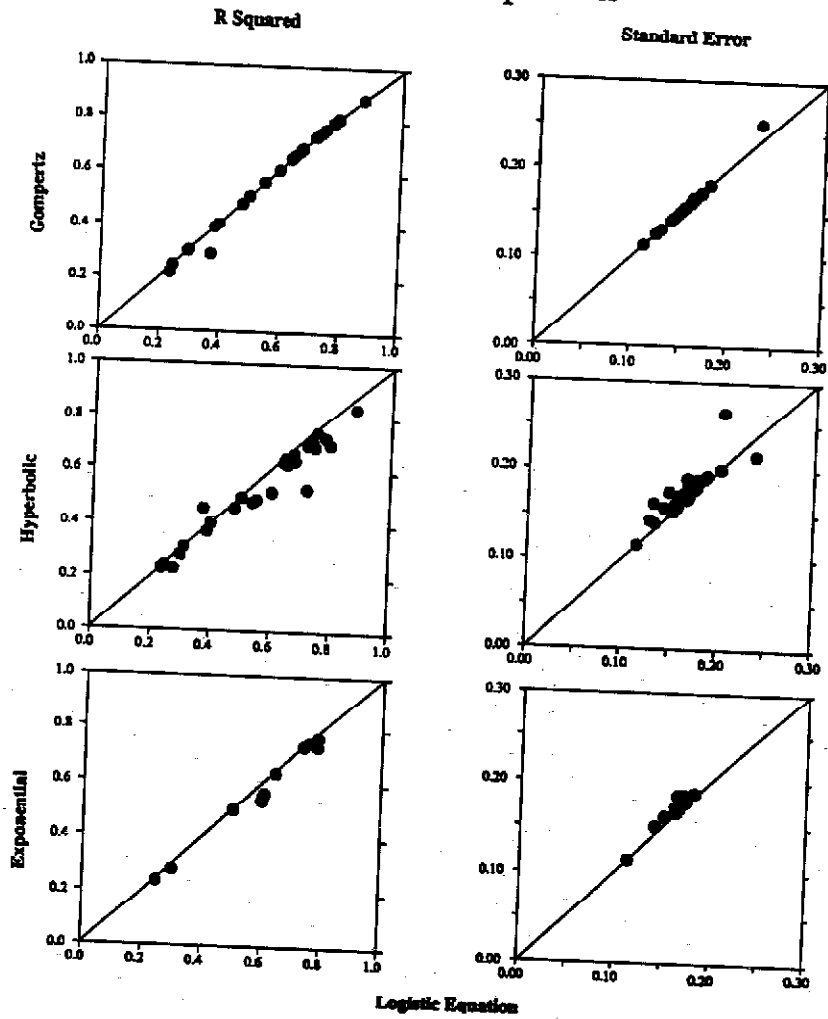


FIG. 7. The result of fitting the different functions described in Table 2 to several single-session transitions. Two figures of merit are included:  $R^2$  is shown on the left, and the standard error of regression on the right. The logistic equation is used as the benchmark against which three other functional forms are compared. Each data point represents a single transition fitted by logistic and Gompertz (top), hyperbolic (middle), or exponential (bottom) equations. The Gompertz and logistic equations were indistinguishable. The hyperbolic and exponential equations produced smaller  $R^2$  and larger standard error of regression than the logistic equation and hence provided poorer fits.

As first described by Boren (1963), in the repeated acquisition procedure subjects are required to learn a new sequence of responses during each session, and each response in the sequence can be associated with a particular stimulus condition. For example, in an early study (Boren and Devine, 1968) monkeys had to learn which 4 of 12 levers made up the correct sequence of responses; the monkey first chose 1 lever from a group of 3 levers. When the monkey pressed the correct lever 5 times, a light was illuminated above the second group of three levers, and so on. If the response was incorrect, a 15-s timeout was initiated and the light was illuminated above the same set of levers. After the monkey completed the entire response chain two times, a food reinforcer was delivered. Since this early study, several modifications have been introduced (Cohn and Paule, 1995; Thompson and Moerschbaeher, 1979), including an especially interesting variation called the incremental repeated acquisition procedure, in which the sequence length is increased by one each time the subject reaches a certain criterion (Paule and McMillan, 1986; Weinberger and Killam, 1977).

The repeated acquisition procedure and its variants focus on changing the relationship between the antecedent and consequent elements of the three-term contingency. In this, the repeated acquisition procedure may be described as a stimulus-control procedure since behavior is guided through the sequence by the presentation of discriminative stimuli, and the relationship between a particular stimulus and the response-reinforcer relationship is reacquired each session. In the concurrent procedure, behavior comes under the control of different reinforcement rates and the quantification is aimed at identifying sensitivity to such reinforcement contingencies. Functionally, then, these two arrangements can be distinguished in that the concurrent schedule procedure permits the examination of the response-reinforcer contingency while repeated acquisition procedure permits the examination of how stimuli come to acquire influence over that relationship. In the former, reinforcement is the focus, and in the latter, discrimination is the focus. Whether these will be important in identifying behavioral or neural mechanisms of toxicity remains to be seen, but the possibility that these different behavioral functions map onto different neural systems has been suggested (Donahoe et al., 1993).

#### CONCLUDING REMARKS: BEHAVIORAL MECHANISMS OF TOXICITY

A central goal in pharmacology and toxicology is the identification of mechanisms of damage. Often this entails the reduction of behavioral events to neural events, but before such a reduction can be accomplished, some parsimonious account of the variables that exert control over behavior must be offered. The concurrent schedule in steady state is widely acknowledged to provide a measure of sensitivity to reinforcement, and this is also a reasonable interpretation of the slow behavior changes seen in lead-exposed monkeys (Newland et al., 1994). Moreover, such an interpretation has been applied to other behavioral disorders, although not those specifically associated

with lead. Nevertheless, it would be of interest to relate observations that lead-exposed children have difficulty with classroom comportment and academic achievement to possible insensitivity to reinforcers available in the classroom.

Reduction to a common mechanism suggests an intervention for overcoming the effects of exposure. In particular, it suggests that increasing the reinforcement density (what we might call "behavior therapy") can facilitate a transition or enhance control over behavior by specifying an explicit intervention, and exactly that sort of intervention was imposed successfully (Newland et al., 1994). Reduction also suggests a common metric. As pointed out earlier, for example, time may be a less useful marker of a transition than events that make contact with behavior, such as obtained reinforcers and visits on a lever.

This approach to reduction may be applicable to the data such as those reported by Needleman (Needleman et al., 1979) where lead-exposed students were described as distractable, unable to stay on task, not persistent, and dependent. They behaved, but their behavior was under the control of something other than what the teacher had in mind. Disruptive behavior, whatever its neural mechanism, is susceptible to similar behavioral interventions, an observation consistent with the proposed mechanism of insensitivity, but not immunity, to reinforcement contingencies and indicative that even academically relevant behavior can be influenced (McDowell, 1982a, 1982b; Neef et al., 1992). Martens et al. (1992), for example, dramatically shifted the behavior of four third-grade students from classroom disruption to engagement in academic tasks by manipulating the reinforcement density for academic tasks. The example is mentioned here because the relationship between target behavior and reinforcement density very closely followed the hyperbolic form specified in Equation (2), lending some support to the utility of the mechanisms proposed here.

Suggesting a common behavioral mechanism for disruptive or even academically retarded behavior does not imply a common neural mechanism; it is possible, even likely, that the insensitivity to consequences could be mediated by many different substrates. Broadening our understanding of what constitutes a mechanism can only broaden the relevance of our research and help in identifying both neural mechanisms and applications.

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