Predicting the Abuse Liability of Drugs with Animal Drug Self-Administration Procedures:
Psychomotor Stimulants and Hallucinogens

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Baltimore, Maryland

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I. INTRODUCTION

This chapter will review the procedures and results of drug self-administration research in laboratory animals which provide information about the abuse liability of drugs in man. Since the majority of studies to date involve psychomotor stimulant compounds, the emphasis of the chapter will be on the stimulant class of drugs, including structurally related compounds, some of which are hallucinogens. Overall, the results reviewed in this chapter show that various aspects of the self-administration and reinforcing functions of drugs can be measured reliably, and that there is a generally good correspondence between these preclinical measures and the available clinical information about the subjective effects and incidence of abuse of the drugs.

The chapter is organized under three major sections. In the first section procedures are described for determining whether a drug will maintain self-administration behavior. The research literature is summarized indicating which psychomotor stimulant and hallucinogen drugs have been shown to be self-administered. In the second section of the chapter more complex self-administration procedures are described which have been developed for assessing the relative reinforcing efficacy of different stimulant drugs. The final section of the chapter addresses a related but conceptually different issue involving the determination of the relationship between the reinforcing effects and the therapeutic effects of drugs. All three sections include a discussion about the correspondence between the animal data and the existing clinical information.

II. PROCEDURES FOR DETERMINING WHETHER DRUGS MAINTAIN SELF-ADMINISTRATION BEHAVIOR

During the last 15 years researchers in the area of operant behavioral pharmacology have developed a variety of methods to examine drug self-administration in animals (Schuster & Thompson, 1969; Spearman & Goldberg,
1978; Thompson & Unna, 1977). Most of the methods involve making a response operandum available to an animal; responses on the operandum activate control equipment which results in delivery of a drug. Results with these methods have shown that animals will increase their response rates on the operandum, and thus self-administer some types of drugs. Such drug self-administration has been established using different species (e.g., rat, cat, dog, monkey, baboon), types of operandum (e.g., lever press, panel press), and routes of administration (e.g., intravenous, oral, intragastric, inhalation, intramuscular). A broad range of experimental questions can be addressed with this experimental methodology involving the basic pharmacological and behavioral mechanisms necessary to the establishment, maintenance, and elimination of drug self-administration behavior.

One interesting set of questions involves differentiating between drugs with respect to their relative ability to maintain self-administration. Interest in this scientific question was stimulated when it was recognized that there is a good correspondence between those drugs self-administered by laboratory animals and those abused by man (Schuster & Thompson, 1969). In 1970, interest was further augmented when Congress passed the Controlled Substances Act which required that drugs be classified under a five-tier schedule system which differentiated between drugs on the basis of several criteria, including their actual or relative potential for abuse.

Many different types of procedures have been developed to determine whether a drug will maintain self-administration. The present section of this chapter will first involve a detailed description of methods and results for testing psychomotor stimulants and hallucinogens for intravenous self-administration in the baboon. Subsequently, a comprehensive literature review of all psychomotor stimulant and hallucinogen self-administration studies will be presented and these data will be discussed in relation to what is known clinically about the abuse potential of these drugs.

A. Self-Administration of Phenylethylamines and Psychomotor Stimulants in the Baboon

The substitution procedure is the most common and reliable method for determining whether a drug will maintain self-administration. The procedure simply involves establishing self-administration using a dose of a standard drug which is known to maintain reliable self-administration behavior. After this behavior baseline has stabilized, a dose of the test drug is substituted for the standard compound to determine whether the test drug will maintain self-administration. Using this basic procedure, Griffiths, Winger, Brady, and Snell (1976) previously reported on the self-administration of eight phenylethylamine compounds. Described below is an expanded version of this experiment in which 17
phenylethylamines and psychomotor stimulants were evaluated in the baboon.

Figure 1 shows the chemical structures of the 14 compounds which are phenylethylamines. Nine of these compounds are clinically used as anorectics (d-amphetamine [Dexedrine®], phentermine [Ionamin®], diethylpropion [Tenuate®], phenmetrazine [Preludin®], benzphetamine [Didrex®], clortermine [Voranil®], chlorphentermine [Pre-Sat®], and fenfluramine [Pondimin®]). Four

<table>
<thead>
<tr>
<th>8-AMPHETAMINE</th>
<th>CLOTERMIN</th>
</tr>
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<tr>
<td><img src="image1" alt="8-AMPHETAMINE" /></td>
<td><img src="image2" alt="CLOTERMIN" /></td>
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<tr>
<td>PHENTERMINE</td>
<td>CHLORPHENTERMINE</td>
</tr>
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<td><img src="image3" alt="PHENTERMINE" /></td>
<td><img src="image4" alt="CHLORPHENTERMINE" /></td>
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<td>DIETHYLPROPION</td>
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<td>PHENMETRAZINE</td>
<td>3,4-METHYLENEDIOXYAMPHETAMINE (MDA)</td>
</tr>
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<td><img src="image8" alt="3,4-METHYLENEDIOXYAMPHETAMINE" /></td>
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<tr>
<td>PHENMETRAZINE</td>
<td>4-METHOXYAMPHETAMINE (PMA)</td>
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<td><img src="image10" alt="4-METHOXYAMPHETAMINE" /></td>
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<tr>
<td>BENZPHERMINE</td>
<td>7,5-DIMETHOXY 4-METHYLAMPHETAMINE (DOM)</td>
</tr>
<tr>
<td><img src="image11" alt="BENZPHERMINE" /></td>
<td><img src="image12" alt="7,5-DIMETHOXY 4-METHYLAMPHETAMINE" /></td>
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<tr>
<td>Δ-L-EPHEDRINE</td>
<td>7,5-DIMETHOXY 4-ETHYLAMPHETAMINE (DOE)</td>
</tr>
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<td><img src="image13" alt="Δ-L-EPHEDRINE" /></td>
<td><img src="image14" alt="7,5-DIMETHOXY 4-ETHYLAMPHETAMINE" /></td>
</tr>
</tbody>
</table>

Fig. 1. Chemical structures of the 14 phenylethylamines tested to determine whether they maintained drug self-administration.
The compounds are not used clinically, and are considered to have hallucinogenic properties (MDA, PMA, DOM, and DOET). The final compound (l-ephedrine) is used clinically for bronchial muscle relaxation, cardiovascular, and mydriatic effects. Figure 2 shows the chemical structures of three additional psychomotor stimulant compounds (cocaine, caffeine, and nicotine) which were also examined in the self-administration procedure. All three of these drugs are used by man in nontherapeutic situations for their CNS effects.

1. Methods

The methods and procedures used in this study were identical to those described in a previously published evaluation of the self-administration of psychomotor stimulant drugs (Griffiths et al., 1976) and therefore the details will be described only briefly here. Fifteen male baboons (Papio anubis and Papio hamadryas) weighing 15–24 kg served as subjects. Animals had histories involving drug self-infusion of a variety of drugs. Each animal was adapted to a standard restraint cart (Findley, Robinson, & Gilliam, 1971) and individually housed in a sound-attenuated chamber approximately $0.8 \times 1.2 \times 1.2$ m. Water via a drinking tube and the opportunity to respond for food (1 g Purina monkey pellets) were continuously available. The food lever was located in the lower right side of the animal's intelligence panel and pellets were available on a fixed-ratio schedule (the response requirement was either 15 or 25).

After training to press a lever for food pellets, each animal was surgically prepared with an intravenous catheter, using the general procedure described by
Deneau, Yanagita, and Seevers (1969). Placement of the catheter tip was near the right atrium by way of the femoral or jugular vein. The catheter passed subcutaneously and exited in the middle of the back. Drug was infused into the catheter by means of a syringe pump and then flushed into the animal with saline from a second syringe pump. This system necessitated a delay of approximately 20 sec between onset of drug delivery and actual infusion into the vein. All drugs were delivered within a 2-min period. The total volume of fluid delivered during each infusion was 10 ml (5 ml drug solution followed by 5 ml saline). In experiments involving manipulation of drug dose, the volume of drug solution per infusion and the duration of infusion remained constant throughout the experiment. Drug solutions were prepared by dissolving the drug in 0.9% saline solution. Drug doses were calculated on the basis of the salt. The following drug doses (mg/kg per infusion) were tested: d-amphetamine sulfate (0.01, 0.05, 0.1, 0.5), phentermine hydrochloride (0.1, 0.5, 1.0), diethylpropion hydrochloride (0.1, 0.5, 1.0, 2.0), phenmetrazine hydrochloride (0.1, 0.5, 1.0, 2.0), phendimetrazine tartrate (0.1, 0.5, 1.0, 2.0), benzphetamine hydrochloride (0.1, 0.5, 1.0, 3.0), ephedrine hydrochloride (0.3, 1.0, 3.0, 10.0), clortermine hydrochloride (0.1, 1.0, 3.0, 5.0), chlorphentermine hydrochloride (0.1, 0.5, 2.5, 5.0), fenfluramine hydrochloride (0.02, 0.1, 0.5, 2.5), 1-3,4-methylenedioxyamphetamine sulfate (MDA) (0.1, 0.5, 1.0, 2.0, 5.0), 4-methoxymethamphetamine hydrochloride (PMA) (0.001, 0.01, 0.1, 1.0), 2,5-dimethoxy-4-methylamphetamine hydrochloride (DOM) (0.001, 0.01, 0.1, 1.0), 2,5-dimethoxy-4-ethylamphetamine hydrochloride (DOET) (0.001, 0.01, 0.1, 0.32, 1.0), cocaine hydrochloride (0.01, 0.032, 0.1, 0.32, 1.0, 3.0, 3.2), caffeine citrate (0.1, 0.32, 1.0, 2.0, 3.2, 5.6, 10.0), and nicotine tartrate (0.001, 0.01, 0.1, 0.32, 1.0, 3.2).

The availability of an infusion was indicated by a 5-sec tone and illumination of a light directly over a lever located slightly to the left of center at the bottom of the intelligence panel. The lever was a standard leaf switch which required a downward force of approximately 150 g for closure. When the light was illuminated, each response produced a brief feedback tone (approximately 0.1 sec). Upon completion of a 160-response fixed-ratio schedule requirement (FR 160), the light over the lever was extinguished and the drug infusion began. Also at this time a 5 x 5 cm light was illuminated in the upper left-hand corner of the intelligence panel for a 1-hr period. A timeout period of 3 hrs followed each infusion, permitting a maximum of eight infusions per day.

Self-infusion performance was first established with cocaine at a dose of 0.4 mg/kg per infusion. After a minimum of 3 consecutive days of cocaine availability, during which six or more infusions were taken each day, a specified dose of a test drug or saline was substituted for the cocaine. Self-administration testing involved access to the test drug for at least 12 days. In several instances (e.g., phentermine, caffeine) the duration of access was extended beyond the usual 12-day period to permit a more complete examination of the pattern of
self-administration. After exposure to each dose of test drug cocaine was reinstated, and when the criterion of a minimum of 3 consecutive days of six or more infusions per day had been met, another dose or drug was again substituted. This procedure of replacing cocaine with a test drug was continued throughout the experiment. The order of exposure to drugs, saline, and different doses was mixed.

2. Results

Figure 3 presents illustrative daily patterns of self-infusion performance maintained by saline and several doses of phentermine in 3 baboons. The figure shows that when saline was substituted for cocaine, the number of infusions per day progressively decreased. At a dose of 0.5 mg/kg phentermine self-infusion performance was maintained at levels similar to cocaine control levels. At a dose of 1.0 mg/kg self-infusion performance was also maintained in all three animals; however, drug intake was characterized by a cyclic pattern in which a number of

![Diagram showing self-infusion patterns]

**Fig. 3.** Daily pattern of self-infusion maintained by saline or phentermine in 3 baboons. Intravenous infusions were delivered upon completion of 160 lever presses; a 3-hr timeout followed each infusion, permitting a maximum of eight infusions per day. The initial 3-day period of each determination shows the number of infusions maintained by cocaine prior to substitution of saline or indicated dose (mg/kg per infusion) of phentermine.
consecutive days of self-infusion at a high rate (six or more infusions per day) was followed by several consecutive days at a lower rate and then a return to the higher rate. Previous research has documented a virtually identical cyclic pattern of self-infusion performance with d-amphetamine (Griffiths et al., 1976).

Figure 4 presents mean levels of self-infusion for the 14 phenylethylamines. Of all the drugs examined, d-amphetamine was the most potent, maintaining levels of self-administration above saline at doses of 0.05 and 0.1 mg/kg. Phenetermine, diethylpropion, phenmetrazine, phendimetrazine, benzphetamine, and MDA all maintained levels of self-administration above saline at doses of 0.5 or 1.0 mg/kg. l-Ephedrine, clortermine, and chlorphentermine were the least potent of the drugs which maintained performance, supporting self-infusion rates above saline control levels at doses of 3.0 and 10.0 mg/kg (l-ephedrine), 3.0 and 5.0 mg/kg (clortermine), and 2.5 and 5.0 mg/kg (chlorphentermine). In contrast to most of the other phenylethylamines which maintained self-infusion behavior, the pattern of self-administration with l-ephedrine was particularly unstable, characterized by either an erratic or cyclic pattern over days. Finally, in contrast to all of the other phenylethylamines tested, fenfluramine, PMA, DOM, and DOET were not self-administered at a level greater than saline at any of the doses studied (means of the determinations at each dose did not exceed the range of saline values).

A comparison of Figs. 1 and 4 provides some information about structure-activity relationships of phenylethylamines. Research with a series of N-ethylamphetamines substituted at the meta position of the phenyl ring has demonstrated that the potency of these compounds either to increase locomotor activity in mice (Tessel et al., 1975b) or to maintain self-administration behavior in rhesus monkeys (Tessel & Woods, 1975, 1978) is inversely related to the size of the meta-substituted steric factor. These results indicate that the failure of fenfluramine (meta-trifluormethyl N-ethylamphetamine) to maintain self-infusion behavior is attributable to the meta-trifluormethyl group. The results of the present study extend these findings and suggest that ring substitutions in general may decrease the potency of the phenylethylamines in maintaining self-infusion behavior. The seven compounds shown in the right columns of Figs. 1 and 4 have substitutions on the phenyl ring and these compounds were generally

---

1Three animals died within the first 3 days of exposure to 1.0 mg/kg per infusion of DOET.

Fig. 4. Average number of infusions per day with 14 phenylethylamines. Intravenous infusions were delivered upon completion of 160 lever presses; a 3-hr timeout followed each infusion, permitting a maximum of eight infusions per day. C indicates mean of all the 3-day periods with cocaine which immediately preceded every substitution of a phenylethylamine or saline. S indicates mean of days 8-12 after substitution of saline (two saline substitutions in each of 15 animals). Brackets indicate ranges of individual animals' means. Drug data points indicate mean of days 8-12 after substitution of a drug for individual animals. Lines connect means at indicated doses of drug.
Predicting the Abuse Liability of Drugs

![Graph showing the relationship between dose per infusion and the number of infusions per day for various drugs.](image)

- **Amphetamine**
- **Clortermine**
- **Phentermine**
- **Chlorphentermine**
- **Diethylpropion**
- **Fenfluramine**
- **Phenmetrazine**
- **2,4-Methylenedioxyamphetamine (MDA)**
- **Pentazocine**
- **4-Methoxyamphetamine (PMA)**
- **Benzphetamine**
- **2,5-Dimethoxy-4-methylamphetamine (DOM)**
- **Ephedrine**
- **2,5-Dimethoxy-4-ethylamphetamine (DOET)**
less potent (on a mg/kg basis) in maintaining self-infusion than the compounds in the left column of Figs. 1 and 4 which do not have ring substitutions. Furthermore, phentermine differs structurally from both chlorphentermine and clortermine only with respect to the addition of Cl at either the para or ortho positions of the phenyl ring, yet both chlorphentermine and clortermine appeared less potent than phentermine in maintaining self-infusion behavior. The only exception to this relationship is l-ephedrine which does not have a ring substitution, but was similar in potency to the ring substituted compounds clortermine and chlorphentermine. This difference may be attributable to the fact that the levorotatory isomers of the phenylethylamines have less potent CNS effects than the d-isomers (e.g., Innes & Nickerson, 1975; Yokel & Pickens, 1973).

Figure 5 shows the mean levels of self-infusion for three additional stimulant

![Graph showing the mean levels of self-infusion for cocaine, caffeine, and nicotine.](image)

**Fig. 5.** Average number of infusions per day with cocaine, caffeine, and nicotine. Details of figure identical to Fig. 4.
compounds: cocaine, caffeine, and nicotine. Cocaine maintained high levels of self-infusion performance through a broader range of doses than any of the 16 other drugs tested (0.032–3.2 mg/kg). Nicotine did not maintain self-infusion performance at any dose tested. As shown in the figure, the highest dose of 3.2 mg/kg nicotine was associated with very low levels of self-administration. Although Fig. 5 shows that the mean levels of self-infusion of caffeine were within the saline control range, Fig. 6 shows that 3.2 mg/kg caffeine maintained steady or erratic daily patterns of self-administration in all 3 baboons tested.

B. Review of Self-Administration Results with Psychomotor Stimulants and Hallucinogens

The preceding section described a specific drug substitution procedure for determining whether drugs maintain self-administration behavior. Many procedural variations are possible, and drugs have been tested for self-administration using different species, routes of administration, response requirements, durations of drug availability, behavioral or pharmacological histories, etc. Obviously, all of these factors could bear significantly on self-administration. However, a comprehensive review of the drug self-administration literature with

![Graph showing self-infusion of caffeine in baboons](image)
psychomotor stimulant and hallucinogenic compounds indicates that for many drugs there is a good correspondence in results across this range of methodological and procedural variation (Table 1). For instance, as shown in Table 1, 36 experiments with d-amphetamine (across five different species and three different routes of administration) have shown that the drug maintained self-administration, while only one report (in two species) described a failure to obtain self-administration. Inspection of Table 1 reveals that the results with a number of other self-administered drugs (e.g., cocaine, diethylpropion, methylphenidate, phenmetrazine) also show this same replicability across studies. Furthermore, this correspondence in results is also apparent for drugs which do not maintain self-administration. With fenfluramine, eight different studies in three different species have uniformly failed to demonstrate self-administration. Finally, Table 1 shows that there are several drugs (e.g., caffeine, chlorphentermine, nicotine) for which there are conflicting reports about self-administration. Such conflicting reports indicate that the self-administration of these drugs is more sensitive to the methodological variations between experiments, and suggest that more research is necessary to determine the range of conditions under which these drugs will maintain self-administration.

C. Correspondence of Animal Drug Self-Administration Data to Human Clinical Information

In general, there is a good relationship between those drugs self-administered by laboratory animals and those abused by man. For instance, using the substitution procedure described previously, baboons will self-administer the opiate drugs heroin, morphine, and codeine, as well as the sedative compounds pentobarbital, secobarbital, and methaqualone (Griffiths, Brady, and Bradford, unpublished observations). All of these compounds have been associated with numerous case reports describing their abuse. In contrast, the baboon will not self-administer the opiate antagonists naloxone and nalorphine, the sedative phenobarbital, and the major tranquilizer chlorpromazine (Griffiths, Brady, & Bradford, unpublished observations). These data correspond well to the fact that human abuse of these drugs is relatively rare. Although these results would appear to suggest that drug self-administration procedures provide a valid estimate of abuse liability, it should be recognized that validation is greatly complicated by the fact that there are no generally accepted measures of drug abuse in the natural environment. Validation must necessarily involve assessment of results relative to the existing clinical literature available about the compounds.

2As shown in Table 1, self-administration was maintained with d-amphetamine in 36 of 38 experiments; with cocaine in 42 of 43 experiments; with methylphenidate in 10 of 10 experiments; with phenmetrazine in 11 of 11 experiments, etc.
TABLE I
SUMMARY OF RESULTS OF SELF-ADMINISTRATION TESTING WITH VARIOUS PHENYLETHYLAMINES, HALLUCINOGENS, AND CNS STIMULANTS*·

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Organism</th>
<th>Reference(s)</th>
<th>Maintains self-administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>d-Amphetamine</td>
<td>i.v.</td>
<td>Rhesus monkey</td>
<td>1,9,25,29,73,74,85,123,143,154</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>Squirrel monkey</td>
<td>37,41,131,133</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>Baboon</td>
<td>64</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>Dog</td>
<td>114-117</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>Rat</td>
<td>11,12,21-23,52-54,105,158-161</td>
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</tr>
<tr>
<td></td>
<td>i.g.</td>
<td>Rhesus monkey</td>
<td>3-5</td>
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<tr>
<td></td>
<td>p.o.</td>
<td>Rat</td>
<td>100</td>
<td>X</td>
</tr>
<tr>
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<td>i.v.</td>
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<td>X</td>
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<td></td>
<td>i.v.</td>
<td>Java monkey</td>
<td>141</td>
<td>X</td>
</tr>
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(continued)
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<th>Organism</th>
<th>Reference(s)</th>
<th>Maintains self-administration</th>
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<td>inhale</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>(gum)</td>
<td>Rhesus monkey</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>i.v.</td>
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<td>85,88</td>
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</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>Baboon</td>
<td>61,64</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>Rat</td>
<td>11,53,54</td>
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</tr>
<tr>
<td>Compound</td>
<td>Route</td>
<td>Species</td>
<td>Dose (mg/kg)</td>
<td>Note</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------</td>
<td>-------------</td>
<td>-------------</td>
<td>------</td>
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<td>DITA</td>
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<td>29</td>
<td>X</td>
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<tr>
<td>(3',4'-dichloro-2-(2-imidazol-2-yl-thio)- acetophenone)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>DOET</td>
<td>i.v.</td>
<td>Baboon</td>
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</tr>
<tr>
<td>(2,5-dimethoxy-4-ethylamphetamine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>DOM</td>
<td>i.v.</td>
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<td>X</td>
</tr>
<tr>
<td>(2,5-dimethoxy-4-methylamphetamine)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>l-Ephedrine</td>
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<td>Baboon</td>
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<td>X</td>
</tr>
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<td>Rhesus monkey</td>
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<td>X</td>
</tr>
<tr>
<td>Fenfluramine</td>
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<td>Rhesus monkey</td>
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<td>X</td>
</tr>
<tr>
<td>i.v.</td>
<td>Baboon</td>
<td>61,64</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>i.v.</td>
<td>Rat</td>
<td>11,53,54</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>meta-iodo N-ethylamphetamine</td>
<td>i.v.</td>
<td>Rhesus monkey</td>
<td>135</td>
<td>X</td>
</tr>
<tr>
<td>Mazindol</td>
<td>i.v.</td>
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<td>X</td>
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<tr>
<td>MDA (±-3,4-methylenedioxyamphetamine)</td>
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<td>Baboon</td>
<td>64</td>
<td>X</td>
</tr>
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<td>meta-methyl N-ethylamphetamine</td>
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<td>Rhesus monkey</td>
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<td>Mescaline (3,4,5-trimethoxyphenylethylamine)</td>
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<td>Rhesus monkey</td>
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<td>X</td>
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<tr>
<td>d-Methylamphetamine</td>
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<td>Rhesus monkey</td>
<td>9.85</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>Cat</td>
<td>7</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>Rat</td>
<td>158</td>
<td>X</td>
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(continued)
<table>
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<tr>
<th>Drug</th>
<th>Route</th>
<th>Organism</th>
<th>Reference(s)</th>
<th>Maintain self-administration</th>
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<tbody>
<tr>
<td>dl-Methylamphetamine</td>
<td>i.v.</td>
<td>Rhesus monkey</td>
<td>25,154,155</td>
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</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>Rat</td>
<td>107,108,110</td>
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</tr>
<tr>
<td>l-Methylamphetamine</td>
<td>i.v.</td>
<td>Rat</td>
<td>158</td>
<td>X</td>
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<tr>
<td>Methylphenidate</td>
<td>i.v.</td>
<td>Rhesus monkey</td>
<td>1,73,87,142,154,155</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>Baboon</td>
<td>14,63</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>Dog</td>
<td>115,117</td>
<td>X</td>
</tr>
<tr>
<td>N-ethylamphetamine</td>
<td>i.v.</td>
<td>Rhesus monkey</td>
<td>134,135</td>
<td>X</td>
</tr>
<tr>
<td>Nicotine</td>
<td>i.v.</td>
<td>Rhesus monkey</td>
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<td>X</td>
</tr>
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<td></td>
<td>i.v.</td>
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<td>20,67,96</td>
<td>X</td>
</tr>
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<td></td>
<td>p.o.</td>
<td>Rat</td>
<td>20</td>
<td>X</td>
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<tr>
<td>Inhale (cigarettes)</td>
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<td>Rhesus monkey</td>
<td>39,40,80,81</td>
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</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>Rhesus monkey</td>
<td>156</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>Baboon</td>
<td>60</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>Rat</td>
<td>96</td>
<td>X</td>
</tr>
<tr>
<td>3-Phenylethylamine</td>
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<td>Dog</td>
<td>118</td>
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<td>Phencyclidine (PCP)</td>
<td>i.v.</td>
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<td>6</td>
<td>X</td>
</tr>
<tr>
<td>Phendimetrazine</td>
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<td>Baboon</td>
<td>60</td>
<td>X</td>
</tr>
<tr>
<td>Substance</td>
<td>Route</td>
<td>Species</td>
<td>Reference Numbers</td>
<td>X</td>
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<tr>
<td>---------------------------------</td>
<td>-------</td>
<td>---------------------</td>
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<tr>
<td>Phenmetrazine</td>
<td>i.v.</td>
<td>Rhesus monkey</td>
<td>142,143,154,155</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>Baboon</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>Dog</td>
<td>115-117</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>i.v.</td>
<td>Rat</td>
<td>11,53,54</td>
<td>X</td>
</tr>
<tr>
<td>Phentermine</td>
<td>i.v.</td>
<td>Baboon</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Phenylpropanolamide</td>
<td>i.v.</td>
<td>Baboon</td>
<td>62</td>
<td>X</td>
</tr>
<tr>
<td>Pipradrol</td>
<td>i.v.</td>
<td>Rhesus monkey</td>
<td>142,143,154,155</td>
<td>X</td>
</tr>
<tr>
<td>PMA (para-methoxyamphetamine)</td>
<td>i.v.</td>
<td>Baboon</td>
<td>60</td>
<td>X</td>
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<tr>
<td>Procaine</td>
<td>i.v.</td>
<td>Rhesus monkey</td>
<td>36</td>
<td>X</td>
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<td>Scopolamine</td>
<td>i.v.</td>
<td>Rhesus monkey</td>
<td>1</td>
<td>X</td>
</tr>
<tr>
<td>SPA (1,2-diphenyl-1-dimethylaminoethane)</td>
<td>i.v.</td>
<td>Rhesus monkey</td>
<td>124,150,155</td>
<td>X</td>
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<tr>
<td>Wy-12,828</td>
<td>i.v.</td>
<td>Rat</td>
<td>11</td>
<td>X</td>
</tr>
</tbody>
</table>

*Reference numbers correspond to numbers in parentheses following each citation in Reference section. This table cites original data; there have been several reviews of various aspects of stimulant self-administration (see, e.g., Brady & Griffiths, 1977a, 1977b; Goldberg, 1973b, 1976b; Goldberg & Kelleher, 1976b, 1977; Goldberg, Kelleher, & Morse, 1975; Johanson & Schuster, 1977b; Kelleher, 1976; Pickens, 1968; Pickens & Thompson, 1971, 1972; Schuster & Johanson, 1974; Schuster & Thompson, 1969, 1970; Spealman & Goldberg, 1978, Thompson & Pickens, 1970, 1975).
Unfortunately, adequate clinical information is not uniformly available on all drugs. The following part of this section will involve a discussion of the self-administration results summarized in Table I in relation to subjective-effect information obtained in clinical studies, and in relation to the incidence of clinical case reports describing abuse obtained from a thorough review of the medical literature.

Amphetamine, diethylpropion, cocaine, methylamphetamine, methylphenidate, and phenmetrazine are all associated with numerous clinical case reports involving abuse (e.g., Allmark & Rylander, 1968; Bejerot, 1970; Hasse, Schönhöfer, & Waldmann, 1973; Rylander, 1968). Furthermore, all of these drugs plus benzphetamine and l-ephedrine have been evaluated on subjective-effect questionnaires (Addiction Research Center Inventory, ARCI) in drug abuser subjects and have been shown to produce a similar constellation of euphoric effects (Fischman, Schuster, Resnekov, Schick, Krasnegor, Fennell, & Freedman, 1976; Griffith, 1977; Jasinski, Nutt, & Griffith, 1974; Martin, Sloan, Sapira, & Jasinski, 1971). This clinical information involving abuse and subjective effects of these drugs is compatible with the fact that the majority of studies abstracted in Table I have shown that all of these drugs maintain self-administration in animals.

In contrast, Table I shows that neither phenylpropanolamine nor fenfluramine maintained self-administration in animals. This corresponds well to the available clinical information about these anorectic phenylethylamines. Both of these drugs are associated with a relatively low incidence of abuse. There are no reports of human abuse of phenylpropanolamine in spite of its wide availability as a nonprescription anorectic sold on an over-the-counter basis. There have been only two reports describing the nonmedical misuse of fenfluramine (Levin, 1972, 1975), and in both instances the drug was apparently used for its hallucinogenic effects. (As discussed below, animal drug self-administration does not provide accurate predictive information about hallucinogens.) Furthermore, fenfluramine was evaluated on questionnaire ratings and the ARCI and produced a subjective-effect profile unlike amphetamine which has been interpreted to indicate dysphoria (Götestam & Gunne, 1972; Griffith, 1977; Griffith, Nutt, & Jasinski, 1975).

Table I shows that chlorphentermine has not uniformly been reported to maintain self-administration in animals (three out of four reports). Furthermore, in one of the reports which demonstrated self-administration, the drug was not self-administered by all the subjects (Griffiths, Brady, & Snell, 1978a). These data suggest that chlorphentermine is a less robust reinforcer than drugs such as cocaine, amphetamine, phenmetrazine, and the other phenylethylamines which were self-administered in a wide range of different experiments. Clinical information about chlorphentermine provides no basis for differentiating this drug from fenfluramine or phenylpropanolamine: the incidence of case reports in-
volving abuse is extremely low, and evaluation of the subjective effects of the
drug on the ARCI indicated that the drug was dissimilar to amphetamine (Griff-


Table I also indicates that both caffeine and nicotine did not uniformly main-
tain self-administration in animals. As discussed previously, this suggests that
caffeine and nicotine are less robust reinforcers than some of the other drugs.
This finding does not adequately predict the fact that human self-administration
and dependence on these compounds are ubiquitous (e.g., Gilbert, 1976; Rus-
sell, 1976). It seems probable that wide social acceptance of these compounds is
responsible for greatly potentiating their use and abuse.

Table I also includes self-administration data for six drugs which are com-
monly accepted as having hallucinogenic or psychedelic effects in man. DOET,
DOM, mescaline, and PMA did not maintain self-administration while MDA and
phencyclidine did. These data suggest that existing animal drug self-
administration procedures are not useful in predicting hallucinogenic drug ef-
fects. It should be recognized that the finding that animals will not consistently
self-administer some hallucinogenic drugs is compatible with the fact that in the
natural environment people use hallucinogenic drugs at an extremely low rate
and most people spontaneously discontinue use of some hallucinogens such as
LSD (Brecher, 1972). It seems plausible that the reinforcing effects of MDA and
phencyclidine in animals may be unrelated to the fact that these drugs produce
hallucinogenic effects.

The foregoing discussion documents the good correspondence between the
results of self-administration testing in laboratory animals and the available cli-

nical information about the subjective effects and abuse in man. There are three
additional areas in which similarities in the human and infrahuman data further
strengthen the supposition that animal drug self-administration procedures pro-
vide valid information about human drug taking.

First, under conditions of relatively free drug availability similar patterns of
drug intake are apparent in animals and man. When psychomotor stimulant drugs
are available to experimental animals on a 24-hr-a-day basis, a characteristic
pattern of drug self-administration emerges, with periods of high drug intake
alternating with periods of low intake (for example, see Fig. 3, phentermine 1.0
mg/kg). This cyclic pattern of intake with psychomotor stimulant drugs has been
reported in baboons, rhesus monkeys, dogs, cats, and rats with a variety of
psychomotor stimulant drugs including cocaine, amphetamine, methylam-
phetamine, phenmetrazine, methylphenidate, and diethylpropion (e.g., Balster,
Kilbey, & Ellinwood, 1976; Griffiths et al., 1976; Johanson, Balster, & Bone-
es, 1976a; Pickens & Harris, 1968; Risner & Jones, 1976b). In contrast, opiate
and barbiturate drugs are not associated with a cyclic pattern of intake in ani-

mals, but are generally self-administered with a more regular pattern in which
total daily doses increase or are stable over time (Deneau et al., 1969; Woods &
Schuster, 1970; Yanagita & Takahashi, 1970). This cyclic pattern of drug intake with psychomotor stimulant drugs in animals is very similar to the pattern described in human intravenous amphetamine abuse by Kramer, Fischman, and Littlefield (1967). During a drug “run” the user injects the drug about every 2 hrs for a period of 3–6 days during which the user remains awake continuously. Following a “run” the user becomes so exhausted, disorganized, tense, or paranoid that he ceases using the drug and goes to sleep. The sleep lasts 12–18 hrs following a 3- or 4-day run. Upon awakening the user is lethargic and may terminate the lethargy by reinjecting amphetamine which begins a new “run.”

A second area of correspondence in animal and human drug self-administration is the profile of behavioral toxicity with high dose self-administration of psychomotor stimulants. When animals self-administer psychomotor stimulants under conditions of unlimited availability, the behavior during drug intake is often characterized by hyperactivity, dyskinesis, stereotypic behavior, and self-grooming behavior which may in some cases develop into self-mutilation (Deneau et al., 1969; Ellinwood & Kilbey, 1977; Johanson et al., 1976a; Pickens, Thompson, & Yokel, 1970; Risner & Jones, 1976b). These effects of high dose amphetamine are similar to those reported in psychomotor stimulant abusers including stereotyped bizarre choreiform movements, repetitive aimless activities, and delusion of parasitosis accompanied by repetitious grooming behavior, primarily manifested as picking and probing of the skin, leaving small lesions (Ellinwood & Kilbey, 1977; Schiørring 1977).

A final area of correspondence which suggests the validity of animal drug self-administration techniques in predicting effects in man is that similar variables have been shown to control self-administration in animals and man. Experimental work with animals and humans has involved establishing drug self-administration behavior under controlled conditions, and has provided a basis for examining the effects of specific manipulations. In spite of vast methodological differences between the human and animal research, a convergence of results is apparent. Griffiths and Bigelow (1978) have reviewed this literature which shows that similar effects on drug self-administration are obtained in human and infrahuman experiments when the following parameters have been manipulated: type of drug, dose of drug, response requirement to obtain drug, punishment of drug self-administration, and drug preloads.

III. PROCEDURES FOR MEASURING THE RELATIVE REINFORCING EFFICACY OF DRUGS

Research discussed in the preceding section has demonstrated a good correspondence between compounds self-administered by laboratory animals and those abused by man. Recently experimental attention has been directed toward
assessing the relative reinforcing efficacy of those drugs which have been shown to maintain self-administration behavior. Behavioral procedures for assessing the relative reinforcing efficacy of drugs are based upon research evaluating the behavior-maintenance properties (i.e., reinforcing properties) of a variety of environmental stimuli (e.g., food, water, drugs, etc.). Observed variation in this performance-maintenance potency has been assumed to reflect the "strength" (Hodos, 1961), "efficacy" (Balster & Schuster, 1973a), or "value" (Miller, 1976) of stimuli as reinforcers, although the hypothetical status of such intervening processes requires interpretative caution. The methodologies developed to date for assessing the relative reinforcing properties of drugs can be viewed within the framework of four general approaches: progressive-ratio schedules, rates of drug-maintained responding, concurrent schedules, and discrete-trial choice procedures. The review of results with these procedures will be limited to experiments involving the psychomotor stimuli.

A. Progressive-Ratio Schedules

Progressive-ratio procedures involve establishing a performance baseline that provides reinforcement contingent upon emission of a specified operant response. The number of responses required for each reinforcement is then systematically increased until the animal's responding falls below some criterion level. The response requirement at which the criterion is met is referred to as the "breaking point." Ordinarily increasing relationships have been reported between breaking point and such variables as degree of food deprivation (Hodos, 1961), the concentration or volume of a liquid reinforcer (Hodos & Kalman, 1963), and the intensity or train duration of reinforcing electrical intracranial stimulation (Hodos, 1965; Keesey & Goldstein, 1968). Since the breaking point varies systematically as a function of these several "motivational" conditions, it has been argued that it provides an index of the relative strength of a reinforcer (Hodos, 1961; Hodos & Kalman, 1963).

Yanagita (1973) first reported on the use of such a progressive-ratio procedure for comparative evaluation of several different reinforcing drugs including cocaine at various doses. Rhesus monkeys were initially permitted to self-administer a compound intravenously on a FR 100 schedule. Free access to drug self-administration under these conditions was allowed on a 24-hr/day basis. During the progressive-ratio test, the response requirement was doubled after a fixed number of injections beginning at 100 responses. A test was terminated when the time interval since the last injection exceeded 24 hrs. Using this procedure, it was demonstrated that larger doses of cocaine (0.03, 0.12, and 0.48 mg/kg per injection) and nicotine (0.05 and 0.2 mg/kg per injection) generally maintained higher progressive-ratio performance than lower doses of these drugs (Yanagita, 1973, 1977). Yanagita (1973) also compared progressive-ratio per-
formance maintained by single doses of cocaine (0.11 mg/kg), SPA (0.25 mg/kg), methylamphetamine (0.02 mg/kg), and amphetamine (0.03 mg/kg) and demonstrated that cocaine generally maintained higher breaking points than the other psychomotor stimulant drugs.

Another experiment which compared progressive-ratio performance maintained by different drugs used a somewhat modified progressive-ratio schedule with baboons (Brady & Griffiths, 1976; Griffiths, Findley, Brady, Dolan-Gutcher, & Robinson, 1975a). Intravenous infusions of drug were contingent upon completion of a FR response requirement (fixed number of lever-press responses), with a 3-hr timeout period following each infusion. When the self-infusion performance was stable, the ratio requirement was increased every 7 days until the “breaking point” at which the self-infusion performance fell below a criterion level. The sequence of ratio values used was: 160, 320, 640, 1280, 2400, 4800. Using this procedure, selected doses of the psychomotor stimulant drugs cocaine and methylphenidate were compared. Within-animal comparison showed that cocaine produced higher breaking points than methylphenidate at the same absolute dose, 0.4 mg/kg. At the range of doses studied, manipulation of doses of methylphenidate (0.1–0.8 mg/kg) and cocaine (0.4–1.6 mg/kg) had little effect on breaking point.

Although the results of the two preceding studies are suggestive that progressive-ratio procedures may provide a comparative measure of the relative reinforcing efficacy of drugs, they are limited to the extent that neither study examined a wide range of doses. A recent study (Griffiths et al., 1978a) has extended the progressive-ratio methodology for comparative drug evaluation by comparing in baboons the performance maintained by cocaine and three amphetamine derivatives (diethylpropion, chlorphentermine, and fenfluramine) over a substantial range of doses. As in the preceding experiment, infusions of drug were contingent upon completion of a FR response requirement, with a 3-hr timeout period following each infusion. Prior to testing each dose of drug, stable self-infusion performance was first established with 0.4 mg/kg cocaine when the FR requirement was 160. Subsequently, a test dose of drug was substituted for the standard dose of cocaine. If the dose of drug maintained a criterion level of self-infusion performance (six or more infusions per day for 2 days), the ratio requirement was systematically increased every day until the “breaking point” at which the self-infusion performance fell below a criterion level (one or zero infusions per day). The progression of ratio values was 160, 320, 640, 1280, 2400, 3600, 4800, 6000, and 7200. Following disruption of performance, the ratio was lowered to FR 160 to determine whether the self-infusion performance would be recovered. A breaking point was defined as the ratio value at which criterion performance disruption occurred, provided that the performance was subsequently recovered. The sequence of exposure to different drugs and doses was mixed.
Figure 7 shows the results of the breaking point determinations in 5 baboons. Fenfluramine did not maintain criterion self-infusion performance at any dose tested (0.02–5.0 mg/kg). Chlorphentermine maintained self-infusion performance at some of the intermediate doses tested in 3 baboons. In the fourth baboon (SA), chlorphentermine did not maintain criterion self-infusion perfor-

![Graph showing breaking point values for fenfluramine, chlorphentermine, diethylpropanol, and cocaine in 5 baboons. Each point represents a single breaking point observation. Lines connect the means of the breaking point observations at different doses of drug. Closed circles indicate data obtained during the first exposure to a drug dose. Open circles indicate data obtained during a second exposure to a drug dose. (From Griffiths, Brady, & Snell, 1978a.)](image-url)
mance at any of the doses examined. Intermediate doses of diethylpropion consistently maintained self-infusion performance in the 5 baboons tested. The overall dose-breaking point function with diethylpropion was an inverted U-shape curve with a peak at 1.0 or 3.0 mg/kg. Finally, some doses of cocaine maintained self-infusion performance in all 5 animals tested. As shown in Fig. 7, for the 4 baboons (SN, CL, SA, AL) exposed to several intermediate doses of cocaine that maintained self-infusion behavior (0.03, 0.1, 0.4 mg/kg), there is a dose-breaking point relationship in which higher doses are associated with higher breaking points. More specifically, in baboons SN and AL, the average breaking point at 0.1 mg/kg was higher than the breaking point at 0.03 mg/kg; in baboon CL, the average breaking point at 0.4 mg/kg was higher than that at 0.1 mg/kg. Finally, in baboon SA, the 0.1 mg/kg dose produced an average breaking point of 4200 in contrast to the 0.03 mg/kg dose which first produced two breaking points at 3600 and upon subsequent replication produced a breaking point of zero (self-infusion performance was not maintained).

Within-animal comparison of the maximum breaking points maintained by the different drugs indicates that cocaine maintained the highest breaking points, followed in order by diethylpropion, chlorphentermine, and fenfluramine. More specifically, within-animal comparison of the data presented in Fig. 7 reveals doses of cocaine that maintained higher average breaking points than all the doses of diethylpropion, chlorphentermine, and fenfluramine tested. Similarly, there were doses of diethylpropion that maintained higher average breaking points than all doses of chlorphentermine and fenfluramine; and finally, there were doses of chlorphentermine that maintained higher average breaking points than all doses of fenfluramine.

The results with cocaine shown in Fig. 7 also explain an apparent discrepancy in results of other progressive-ratio experiments. As previously discussed, Yanagita (1973) showed that higher cocaine doses maintained higher breaking points than lower doses of the drug (0.03, 0.12, and 0.48 mg/kg), whereas Griffiths et al. (1975a) showed that manipulation of cocaine dose did not affect breaking point. The most recent results reconcile the apparent differences between these studies by demonstrating that the dose-breaking point function with cocaine is biphasic. Within-animal examination of the data (see Fig. 7) shows that at low and intermediate doses of cocaine (0.01, 0.03, 0.1, and 0.4 mg/kg per infusion) the higher of these doses tend to be associated with higher breaking points; however at the higher dose levels of drug (0.1, 0.4, and 1.0 mg/kg per infusion) the dose-breaking point function becomes relatively flat.

B. Rates of Drug-Maintained Responding

A number of studies have shown that when responding is maintained by intravenous drug administration, there is a negative correlation between rein-
forcing magnitude (i.e., drug dose) and response rate. For instance, the majority of studies examining the relationship between response rate and cocaine dose under continuous reinforcement (CRF) and FR schedules have shown that increasing doses (above the minimum that maintained response rates above control levels) were associated with decreases in response rates (Downs & Woods, 1974; Goldberg, Hoffmeister, Schlichting, & Wuttke, 1971; Pickens & Thompson, 1968; Wilson, Hitomi, & Schuster, 1971). This same relationship has also been demonstrated with other stimulant drugs such as d-amphetamine (Pickens & Harris, 1968) and methylphenidate (Wilson et al., 1971). It should be noted that the decreases in response rates observed under CRF and FR schedules may be due, in part, to the direct rate-decreasing effect of the drug on behavior. For instance, it is well known that cocaine can decrease FR responding maintained by other reinforcers such as food.

Under conditions where the schedule of reinforcement does not involve such a close relationship between response rate increases and elevations in drug intake, response rate may reflect drug reinforcer efficacy. Balster and Schuster (1973a) have shown that under certain conditions response rates on fixed-interval (FI) schedules of drug reinforcement may be used as a measure of reinforcer efficacy. When rhesus monkeys were exposed to a FI 9-min schedule of drug reinforcement with a 15-min timeout between intervals, response rates maintained by cocaine (0.025, 0.05, 0.1, 0.2, 0.4, and 0.8 mg/kg) generally increased with higher doses of cocaine; however, at the highest cocaine dose increasing rate relationships were not uniformly discernible. Goldberg and Kelleher (1976) have also demonstrated increases in FI response rates with increases in cocaine doses (0.012, 0.025, and 0.05 mg/kg) in squirrel monkeys. The use of relatively short FI and timeout durations (5-min and 1-min, respectively) probably prevented the possibility of further rate increases at higher doses. In another study Kelleher and Goldberg (1977) examined performance in squirrel monkeys on a second-order schedule (FR 10 [FI 5-min:S]) maintained by cocaine injections. The minimum interinjection interval with this schedule was 50 min. Under these conditions, increasing cocaine doses (0.01, 0.03, 0.1, 0.3, and 0.6 mg/kg) were associated with increasing response rates except at the highest dose tested. Finally, Goldberg, Morse, and Goldberg (1976) have also examined the effects of several cocaine doses (0.38, 0.75, 1.5, 3.0 mg/kg) in rhesus monkeys on response rates on a second-order schedule (FI 60-min [FR 10:S]) in which timeout periods of 47 or 71 hrs occurred after each intramuscular drug injection. In contrast to the other response rate procedures, these conditions were relatively insensitive to the cocaine dose manipulations. It is possible that an examination of doses lower than 0.38 mg/kg might have revealed an orderly ascending limb of the dose-response relationship. It is also possible that the insensitivity of the procedure to dose manipulations was due to the intramuscular route of administration — all previously described studies have involved the intravenous route.
C. Concurrent Schedules

Relative response rates on two concurrently available, equally valued variable interval (VI) schedules (on two separate operandi) have also been used as a measure of relative reinforcing efficacy. For instance, response rates on concurrent VI schedules of different durations of food reinforcement have been shown to reflect the magnitude of the reinforcer (Catania, 1963). This procedure has also been used to measure relative preference between qualitatively different reinforcers (Holland & Davison, 1971; Miller, 1976). Concurrent schedules have been used in a series of experiments to assess the relative reinforcing properties of different cocaine doses in rhesus monkeys (Iglauer, Llewellyn, & Woods, 1975; Iglauer & Woods, 1974; Llewellyn, Iglauer, & Woods, 1976). VI 1-min schedules were employed in which each injection was followed by a 5-min timeout. Responding on one lever produced a constant dose of 0.05 or 0.1 mg/kg, while on the other lever the dose was systematically varied over the range of 0.013-0.8 mg/kg. Higher relative response rates were generally associated with higher doses of cocaine, although these rates became asymptotic at the highest doses studied (0.2, 0.4, and 0.8 mg/kg).

D. Discrete-Trial Choice Procedures

Measuring an animal's choice or preference between two or more concurrently available stimuli on a discrete trial basis is another method of assessing the relative reinforcing efficacy of stimulus events. Such choice procedures have been reported to discriminate between the differential reinforcing properties of various durations of food presentation (Nevin, 1967).

The basic procedure involves the presentation of choice trials on which two different color stimulus lights are presented either sequentially (e.g., Brady & Griffiths, 1977a) or simultaneously (e.g., Johanson & Schuster, 1975). Each of the light colors is associated with the delivery of a specific dose of drug, and responding on a lever results in delivery of the drug dose appropriate to the light color present when the response requirement is completed. Choice is indicated simply by the number of times one stimulus-drug condition is selected, compared with the total number of selections.

A number of experiments have utilized such procedures to investigate drug choice in baboons and rhesus monkeys with sedatives, opiates, and psychomotor stimulants (Balster & Schuster, 1977; Brady & Griffiths, 1977a; Brady, Griffiths, & Winger, 1975; Findley, Robinson, & Peregrine, 1972; Griffiths, Wurster, & Brady, 1975b; Johanson, 1975, 1977; Johanson & Schuster, 1975, 1977a, 1977b; Wurster, Griffiths, Findley, & Brady, 1977). Only those studies involving choice between psychomotor stimulant drugs will be discussed below.

In one study (Brady & Griffiths, 1977a) baboons were trained on a discrete-
trial choice procedure that involved 30 trials each day with a 10-min timeout following each trial. At the beginning of each trial the animal was presented with one of two differently colored stimulus lights and a switching lever which changed the light colors. In order to proceed with the trial, the baboon was required to switch colors so that each stimulus light appeared at least twice. The animal was then permitted to continue changing colors or proceed with the trial in the color of his choice by completing a response requirement on a second lever (15 responses on a Lindsley lever, FR 15 schedule). Completion of the trial in the presence of one color produced an injection of dose A, while completion in the other color produced dose B. The bottom panel of Fig. 8 shows the results of seven consecutive choice determinations with various cocaine doses in baboon S-HR. Prior to drug introduction, S-HR showed a strong bias toward the blue stimulus, as indicated by the low rate of red choices during the first 3 days plotted on the graph. When an infusion of 0.1 mg/kg cocaine was associated with the red stimulus on day 4, while an infusion of saline was associated with selection of blue, there was a clear shift in preference toward the red color over the next 5

![Graph showing daily choice performance in 2 baboons. Trials involved choosing between two different color options, each associated with a different dose of cocaine. Thirty trials were scheduled daily, each followed by a 10-min timeout. Note that the higher dose of cocaine (0.1 mg/kg) was consistently selected over all lower doses.](image-url)
days. Reversal of the options on day 9 so that the 0.1 cocaine dose was associated with selection of the blue stimulus and saline was associated with selection of red produced a clear shift in preference toward the blue stimulus. Subsequent choice determinations, as shown in the figure, involved options associated with several different doses of cocaine (i.e., 0.01 vs. 0.1 mg/kg per infusion; 0.05 vs. 0.1 mg/kg per infusion; 0.075 vs. 0.1 mg/kg per infusion); and on each of these determinations the higher dose of cocaine (0.1 mg/kg) was preferred to the lower doses. The top panel of Fig. 8 shows that similar results were obtained in baboon S-HE: a cocaine dose of 0.1 mg/kg was consistently selected over the lower doses of cocaine (0.03, 0.056, and 0.075 mg/kg). Not shown in the figure, when S-HE was subsequently exposed to a series of comparisons between 0.1 mg/kg and a number of higher doses (0.133, 0.17, 0.3, and 0.4 mg/kg), preference was only erratically displayed for the higher cocaine dose. The results of this experiment show clearly that a dose of 0.1 mg/kg cocaine can be preferentially discriminated by baboons from a range of lower doses, including alternatives as close as 0.075 mg/kg. The unique finding that the relative reinforcing properties of different cocaine doses can be discriminated with such small magnitude variations suggests that the slope of the dose–effect curve may be quite steep over this lower range of doses. At higher doses (i.e., above 0.1 mg/kg), in contrast, choice determinations were less reliable (though higher dose preferences can be demonstrated under some conditions), and the results point to a more shallow dose–response curve at cocaine dose levels above 0.1 mg/kg.

Similar findings have been reported (Johanson & Schuster, 1975) using a two-lever discrete-trial choice procedure with rhesus monkeys to examine preference for a range of cocaine doses (0.05, 0.1, 0.5, 1.0, and 1.5 mg/kg). As with the previous study, higher doses of cocaine were preferred to lower doses, except when both doses were high (0.5, 1.0, or 1.5 mg/kg). These investigators have extended this research by examining preference between two concurrently available drugs. When cocaine (0.1 and 0.5 mg/kg) and methylphenidate (0.075–0.7 mg/kg) were compared, the higher dose was generally preferred regardless of drug (Johanson & Schuster, 1975). In contrast, when cocaine (0.1 and 0.5 mg/kg) was compared with diethylpropion (0.5 and 1.0 mg/kg), cocaine was generally preferred (Johanson & Schuster, 1977a).

E. Similarities among the Different Measures of Reinforcing Efficacy

There is a remarkably good correspondence in the results obtained with these different procedures for assessing relative reinforcing efficacy of drugs. Examination of a range of cocaine doses has revealed that higher cocaine doses are associated with higher measures of reinforcing efficacy than lower doses, except that doses exceeding 0.1 or 0.5 mg/kg are usually shown to be equally reinforc-
ing. In spite of wide procedural differences, this relationship was demonstrated with progressive-ratio schedules, FI schedules, second-order schedules, concurrent schedules, and discrete-trial choice procedures. In addition, both progressive-ratio schedules and discrete-trial choice procedures have shown that cocaine is a more efficacious reinforcer than diethylpropion. Although this replication of results across different procedures is encouraging, there are many unanswered questions, and it would be premature to assume that any of these procedures provide an unequivocal measure of reinforcing efficacy. Additional research is needed to determine the range of conditions under which the measurement of reinforcer efficacy is unaltered or altered. These studies should determine both the robustness of the measure and the conditions of maximal sensitivity.

F. Correspondence of Animal Measures of Reinforcing Efficacy to Human Clinical Information

The results to date which have demonstrated differences in reinforcing efficacy between different doses and different drugs show a good correspondence to the limited clinical information available. Progressive-ratio schedules, FI schedules, second-order schedules, concurrent schedules, and discrete-trial choice procedures have all shown that higher cocaine doses are associated with higher measures of reinforcing efficacy than lower doses. These findings with cocaine correspond to the results of several clinical studies with cocaine abuser subjects which found that higher doses of cocaine were associated with overall increases in subjective intensity, pleasantness, and euphoria, as measured by subjective effect questionnaires (Fischman et al., 1976; Resnick, Kesternbaum, & Schwartz, 1977). In addition, existing data from progressive-ratio and discrete-trial choice procedures suggest the following ranking of reinforcing efficacy for four drugs: cocaine highest, followed in order by diethylpropion, chlorphentermine, and fenfluramine. This ranking corresponds reasonably well to the available clinical information about the subjective effects and relative incidence of abuse of these compounds. This clinical information is presented in Section IV,B.

G. Reinforcing Efficacy—A Theoretical Construct which Provides a Useful Unifying Framework

The methods and procedures described above are considered to provide measures of "reinforcing efficacy" for different drugs and doses of drug. Although terms such as reinforcing efficacy have been used freely in the drug self-administration literature, only limited consideration has been given to their empirical referents and conceptual definition. The ensuing brief discussion directs
attention to some of the more salient experimental and theoretical issues raised by
appeal to such theoretical constructs.

Reinforcing efficacy refers to the behavior-maintenance potency of a dose of
drug which can be manifest under a range of different experimental conditions.
The meaning of the term is derived from and established by the convergence of
operations on which multiple outcome measures can be taken to be more or less
interchangeable. For instance, it could be expected that with a progressive-ratio
procedure, if dose A maintains higher breaking points than dose B, then with the
choice procedure dose A should be preferred to dose B, and with a response rate
measure dose A should maintain higher rates than dose B.

The concept of reinforcing efficacy is useful because it provides a unifying
framework which encompasses a range of different behavioral measures. Specifically,
the concept of relative reinforcing efficacy demonstrates a robust trans-
situationality, since similar results are obtained using widely different methods
and parameter values (as discussed in preceding sections). Furthermore, the
limited data collected to date also correspond to the available clinical information
about the drugs. The utility of the concept of reinforcing efficacy depends on the
continued demonstration of this broad transsituationality of the relations. If there
does not continue to be a good correspondence in ratings of reinforcing efficacy
across different procedures, then the concept of reinforcing efficacy should be
reevaluated.

It is, of course, recognized that a number of historical and contemporary
environmental circumstances interact with properties of a drug (or an event) to
determine its current reinforcing functions. A number of animal studies, for
example, have shown that under certain conditions electric shock can maintain
responding (i.e., serve as a reinforcer) when shock is delivered as a consequence
of responding (Morse & Kelleher, 1970). A subsequent study has extended this
work by demonstrating that morphine-dependent monkeys with certain histories
will self-administer the opiate antagonist naloxone (Woods, Downs, & Carney,
1975). Although such findings define, to some extent, the limits of construct
generality, the usefulness of reinforcing efficacy as a unifying concept is not
compromised by the experimental demonstration of such interactive effects. In
fact, it would be surprising indeed if a behavior-controlling relation could be
discovered that was not substantially influenced by other behavior-controlling
circumstances.

From a more conservative perspective the use of theoretical concepts such as
reinforcing efficacy should be treated cautiously since the introduction of such
"intervening" constructs to explain behavioral observations and/or behavioral-
pharmacological effects has not uniformly produced scientific advances. For
example, the construct of "anxiety" which provided the focus for extensive
research investments during the 1950s and 1960s on drug effects and conditioned
suppression procedures has ultimately proved to be somewhat less than adequate
to the task of "conceptual unification" across experimental conditions. The presumption that the shock-suppressed behavior in the conditioned suppression paradigm could be attributed to a general anxiety construct suggested that the procedure would provide a model for evaluating the antianxiety or tranquilizing effects of drugs. In fact, subsequent research efforts failed to support the assumed transsituationality of anxiety as a construct. Drugs which attenuated shock-suppression effects upon behavior under one set of experimental anxiety conditions failed to do so under somewhat different experimental anxiety conditions, and it has become apparent that the procedural differences are far more important determinants of such drug action than the conceptually enfeebled anxiety components (Kelleher & Morse, 1968). This example emphasizes the continuing need for exercising caution in the introduction and use of theoretical constructs such as reinforcing efficacy. At a minimum, careful attention will be required to the broad range of influential parametric variables in the continuing elaboration of drug-behavior relations to be encompassed within the framework of a reinforcing efficacy construct.

Finally, the introduction of a theoretical term such as reinforcing efficacy is consistent with the overall approach which has been developed for the experimental analysis of behavior. In general, this approach has opposed the introduction of theory into the experimental analysis of behavior when theory referred to any explanation of observed fact which appeals to events taking place at some other level of observation. Nonetheless, even Skinner has recognized the possibility of theory in another sense:

Beyond the collection of uniform relationships lies the need for a formal representation of the data reduced to a minimal number of terms. A theoretical construction may yield greater generality than any assemblage of facts. But such a construction will not refer to another dimensional system...[nor] stand in the way of our search for functional relations because it will arise only after relevant variables have been found and studied. (Skinner, 1950, pp. 215-216)

The term reinforcing efficacy is a theoretical construction in this latter sense, and serves to unify a growing body of data on drugs as reinforcers.

IV: ASSESSMENT OF THE RELATIONSHIP BETWEEN REINFORCING EFFECTS AND THERAPEUTIC EFFECTS OF DRUGS: IMPLICATIONS FOR ABUSE LIABILITY

The previous sections have addressed the questions: Does a drug maintain self-administration behavior? And, what is the reinforcing efficacy of the drug relative to other drugs? The present section addresses a related but conceptually different question: What is the relationship between the relative potency of the drug as a therapeutic agent vs. the relative potency as a reinforcer? Underlying
this question is the supposition that the reinforcing properties of a drug should not be considered independently of the therapeutic properties. It is the relationship between the reinforcing and therapeutic properties that is important. Knowledge about this relationship provides important information about the extent to which therapeutic applications of a drug will necessarily involve exposure to the drug’s reinforcing effects.

Using baboon drug self-administration data, Griffiths, Brady, & Snell (1978b) have recently developed a quantitative measure of this relationship between the reinforcing and therapeutic properties for a series of anorectic compounds. Although the following discussion will involve an analysis of only anorectic drugs, it should be noted that analogous measures could be developed for other therapeutic classes of compounds which may have some abuse liability (e.g., antinociceptive drugs and antianxiety drugs).

A. Anorectic—Reinforcement Ratio

The most desirable anorectic drug would have potent anorectic properties, but minimal reinforcing properties. An undesirable anorectic drug would be a weak anorectic but powerful reinforcer. Existing anorectic drugs may fall anywhere on the continuum defined by these parameters. A quantitative measure of this continuum is provided by the anorectic—reinforcement ratio which compares the relative potency of a drug as an anorectic with its relative potency as a reinforcer (Griffiths, Brady, & Snell, 1978b).

1. Measurement of Reinforcement Effects

A standardized drug self-administration substitution procedure with baboons similar to that described in an earlier section of this chapter (Griffiths et al., 1976) was used to determine the lowest drug dose which maintained intravenous self-administration above saline control levels. Figure 9, for example, shows the effects of dose level on the number of diethylpropion infusions per day (a) self-administered by 2 of the baboon subjects in the study, and illustrates determination of the lowest reinforcing dose values shown in Table II, column B, for each of the indicated compounds. Two of the drugs, fenfluramine (0.02–5.0 mg/kg per infusion) and phenylpropanolamine (0.1–30.0 mg/kg per infusion), failed to maintain self-infusion rates above saline levels at any dose tested, and the indicated values were assumed to be infinitely high.

2. Measurement of Anorectic Effects

In the course of evaluating the reinforcing properties of the drugs under study, concurrent assessments were made of the effects of these compounds on food intake. One-gram Purina monkey pellets were continuously available to all ani-
mals on a reinforcement schedule which required 15 or 25 lever responses per pellet (FR 15 or 25). Increasing doses of all nine drugs were associated with decreases in the total number of food pellets taken per day as illustrated in Fig. 9 (b) for diethylpropion. The dose which suppressed food intake to 50% of saline control levels was calculated individually for all nine compounds on the basis of a regression line fitted to the raw data as shown in Table II, column C, for each of the indicated drugs.
<table>
<thead>
<tr>
<th>Drug</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lowest reinforcing dose in baboon (mg/kg/infusion)</td>
<td>Dose suppressing baboon food intake 50% (mg/kg/day)</td>
<td>Ratio C/B</td>
<td>Lowest recommended human anorectic dose (mg/day)</td>
<td>Ratio E/B</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>0.03</td>
<td>16.0</td>
<td>14.81</td>
<td></td>
<td>75</td>
<td>0.75</td>
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<tr>
<td>Diethylpropion</td>
<td>0.5</td>
<td>22.0</td>
<td>1.22</td>
<td></td>
<td>10</td>
<td>1.0</td>
</tr>
<tr>
<td>d-Amphetamine</td>
<td>0.05</td>
<td>1.8</td>
<td>1.0</td>
<td></td>
<td>10</td>
<td>1.0</td>
</tr>
<tr>
<td>Phenmetrazine</td>
<td>0.5</td>
<td>7.4</td>
<td>0.41</td>
<td></td>
<td>50</td>
<td>0.50</td>
</tr>
<tr>
<td>Chlorphentermine</td>
<td>2.5</td>
<td>20.3</td>
<td>0.23</td>
<td></td>
<td>77.9</td>
<td>0.16</td>
</tr>
<tr>
<td>Pherentermine</td>
<td>0.5</td>
<td>3.7</td>
<td>0.21</td>
<td></td>
<td>18.7</td>
<td>0.19</td>
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<tr>
<td>Clomipramine</td>
<td>3.0</td>
<td>21.0</td>
<td>0.19</td>
<td></td>
<td>50</td>
<td>0.08</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>0.0</td>
<td>7.0</td>
<td>0</td>
<td></td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Phenylpropanolamine</td>
<td>0.0</td>
<td>48.1</td>
<td>0</td>
<td></td>
<td>75</td>
<td>0</td>
</tr>
</tbody>
</table>

*Calculation of doses is described in text. All doses are expressed on the basis of the hydrochloride salts except for d-amphetamine which is expressed as the sulfate. To facilitate comparison, ratios were adjusted to an arbitrarily assigned d-amphetamine values of 1.0. From Griffiths, Brady, & Snell (1978b).
Fig. 10. Anorectic-reinforcement ratios for cocaine and eight anorectic drugs. Filled bars show data derived entirely from baboon experiments. Striped bars show data derived from both human clinical information and baboon experiments. Compounds with high ratio values are more potent reinforcers (relative to their anorectic potency) than compounds with lower ratio values.

Column D, Table II, and the filled bars of Fig. 10 show the resulting anorectic-reinforcement ratios (based upon adjustment to an arbitrarily assigned d-amphetamine value of 1.0) derived from the relationship between food suppression dose (i.e., column C, numerator) and lowest reinforcing dose (i.e., column B, denominator), for each of the nine drugs studied. The ratio values range from a low of zero for fenfluramine and phenylpropanolamine to a high of 14.81 for cocaine, and reflect the fact that compounds with high ratio values are more potent reinforcers (relative to their anorectic potency) than compounds with lower ratio values.

The measure of anorectic potency as determined with the baboon could be confounded by nonspecific psychopharmacological effects such as drug-induced sensory or motor decrements. To provide more information about anorectic potency of the drugs, an alternative set of values was derived by utilizing the lowest recommended daily human anorectic doses. These doses appear in column E of Table II, and provide the numerator for computing a comparative set of ratio values (column F). Since cocaine is not used clinically as an anorectic, no entry appears in column E. Comparison of the values in columns D and F (also the striped bars vs. the filled bars in Fig. 10) show the correspondence between the ratios based upon these two independent measures of anorectic potency.
B. Correspondence of Anorectic–Reinforcement Ratio: Data to Clinical Information

The ordering of compounds derived from this laboratory analysis bears a reasonable correspondence to the available clinical information about the reinforcing, anorectic, and subjective effects of these drugs. Cocaine has an anorectic–reinforcement ratio that is more than 10 times greater than the highest phenylethylamine anorectic. This high ratio value corresponds well to clinical observations confirming that cocaine is widely abused (i.e., reinforces drug-taking), produces euphoric subjective effects as measured by the Addiction Research Center Inventory (ARCI), and is not currently recommended as an anorectic, although historically it was used to reduce hunger (Fischman et al., 1976; Woods & Downs, 1973). Of the eight phenylethylamine anorectics studied, diethylproplion, d-amphetamine, and phenmetrazine were associated with the highest anorectic–reinforcement ratios, ranging between 0.41 and 1.22. Although these drugs produce significant clinical anorectic effects (Innes & Nicker-son, 1975), they are associated with numerous clinical case reports involving abuse (Allmark & Rylander, 1968; Bejerot, 1970; Rylander, 1968), and all these drugs produce euphoric subjective effects similar to cocaine as measured by the ARCI (Fischman et al., 1976; Jasinski et al., 1974; Martin et al., 1971). The remaining five phenylethylamine anorectics were all associated with relatively low or zero anorectic–reinforcement ratios. Clinically, all of the latter five compounds have anorectic properties (Dykes, 1974; Hoebel, Cooper, Kamin & Willard, 1975; Innes & Nicker-son, 1975); there are, however, relatively few case reports involving abuse of these drugs. There have been two reports describing nonmedical misuse of fenfluramine as a psychomimetic (Levin, 1972, 1975). Significantly, the source of fenfluramine was invariably illicit and none of the users admitted to having been treated with fenfluramine for weight reduction. There are no reports of human abuse of phenylpropanolamine in spite of its wide availability as a nonprescription anorectic sold on an over-the-counter basis. Additionally, two of the remaining five compounds (chlorphenetermine and fenfluramine) have been evaluated with the questionnaire ratings as well as the ARCI and produced a subjective-effect profile unlike amphetamine, and which was interpreted to indicate dysphoria (Götestam & Gunne, 1972; Griffith, 1977; Griffith et al., 1975, 1976).

The anorectic–reinforcement ratio provides a basis for comparing the anorectic and reinforcing potency of drugs, and thus provides for a potentially useful assessment of the extent to which anorectic applications of a compound involve exposure to the drug’s reinforcing effects. Therefore, this measure may indicate the degree to which a patient might be expected to continue to self-administer the drug for these nontherapeutic effects. In addition, such a measure of exposure may provide a guide for governmental regulation of drugs to prevent widespread
drug abuse epidemics. An historical analysis of major CNS stimulant epidemics has revealed that the epidemics have been preceded by introduction of large population segments to a given compound's effects for apparently legitimate medical or recreational purposes (Ellinwood, 1974). People exposed to the reinforcing effects of an anorectic drug during the course of legitimate medical treatment may subsequently represent an "at risk" population group for later development of stimulant drug abuse problems.

V. SUMMARY

This chapter reviews the current status of animal drug self-administration procedures in predicting the abuse liability of psychomotor stimulant and hallucinogenic drugs. Procedures have been developed for reliably determining whether a drug will maintain self-administration in animals. A variety of psychomotor stimulant drugs have been examined and there is a good correspondence between the results of such self-administration testing in animals and the available clinical information about the subjective effects and abuse in man. These procedures are not useful for predicting hallucinogenic drug effects. Other self-administration procedures have been developed for measuring the relative reinforcing efficacy of drugs. The reliability of these results has been demonstrated by the fact that similar relative ratings of reinforcing efficacy have been obtained in spite of widely differing procedures. Although relatively few drugs have been evaluated with these procedures, the results to date correspond to the available clinical information. Finally, a measure is described which provides information about the relationship between the reinforcing effects and the therapeutic effects of anorectic drugs. The measure appears to provide important supplementary information about the abuse liability of anorectic drugs which corresponds well with the clinical information on the anorectic effects, subjective effects, and abuse of these drugs. Overall, the results reviewed in this chapter show that animal drug self-administration procedures provide useful measures for preclinical screening of drugs for abuse liability.

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