be injected by comets and asteroidal debris. In any event, the total mass of dust in the solar system is of the order of 10^{-17} the mass of the sun, whereas a supergiant M star might have 10^{-7} solar mass of silicates in its shell.

Summary

Infrared astronomy has shown that certain classes of stars are abundant producers of refractory grains, which condense in their atmospheres and are blown into interstellar space by the radiation pressure of these stars. Metallic silicates of the kind that produce terrestrial planets are injected by the oxygen-rich stars and carbon and its refractories by carbon stars. Much of the interstellar dust may be produced by this mechanism. A number of "infrared stars" are completely surrounded by their own dust, and a few of these exhibit a unique morphology that suggests the formation of a planetary system or a stage in the evolution of a planetary nebula. Certain novae also condense grains, which are blown out in their shells.

In our own solar system, comets are found to contain the same silicates that are present elsewhere in the galaxy, suggesting that these constituents were present in the primeval solar nebula.

References and Notes

1. α, β, γ, *Phys. Rev.* **73**, 803 (1948).
2. E. M. Burbidge, G. R. Burbidge, W. A. Fowler, F. Hoyle, *Rev. Mod. Phys.* **29**, 547 (1975).
3. E. Loreta, *Astron. Nachr.* **254**, 151 (1934).
4. J. A. O'Keefe, *Astrophys. J.* **90**, 254 (1939).
5. W. A. Stein, J. E. Gaustad, F. C. Gillett, R. F. Knacke, *Astrophys. J. Lett.* **155**, L3 (1969).
6. A. J. Deutsch, *Stars and Stellar Systems*, vol. 6, *Stellar Atmospheres*, J. L. Greenstein, Ed. (Univ. of Chicago Press, Chicago, 1960), chap. 15.
7. R. C. Gilman, *Astrophys. J. Lett.* **155**, L185 (1969).
8. N. J. Woolf and E. P. Ney, *ibid.*, p. L181.
9. F. J. Low and K. S. Krishna Swamy, *Nature (London)* **227**, 1333 (1970).
10. R. J. P. Lyon, *NASA Tech. Note TN-D-1871* (1963).
11. R. D. Gehrz, E. P. Ney, D. W. Strecker, *Astrophys. J. Lett.* **161**, L219 (1970).
12. W. A. Stein and F. C. Gillett, *ibid.* **155**, L197 (1969).
13. R. W. Maas, E. P. Ney, N. J. Woolf, *ibid.* **160**, L101 (1970).
14. J. A. Hackwell, R. D. Gehrz, N. J. Woolf, *Nature (London)* **227**, 822 (1970).
15. D. K. Aitken and B. Jones, *Astrophys. J.* **184**, 127 (1973).
16. F. C. Gillett and W. J. Forrest, *ibid.* **174**, 483 (1973).
17. R. Hanel, *Science* **175**, 305 (1972).
18. R. M. Humphreys, D. W. Strecker, E. P. Ney, *Astrophys. J.* **172**, 75 (1972).
19. R. D. Gehrz and N. J. Woolf, *ibid.* **165**, 285 (1971).
20. E. P. Ney, D. W. Strecker, R. D. Gehrz, *ibid.* **180**, 809 (1973).
21. R. M. Humphreys, D. W. Strecker, E. P. Ney, *Astrophys. J. Lett.* **167**, L35 (1971).
22. R. Stothers, *ibid.* **197**, L25 (1975).
23. K. M. Merrill, thesis, University of California at San Diego (1975). The impressive and extensive results of this work are presented in K. M. Merrill and W. A. Stein, *Publ. Astron. Soc. Pac.* **88**, 285 (1976); *ibid.*, p. 294; *ibid.*, in press.
24. R. Treffers and M. Cohen, *Astrophys. J.* **188**, 545 (1974).
25. R. H. Gammon, J. E. Gaustad, R. R. Treffers, *ibid.* **175**, 687 (1972).
26. E. E. Becklin and J. A. Westphal, *ibid.* **145**, 445 (1966).
27. R. W. Maas, E. P. Ney, N. J. Woolf, *Astrophys. J. Lett.* **160**, L101 (1970).
28. E. P. Ney, *ibid.* **189**, L141 (1974).
29. I. Gatley, E. E. Becklin, G. Neugebauer, M. W. Werner, *Icarus* **23**, 561 (1974).
30. K. M. Merrill, *ibid.*, p. 566.
31. E. P. Ney, *ibid.*, p. 551.
32. G. H. Rieke and T. A. Lee, *Nature (London)* **248**, 737 (1974).
33. M. Zeilik, *ibid.*, p. 120.
34. Z. Sekanina, *Sky Telesc.* **47**, 374 (1974).
35. ———, *Icarus* **23**, 502 (1974).
36. E. P. Ney, *Bull. Am. Astron. Soc.* **7** (No. 4), 508 (1975).
37. ——— and K. M. Merrill, *Science* **194**, 1051 (1976).
38. A. R. Hyland and G. Neugebauer, *Astrophys. J. Lett.* **160**, L177 (1970).
39. S. L. Geisel, D. E. Kleinman, F. J. Low, *Astrophys. J.* **161**, L101 (1970).
40. S. Kleinman, personal communication.
41. J. S. Gallagher and E. P. Ney, *Astrophys. J. Lett.* **204**, L35 (1976).
42. G. Neugebauer and J. A. Westphal, *ibid.* **152**, L89 (1968).
43. G. Robinson, A. R. Hyland, J. A. Thomas, *Mon. Not. R. Astron. Soc.* **161**, 281 (1973).
44. R. D. Gehrz, E. P. Ney, E. E. Becklin, G. Neugebauer, *Astrophys. Lett.* **13**, 89 (1973).
45. G. Neugebauer, D. E. Martz, R. B., Leighton, *Astrophys. J.* **142**, 399 (1965).
46. G. H. Herbig, *ibid.* **172**, 375 (1972).
47. ———, *ibid.* **200**, 1 (1975).
48. E. P. Ney, *Sky Telesc.* **49**, 21 (1975).
49. S. J. Shawl and M. Tarenghi, *Astrophys. J. Lett.* **204**, L25 (1976).
50. D. Crampton, A. P. Cowley, R. M. Humphreys, *ibid.* **198**, L135 (1975).
51. E. P. Ney *et al.*, *ibid.*, p. L129.
52. B. Zuckerman, D. P. Gilra, B. E. Turner, M. Morris, P. Palmer, *ibid.* **205**, L15 (1976).
53. K. Y. Lo and K. P. Bechis, *ibid.*, p. L21.
54. E. W. Gottlieb and W. Liller, *ibid.* **207**, L135 (1976).
55. L. A. Rose, in preparation.
56. K. L. Day, *Astrophys. J. Lett.* **192**, L15 (1974).
57. C. L. Hemmenway, D. C. Hallgren, D. C. Schmalberger, *Nature (London)* **238**, 256 (1972).
58. I am grateful for research support from the National Aeronautics and Space Administration and the National Science Foundation and thank K. M. Merrill for his helpful comments on the manuscript.

Mathematics Underlying the Rate-Dependency Hypothesis

The mathematics of rate-dependency interpretations of the effects of drugs on behavior are examined.

Fernando A. Gonzalez and Larry D. Byrd

The sensitivity of operant behavior (behavior controlled by its past consequences) to drugs acting on the central nervous system was demonstrated in laboratory experiments nearly four decades ago (*1*), yet the impetus for the use of experimentally controlled operant behavior as a tool in behavioral pharmacology came in the 1950's, when Dews undertook a systematic analysis of the behavioral effects of drugs, using the procedures developed by Skinner (*2*) to study operant behavior. Dews performed his experiments on food-deprived pigeons trained to peck a small plastic disk to obtain temporary access to grain (*3*). A microswitch behind the disk was operated by each peck, providing an objective measure of pecking responses. Food presentation—that is, access to grain—was dependent on the pigeons' responding and occurred intermittently in accordance with one or more rules, commonly called schedules, which were programmed by means of electronic equipment. Under a fixed-ratio schedule, for example, every nth response was immediately followed by food presentation; under a fixed-interval schedule, the first response occurring after a fixed time had elapsed was followed by food presentation. These and other schedules of reinforcement maintained characteristic patterns of responding that were consistent and reproducible across sessions and subjects, and provided stable baselines for studying the effects of drugs (*4*).

Initially, reports by Dews and other investigators describing the effects of drugs on schedule-controlled operant behavior emphasized the role of the schedule, the distinctive stimuli associated

Fernando Gonzalez is a research associate and Larry Byrd is chairman of the Division of Primate Behavior, Yerkes Regional Primate Research Center, Emory University, Atlanta, Georgia 30322.

with the schedule, and the nature of the consequent event controlling and maintaining the behavior as factors determining the type of drug effect (*5*). Subsequently, the hypothesis was proposed that response rates (number of responses per unit time) observed after the administration of certain drugs were systematically related to response rates in the absence of the drugs (*6–8*). When drug-induced changes in response rates were plotted as a function of control (nondrug) response rates on logarithmic paper, the distribution of points often fell along a straight line, as in Fig. 1.

The data comprising Fig. 1 were obtained with a baboon (*Papio anubis*) trained to press a lever under a 10-minute fixed-interval schedule of food presentation. Performance under nondrug conditions was characterized by a period of no responding followed by acceleration of responding to a rate that was maintained until food presentation. This pattern of positively accelerated responding recurred during each of the nine fixed-interval schedule components that comprised a session. Responding was recorded separately during individual 1-minute segments of each 10-minute fixed-interval schedule component and used to compute the mean rate during each 1-minute segment. Figure 1 shows the effect of intramuscular administration of *d*-amphetamine (0.3 milligram per kilogram of body weight) on responding during individual 1-minute segments of the fixed interval as a function of response rate in the absence of the drug. The change in response rate following drug administration (drug rate) is expressed on the ordinate as a percentage of the response rate in the respective 1-minute segments during experimental sessions when no drugs were administered (control rate). The scale on both axes is logarithmic. Data of this type have been interpreted as indicating that the effect of the drug is dependent on the control rate of responding.

Since its initial formulation by Dews (*6, 8*), the concept of rate dependency has enjoyed increasing popularity because of its usefulness for characterizing the effects of drugs on operant behavior. Studies continue to broaden the empirical support for the rate-dependency hypothesis by showing that the effects of a variety of drugs under a diversity of conditions appear to be a function of the control rate of responding (*9–21*). Yet, despite the widespread application of rate dependency to characterize the behavioral effects of drugs, there has been no formal examination of the mathematics underlying rate dependency or of constraints on interpretations of linear regression lines fit to the data plotted on logarithmic paper. In the absence of a clear understanding of the mathematical rules, there is opportunity for misinterpretation of the meaning of the regression lines and erroneous conclusions about the determinants of drug effects. In this article we briefly examine the mathematics relevant to linear regression lines on log-log plots and evaluate various interpretations that can be made of data plotted in this manner.

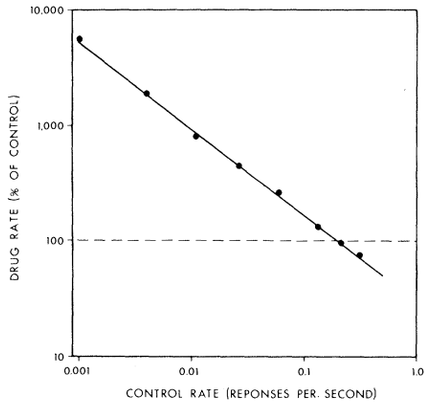

Fig. 1. Effect of *d*-amphetamine on responding in a baboon. Responding after intramuscular administration of *d*-amphetamine (0.3 mg/kg) expressed as a percentage of the control rate ($100R_d/R_c$) is plotted against the mean rate of responding during individual 1-minute segments of a 10-minute fixed-interval schedule during control (nondrug) sessions. The regression line through the points was fitted by least squares. The two missing data points correspond to 1-minute segments at the beginning of the interval during which the control rate was zero.

Significance of the Slope and *y*-Intercept

Data of the type comprising Fig. 1 have been interpreted as indicating that *d*-amphetamine increases low response rates proportionally more than it increases intermediate rates, while at the same time decreasing high rates. Such data are said to demonstrate that the drug effects are dependent on the control rates of responding. This interpretation is usually proposed when the distribution of data points approximates a straight line, as in Fig. 1. Assuming that a straight line best fits the data, the relation between percentage changes in response rate (that is, changes in the ratio of drug rate to control rate) and control rate of responding can be expressed as

$$\log(R_d/R_c) = \log k + j\log R_c \qquad (1)$$

where R_d is the rate of responding in the presence of a drug (drug rate), R_c is the rate of responding in the absence of a drug (control rate), and k (> 0) and j are values selected for best fit for each specific subject, procedure, drug, and dose.

It follows from Eq. 1 that

$$\log R_d = \log k + (j + 1)\log R_c \qquad (2)$$

and

$$R_d = kR_c^{\,j+1} \qquad (3)$$

Note that while Eq. 3 suggests that the drug rate can depend on the control rate, the values of k and j determine the precise form of the relationship between R_d and R_c and thus the extent to which R_d is dependent on R_c. If $j = 0$ then $R_d = kR_c$, and R_d is directly proportional to R_c. If $j = -1$, then $R_d = k$, and R_d is independent of R_c. If $j = -2$, then $R_d = k/R_c$, and R_d is inversely proportional to R_c. One can see that as $j \to 0$ and $k \to 1$, $R_d \to R_c$; that is, the drug effect becomes progressively smaller. Moreover, as $|j + 1| \to 0$, R_c becomes less important as a factor determining R_d. Consequently, when the ratio R_d/R_c is plotted against R_c, as in Fig. 1, R_c becomes less important in determining R_d as the slope of the regression line approaches -1. A linear regression line with a slope (j) of -1 indicates that R_d, the drug rate, is constant and therefore is independent of R_c, the control rate.

The relation between R_d and R_c can be unclear when the ratio R_d/R_c is plotted as a function of R_c, as in Fig. 1; it can be made more apparent and less subject to misinterpretation by plotting R_d as a function of R_c. In Fig. 2, seven representative curves are plotted with respect to four different sets of axes to illustrate how the relation between R_d and R_c can be made more or less clear by the manner in which the data are plotted. Each of the seven curves represents a specific relation between R_d and R_c. All the curves were obtained from Eq. 3 by assigning different values to j and k, as indicated in the legend of Fig. 2. Curve a represents equality between R_d and R_c and indicates no effect of the drug; curve b represents a constant R_d and indicates that R_d is independent of R_c; curve c indicates that R_d is inversely proportional to R_c; the other curves represent other possible relationships between R_d and R_c. In Fig. 2, A and B, R_d is plotted as a function of R_c. However, in Fig. 2A the scale on the axes is logarithmic, and in Fig. 2B the scale is arithmetic. In Fig. 2, C and D, the ratio R_d/R_c is plotted as a function of R_c, but in Fig. 2C the scale on the axes is logarithmic whereas in Fig. 2D it is arithmetic. The relation between R_d and R_c is more clearly indicated by

each of the seven curves in Fig. 2, A and B, than in Fig. 2, C and D. For example, equality between R_d and R_c (curve a), independence of R_d and R_c (curve b), and inverse proportionality between R_d and R_c (curve c) are more readily apparent in Fig. 2, A and B. Accordingly, studies of the rate-dependent effects of drugs would be less subject to misinterpretation if the data were plotted with R_d rather than the ratio R_d/R_c on the ordinate.

Constraints Imposed by the Limits of Response Rate

Although the rate-dependency hypothesis has generated much interest in the relation between control rate of responding, R_c, and the ratio R_d/R_c, surprisingly little attention has been given to the range of values R_d and R_c can possibly assume. Yet there obviously are limits on the values of these two variables, and the limits can, in turn, constrain the relation between R_d/R_c and R_c. Clearly, R_d and R_c must be greater than or equal to zero since response rates cannot be negative. Each must also be less than or equal to a value R_m, the maximum response rate possible. Presumably, R_m is determined by numerous factors, including the biological limitations of the organism, the characteristics of the recording system, the topography of the behavior, and the operational definition of the response. It is assumed, for simplicity, that R_m is constant for each specific subject and procedure (*22*).

Because R_d and R_c are values between zero and R_m, the value of the ratio R_d/R_c can be no less than zero but it can be infinitely large as $R_c \rightarrow 0$. Since $R_d/R_c = 1$ (or 100 on a percent scale) when there is no change in response rate due to drug administration, the maximum decrease in R_d/R_c due to drug administration will be from 1 to 0 (or 100 percent) regardless of the value of R_c. However, increases in R_d/R_c can be infinitely large and dependent on R_c. The maximum increase in R_d/R_c for a particular R_c occurs when $R_d = R_m$. Moreover, as R_c increases from zero to R_m the maximum value of R_d/R_c, $(R_d/R_c)\max$, decreases according to the equation $(R_d/R_c)\max = R_m/R_c$. Thus, increases in R_d/R_c can range from 0 to ∞, depending on the value of R_c/R_m. As R_c gets smaller and $R_c/R_m \rightarrow 0$, then $(R_d/R_c)\max \rightarrow \infty$; that is, the maximum possible increase approaches infinity. If $R_c/R_m = 0.5$, then $(R_d/R_c)\max = 2$, and the maximum possible increase is twofold. If $R_c/R_m = 1$, then $(R_d/R_c)\max = 1$, and there can be no increase. Therefore, given that there is an upper limit of response rate (R_m), the maximum proportional increase in rate has to decrease as control rate (R_c) increases; hence, the magnitude of proportional increments in rate necessarily depends on the control rate.

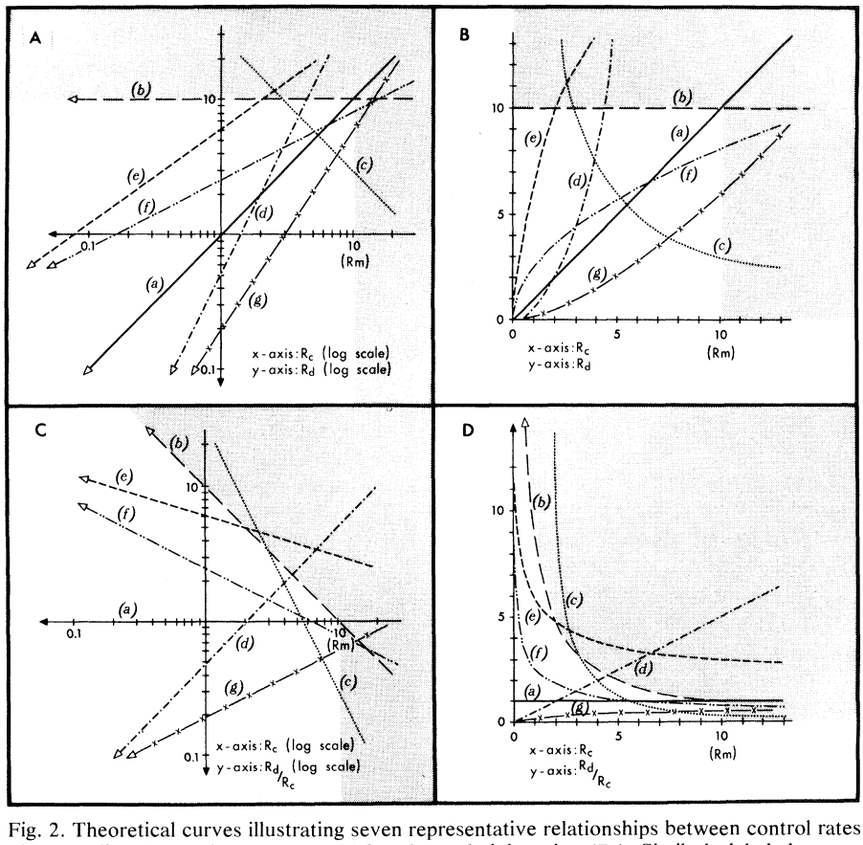

Fig. 2. Theoretical curves illustrating seven representative relationships between control rates of responding (R_c) and response rate after drug administration (R_d). Similarly labeled curves represent the same relation plotted in four different ways. All curves were obtained from the equation $R_d = kR_c^{j+1}$, where k and j are constants and $k > 0$. The unshaded area in each panel is the region within which the equations can accurately describe the relation between R_c and R_d within the restrictions imposed on the possible values of R_c and R_d by the assumption of a constant maximum possible rate (R_m), such that $R_c \leq R_m$ and $R_d \leq R_m$. Here R_m was assumed to have a value of 10. The values of the constants k and j for each curve and the range of values of R_c for which each curve can accurately describe the relation between R_c and R_d (assuming $R_m = 10$) are: (a) $k = 1.0, j = 0, 0 \leq R_c \leq 10$; (b) $k = 10, j = -1.0, 0 \leq R_c \leq 10$; (c) $k = 30$, $j = -2.0$, $3.0 \leq R_c \leq 10$; (d) $k = 0.5$, $j = 1.0$, $0 \leq R_c \leq 4.472$; (e) $k = 6$, $j = -0.3$, $0 \leq R_c \leq 2.074$; (f) $k = 2.5, j = -0.5, 0 \leq R_c \leq 10$; and (g) $k = 0.2, j = 0.5, 0 \leq R_c \leq 10$.

Since the maximum possible increases in rate are determined by the value of R_c and the value of R_m, it is of interest and importance to examine precisely how R_m can affect the relation between R_d and R_c. One effect of R_m is apparent if we consider the relation between the ratios R_d/R_m and R_c/R_m. Assuming that Eq. 3 accurately describes the relation between R_d and R_c, then from Eq. 3

$$R_d/R_m = kR_c^{j+1}/R_m$$

and

$$\log R_d/R_m = \log k + (j + 1)\log R_c - \log R_m$$

Since

$$\log R_c = \log R_c/R_m + \log R_m$$

then

$$\log R_d/R_m = \log k + (j + 1)(\log R_c/R_m + \log R_m) - \log R_m$$

and

$$\log R_d/R_m = \log k R_m^j + (j + 1)\log R_c/R_m \quad (4)$$

Equation 4 describes a line with a slope equal to $(j + 1)$ and a y-intercept determined by the value of R_m. Therefore, if the administration of a drug across subjects or procedures (for which R_m may differ) results in linear relationships between $\log R_d$ and $\log R_c$ (Eq. 2) with different y-intercepts (k) but similar slopes $(j + 1)$, it would be possible to plot $\log R_d/R_m$ as a function of $\log R_c/R_m$

(Eq. 4) and find a common regression line. Conversely, similar relations between R_d and R_c across subjects or procedures may appear less similar if R_m is taken into account. Hence, knowledge of the value of R_m is necessary to compare linear regression lines obtained for different subjects or across different procedures.

The role of R_m discussed above is predicated on the assumption that Eq. 3 provides a good description of the data; that is, the distribution of data points on a log-log plot conforms to a straight line. A more important effect of R_m, however, is that it can restrict the range of values of R_c for which Eq. 3 can, in fact, be an accurate model of the relation between R_d and R_c. The unshaded areas in Fig. 2 denote the range of values R_d (Fig. 2, A and B) or R_d/R_c (Fig. 2, C and D) can assume as a function of R_c when R_m is 10. The seven curves in each panel were obtained from Eq. 3 with values of k and j as specified in the legend to Fig. 2. In each panel, curve b represents a constant R_d that is equal to R_m, and therefore curve b represents the maximum possible rate or maximum rate increase. Another boundary of the unshaded area is the point along the abscissa where R_c is equal to R_m. Each curve can accurately describe a relation between R_d and R_c (or R_d/R_c and R_c) only over the range of values of R_c corresponding to the portion of the curve within the unshaded area of the panel. Thus, curves a, b, f, and g can describe the relation between R_d and R_c over all possible values of R_c; that is, $0 \leq R_c \leq 10$. On the other hand, the value of R_c at which curves c, d, and e intersect curve b (that is, the curve representing $R_d = R_m$) limits the range of values of R_c over which those curves can accurately represent the data.

The range of values of R_c for which Eq. 3 will be an accurate model of the empirical relation between R_d and R_c depends on the values of j, k, and R_m, and can easily be determined. Since $R_d \leq R_m$, then from Eq. 3

$$R_m \geq kR_c^{j+1}$$

and

$$R_c \leq (R_m/k)^{1/(j+1)}$$

Multiplying and dividing the right sides of the inequalities by R_m we have

$$R_c \leq [R_m^{-j/(j+1)}R_m]/k^{1/(j+1)}$$

or

$$R_c \leq (kR_m^{j})^{-1/(j+1)}R_m \qquad (5)$$

Therefore, Eq. 3 will accurately describe the relation between R_d and R_c only for values of R_c for which inequality 5 holds; that is,

for all R_c

$$\text{if } k \leq R_m^{-j} \text{ and } j \geq -1$$

for no R_c

$$\text{if } k \geq R_m^{-j} \text{ and } j \leq -1$$

for $R_c \leq (R_m/k)^{1/(j+1)}$

$$\text{if } k > R_m^{-j} \text{ and } j > -1$$

for $R_c \geq (R_m/k)^{1/(j+1)}$

$$\text{if } k < R_m^{-j} \text{ and } j < -1$$

The range of values of R_c for which each curve in Fig. 2 could describe a specific relation between R_d and R_c was calculated by applying inequality 5 and is given in the legend.

The importance of R_m as a factor affecting the relation between R_d and R_c can be further emphasized by introducing it as a term in Eq. 3. Thus, if A is the antilogarithm of the y-intercept in Eq. 4, then $A = kR_m^{j}$ and $k = AR_m^{-j}$. Substituting for k in Eq. 3 we have

$$R_d = AR_m^{-j}R_c^{j+1} \qquad (6)$$

where A (> 0) and j are values selected for best fit for each specific subject, procedure, drug, and dose; R_m is a constant for each specific subject and procedure; and $0 \leq (R_d, R_c) \leq R_m$.

Discussion

The foregoing analysis (i) emphasizes the importance of the slope and the y-intercept, as well as the maximum possible response rate, in the interpretation of linear regression lines fitted to data points representing proportional changes in response rate (R_d/R_c) as a function of control response rate (R_c) on logarithmic axes (Fig. 1), and (ii) reveals the limitations of the model of rate dependency that is based on the assumption that linear regression lines provide best fits to such data. Data of the type shown in Fig. 1 have often been proposed as evidence that the behavioral effects of a variety of psychoactive drugs depend on the rate of responding in the absence of the drug. Although it is generally acknowledged that the slope and y-intercept of straight lines fitted to such data are important features of the data, their significance has seldom been discussed. In the few papers where we found allusion to the meaning of specific values of slope and y-intercept, the interpretations offered were incorrect. For example, it has been suggested that in plots of R_d/R_c as a function of R_c a linear regression line with slope (j) of 0 and y-intercept (k) other than 1 indicates that the effects of a drug are independent of control rate, and that a linear regression line with a slope of -1 indicates that the effects of the drug are inversely proportional to the control rate (*10, 11*). Our analysis demonstrates, however, that a linear regression line with a slope of 0 indicates no effect of a drug if the y-intercept is 1 ($R_d = R_c$) and indicates proportionality between drug rate and control rate if the y-intercept is other than 1 ($R_d = kR_c$). Similarly, our analysis shows that a regression line with a slope of -1 indicates that the effect of the drug is independent of control rate ($R_d = k$), and that a slope of -2 would be required to indicate inverse proportionality. In general, as $j \rightarrow 0$ and $k \rightarrow 1$, the drug effect becomes smaller ($R_d \rightarrow R_c$); as $|j + 1| \rightarrow 0$, the value of R_c becomes less important as a factor determining the value of R_d. A linear regression line of good fit with a slope of -1 indicates that R_d is constant and therefore independent of R_c. Consistent with this present analysis, a recent report showed that if drug rate is constant, a linear regression line with slope -1 necessarily describes the relationship between percentage change in response rate ($100R_d/R_c$) and the control rate (R_c) when plotted on logarithmic paper (*23*).

A cursory examination of publications reporting rate-dependent effects of drugs reveals that the slopes of regression lines fitted to logarithmic plots of drug data are seldom more negative than -1 and seldom positive, and that the slopes of many of the regression lines are close to -1 (*10–14, 16–21*). Published data also suggest that when the slope is close to 0, the y-intercept is usually close to 1, indicating that the effect of the drug is small. Generally, as the dose and effect of the drug increase, the slope of the regression line becomes more negative and approaches -1. According to our analysis, this indicates that as drug dose increases, rate of responding becomes more and more constant. Eventually, of course, a dose is reached that suppresses or disrupts responding. Therefore, many of the data interpreted as demonstrating rate-dependent drug effects can also be interpreted as indicating that drugs cause responding to approach a more constant

rate or level. The constant rate approached will depend on the drug, dose, subject, procedure, and maximum possible rate (R_m).

Interpretations of regression lines resulting in misunderstanding of the relation between R_c and R_d have presumably derived from the traditional use of the ratio R_d/R_c as the dependent variable. The value of R_d/R_c is obviously dependent on the value of R_c, since R_c is the denominator of the fraction. Whether or not R_d varies as a function of R_c, the value of R_d/R_c will always depend on the value of R_c. For example, when R_d is constant, as in curve b of Fig. 2, the value of R_d/R_c will change as a function of R_c. Therefore, in the absence of an explicit rationale for the use of R_d/R_c as the dependent variable, we believe that a clearer and more revealing way to display the dependence of response rate after drug on control rate of responding is to plot R_d as a function of R_c (*24*).

The present analysis also specifies how the existence of an upper limit of response rate (R_m) can constrain the possible form of the relation between R_c and R_d. Thus, in order to appropriately interpret data relating R_d and R_c, it is essential to know the value of R_m. If R_m is not known, for example, it is inappropriate to compare drug effects among different subjects or procedures for which R_m may be a confounding factor. Moreover, knowing the value of R_m is of importance not only when analyzing data in terms of possible rate-dependent effects, but also when performing other types of analyses, such as the effects of drugs on mean response rates.

Heretofore, maximum response rate has not been generally recognized as an important parameter that can limit or determine changes in performance following drug administration. Presumably because of this, no study has been conducted in which the value of R_m is either measured or controlled. Such studies will be required to assess more precisely the importance of R_m in determining drug effects. We believe that this will become an important area for research, and one which can provide answers to many questions about the behavioral effects of drugs. Of course, some answers may be provided by a retrospective examination of existing data. It is possible, for example, that occasional systematic deviations of data points from linear regression lines reflect attainment of the maximum rate. An appropriate analysis of such data may provide estimates of the value of R_m, which may then be used to reanalyze the effects of other drugs in the same subject. We must bear in mind, however, that R_m is presumed to be constant for each subject under a given set of specifiable conditions. Therefore, while the values of j and A in Eq. 6 are chosen for best fit of the equation to the data, the value of R_m should be determined from data other than those being fitted. Also, instead of deriving the value of R_m from the data in accordance with the assumptions of the model, it is preferable to measure R_m more directly. Thus, we believe that the retrospective approach will be less fruitful than the development of procedures for the experimental control and prospective analysis of R_m.

Much of the foregoing analysis is based on the assumption that a straight line provides a good fit to drug data displayed on log-log plots of R_d/R_c as a function of R_c (Fig. 1), and therefore on the assumption that Eq. 3 satisfactorily describes the relationship between R_d and R_c. We have not attempted to critically evaluate the empirical support for Eq. 3, but to correct erroneous interpretations that have apparently been made on the basis of that model, and also to describe some of the logical implications and limitations of the model. As previously noted, there are published data that have been generally accepted as supporting the rate-dependency hypothesis. However, in view of our analysis, Eq. 3 (or Eq. 6) can be said to provide an accurate and parsimonious account of drug effects only if it is shown that with values of j significantly different from -1, the equation provides a statistically "good" description of the data. While there is evidence that this may be true, it has not been demonstrated conclusively. Whether Eq. 3 is a good model of the relation between R_d and R_c and whether R_m proves to be constant will determine the usefulness of this analysis. Although it could be argued that R_m is not constant over the period of observation, whereas our analysis assumes it is, the existence of a maximum rate can hardly be doubted. We believe that whatever the form of the relation between R_d and R_c, R_m will be an important factor in the equation. Furthermore, it is likely that R_m is also an important factor determining the effects of other (nondrug) independent variables on response rate.

References and Notes

1. B. F. Skinner and W. T. Heron, *Psychol. Rec.* **1**, 340 (1937).
2. B. F. Skinner, *The Behavior of Organisms* (Appleton-Century-Crofts, New York, 1938); C. F. Ferster and B. F. Skinner, *Schedules of Reinforcement* (Appleton-Century-Crofts, New York, 1957).
3. P. B. Dews, *Ann. N.Y. Acad. Sci.* **65**, 268 (1956).
4. ———, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **17**, 1024 (1958); in *Methods in Psychobiology*, R. D. Myers, Ed. (Academic Press, New York, 1972), pp. 83–124.
5. ———, *J. Pharmacol. Exp. Ther.* **115**, 380 (1955); J. V. Brady, in *The Effects of Pharmacologic Agents on the Nervous System*, P. J. Braceland, Ed. (Williams & Wilkins, Baltimore, 1959), pp. 104–125; A. Weissman, *J. Exp. Anal. Behav.* **2**, 271 (1959); P. B. Dews and W. H. Morse, *Annu. Rev. Pharmacol.* **1**, 145 (1961); L. Cook and R. T. Kelleher, *Ann. N.Y. Acad. Sci.* **96**, 315 (1962).
6. P. B. Dews, *J. Pharmacol. Exp. Ther.* **122**, 137 (1958).
7. L. Cook and A. C. Catania, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **23**, 818 (1964); F. C. Clark and B. J. Steele, *Psychopharmacologia* **9**, 157 (1966); R. T. Kelleher and W. H. Morse, *Ergeb. Physiol. Biol. Chem. Exp. Pharmakol.* **60**, 1 (1968).
8. P. B. Dews, *Naunyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol.* **248**, 296 (1964).
9. C. B. Smith, *J. Pharmacol. Exp. Ther.* **146**, 167 (1964); D. E. McMillan, *ibid.* **163**, 172 (1968); F. C. Clark, *J. Exp. Anal. Behav.* **12**, 977 (1969); J. W. McKearney, *ibid.* **14**, 167 (1970); W. Wuttke, *Psychopharmacologia* **17**, 70 (1970); D. J. Sanger and D. E. Blackman, *J. Pharmacol. Exp. Ther.* **194**, 343 (1975).
10. M. J. Marr, *J. Exp. Anal. Behav.* **13**, 291 (1970).
11. J. D. Leander, *J. Pharmacol. Exp. Ther.* **193**, 689 (1975).
12. D. E. McMillan, *Psychopharmacologia* **30**, 61 (1973).
13. ———, *J. Exp. Anal. Behav.* **19**, 133 (1973).
14. J. E. Barrett, *ibid.* **22**, 561 (1974).
15. M. N. Branch and L. R. Gollub, *ibid.* **21**, 519 (1974).
16. M. Stitzer, *J. Pharmacol. Exp. Ther.* **191**, 172 (1974).
17. N. W. Bond, D. J. Sanger, D. E. Blackman, *ibid.* **194**, 327 (1975).
18. L. D. Byrd, *ibid.* **193**, 861 (1975).
19. R. C. MacPhail and L. R. Gollub, *ibid.* **194**, 332 (1975).
20. G. R. Wenger, *ibid.* **196**, 172 (1976).
21. ——— and P. B. Dews, *ibid.*, p. 616.
22. The maximum possible rate (R_m) has no theoretical status in our formulation. We propose that the value of R_m should be measured directly. Thus, R_m differs from k, the asymptotic rate in Herrnstein's matching law [R. J. Herrnstein, *J. Exp. Anal. Behav.* **21**, 159 (1974)], in that k is not measured directly, but is instead a curve-fitting parameter.
23. C. Ksir, *Pharmacol. Biochem. Behav.* **4**, 165 (1976).
24. To our knowledge, only Branch and Gollub (*15*) and M. Stitzer, J. Morrison, and E. F. Domino [*J. Pharmacol. Exp. Ther.* **171**, 166 (1969)] have plotted their data in this manner.

25. Supported by PHS grants DA 01161 and RR 00165. We thank W. S. Mahavier, P. B. Dews, and M. J. Marr for helpful comments and P. Plant for technical assistance.