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THEORETICAL REVIEW

Discriminative Stimulus Properties of Narcotic Analgesic Drugs[1,2]

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COLPAERT, F. C. *Discriminative stimulus properties of narcotic analgesic drugs*. PHARMAC. BIOCHEM. BEHAV. 9(6) 863–887, 1978.—This paper presents a comprehensive review on the experimental data relevant to the discriminative stimulus properties of narcotic analgesic drugs. The narcotic cue is defined as the discriminative stimulus complex which is exclusively associated with the specific central action(s) of narcotic analgesic drugs. The first part of this review discusses evidence that narcotics can act as a discriminative stimulus, and that this cue is an exclusive, complexly composed, and centrally originating property of narcotics. The pharmacological and biochemical specificity of the narcotic cue is supported by findings indicating (1) that chemically heterogenous narcotics generalize with narcotic agonist training drugs, (2) a close correlation between narcotic cuing and analgesic potency of narcotics, (3) that the requirement of steric specificity applies, and (4) the naloxone-reversibility of this cue. The comparative data so far available are thus consistent with the assumption that the narcotic cue in laboratory animals relates intimately to, and can serve as a preclinical model for opiate-like subjective effects in man. Further discussion is concerned with the involvement of various neurotransmitter substances in the narcotic cue; much as it appears likely that multiple and diffusely organized brain sites rather than discrete brain areas are involved, there is no evidence at this stage that any single transmitter would play a unique role in this cue. The other issues being discussed here are (1) the role of training drug dose, (2) the tolerance problem, (3) the relation between the narcotic cuing and the analgesic activity of narcotics, (4) the involvement of neuropeptides, (5) drug cue conditioning to environmental stimuli; (6) drug cues and drug states, and (7) the internal discriminative stimulus control of behavior by endogenous opioid substances.

Narcotic cue Drug discrimination Narcotic state Fentanyl Morphine Narcotic drugs
Internal stimulus control Discriminative stimulus Specificity Subjective effects Tolerance
Analgesia Neurotransmitters Conditioning Central nervous system Drug abuse
Drug dependence Neuropeptides Opioid neuropeptides

THE recognition of the discriminative stimulus properties of morphine and other narcotic analgesic drugs is a major and relatively recent advance in the experimental analysis of the ability of these drugs to control behavior. Through this analysis, considerable insight is being gained not only into the mechanism of action of narcotic drugs, but also into the physiology of the many systems whose functioning is affected by narcotics. Perhaps most significantly, the analysis has revealed much about how the central nervous system proceeds so as to make the physiological action(s) of narcotics operate as stimuli which control behavioral output in so many and so diverse ways as is factually apparent. The term "stimulus control of behavior" refers to the relation between a stimulus and a response. Different types of relations between a stimulus and a response can exist, and Skinner [140] distinguishes four stimulus functions, i.e., eliciting, reinforcing, discriminative and emotional. Historically, the above-mentioned analysis has proceeded along successive steps by which the different stimulus functions of narcotics became recognized. The analysis probably commenced with Pavlov [119] and his tradition (see [13]) showing that a narcotic may act as an unconditioned stimulus in a classical conditioning paradigm [20,55]. The conditioning of responses elicited by narcotics has later been attributed a considerable role in narcotic drug abuse and dependence [68, 101, 124, 155, 157]. The next step consisted of showing that a narcotic may act as a reinforcing stimulus [6, 76, 145]. Finally, recent evidence has shown that a narcotic may act as a discriminative stimulus, and it is this stimulus property on which the present review will focus.

1. NARCOTIC CUE: POSTULATE AND EVIDENCE

This section is concerned with the discriminative stimulus (DS) properties of narcotics and, more specifically, with what is now commonly referred to as the narcotic cue. The notion "cue" denotes that particular part of a drug's DS properties which is actually relevant for its discrimination from saline in a discrimination paradigm where the drug is being used as the training drug. Regardless of some altera-

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tions in terminology, the *narcotic cue* has been defined [27] as *the discriminative stimulus complex which is exclusively associated with the specific central action(s) of narcotic analgesic drugs*. What follows is an analysis of the experimental data which have accumulated systematically to substantiate this postulate.

1.1 Discriminative Stimulus

To show that narcotics possess DS properties requires evidence indicating that animals can be trained to use the administration of a narcotic and that of its vehicle as a pair of discriminative stimuli (discriminandum) which effectively control differential operant responding.

Belleville [8] trained rats to bar-press for food after morphine treatment and found that, after this training, part of the responding failed to transfer to the placebo condition. This finding confirmed earlier studies [51, 86, 87] indicating that responses acquired under one drug condition may demonstrate a decrement when tested under another condition. The phenomenon of learning effects being conditional on the inferred "state" of an organism is referred to as "dissociation of learning" [67] or "state-dependent learning" [118], and this study [8] thus indicated that narcotics can induce a state upon which bar-pressing can be made at least partly conditional *(narcotic state)*. Claiming that they were studying "state-dependent control of discrimination by morphine," Hill *et al.* [78] failed to obtain morphine-state-dependency in the T-maze shock escape apparatus described by Overton [118]. However, in the third experiment of this study [78], differential responding did occur when morphine and saline trials were given alternately, and it is possible that this finding represents the first evidence of responding being controlled at least in part by a morphine-induced DS. A similar difficulty in distinguishing between response control by the narcotic cue and response dependence on the narcotic state, is presented by the early studies of Rosecrans and associates, in which a shock escape [125] or a milk-reinforced bar-press response [80,81] were acquired by rats while being treated with morphine. In these studies, response control by morphine appeared disrupted by p-chlorophenylalanine [125] and was susceptible to the development of tolerance [80]. In view of later evidence (see [21]) it is likely that responding in these studies was dependent on the narcotic state, rather than being controlled by the narcotic cue. This issue will be considered further in a following section (section 3.6).

Later studies seem to have suffered considerably less from the indiscriminate use of drug discrimination and state-dependency methodology and -terminology, and have presented data which are probably more adequate in demonstrating that narcotic drugs can function as a DS. In the studies being considered here, the narcotic analgesics fentanyl and morphine (Fig. 1) were used as the training drugs. It has been shown, then, that these narcotics can control differential responding in two-lever procedures with either food [27,65] or electric shock [134] as a reinforcer in rats, or with shock-reinforcement in monkeys [128]. For example, in one of these procedures, rats are first trained to press two levers for food: the stimulus conditions (e.g., fentanyl and saline) whose DS potential is being investigated are introduced only after the responses which are to become discriminative responses, have been acquired [27]. With lever selection or, more generally, response selection being the discrimination index, the differential responding which then develops is likely to be controlled by the DS properties of the

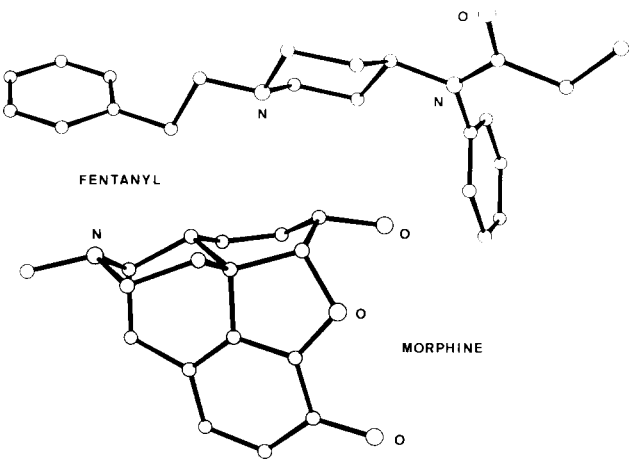

FIG. 1. Three-dimensional representation (J.P. Tollenaere and H. Moereels, unpublished data) of fentanyl and morphine obtained by X-ray crystallographic techniques [73,95]. For the sake of clarity, hydrogen atoms and double bonds are not shown.

training drug, rather than being conditional upon the state possibly induced by the drug [31]. An empirical verification of this point has been presented [22] for 0.04 mg/kg fentanyl as the training drug in the above-mentioned two-lever food-reward procedure.

Figure 2 demonstrates how acquisition of discriminative responding proceeds as a function of training. Initially, the animals select the appropriate lever on approximately 50% of either saline or 0.04 mg/kg fentanyl sessions. This is followed by a relatively rapid decrease of errors in the course of the first 40 sessions; thereafter, errors occur at a progressively decreasing rate, and after 100 sessions, the overall error rate in the group being considered here, amounted to only 1%. It is apparent (Fig. 2) that as error rate decreases, its further decrease decelerates. This accords well with the observation that learning about the discriminative stimulus condition proceeds at a higher rate in erroneous trials than in correct trials [147], and supports a discrimination interpretation of this data.

1.2 Stimulus Generalization

The data discussed above demonstrate that rats can be trained to discriminate fentanyl from saline, and serve to substantiate that a narcotic analgesic can function as a DS. In animals trained to discriminate a given stimulus from its mere absence, the presentation of physically different stimuli may sometimes yield the discriminative response appropriate to the training stimulus, a phenomenon denoted as stimulus generalization. Stimulus generalization is considered to reflect perceptual similarity of the test stimulus to the DS. In rats trained to discriminate 0.04 mg/kg fentanyl from saline, lower doses (0.0025 to 0.02 mg/kg) were tested for stimulus generalization with the training drug [27]. Thus, the animals were injected with the doses being studied, and were then free to select either the saline lever (appropriate to the standard saline condition) or the drug lever (appropriate to the standard 0.04 mg/kg fentanyl condition). The lever selection data so obtained are presented in Fig. 3 (top section). It was found that the lowest dose (i.e., 0.0025 mg/kg) induced saline lever selection in all rats tested. However, with increasing doses, an increasing number of animals selected the

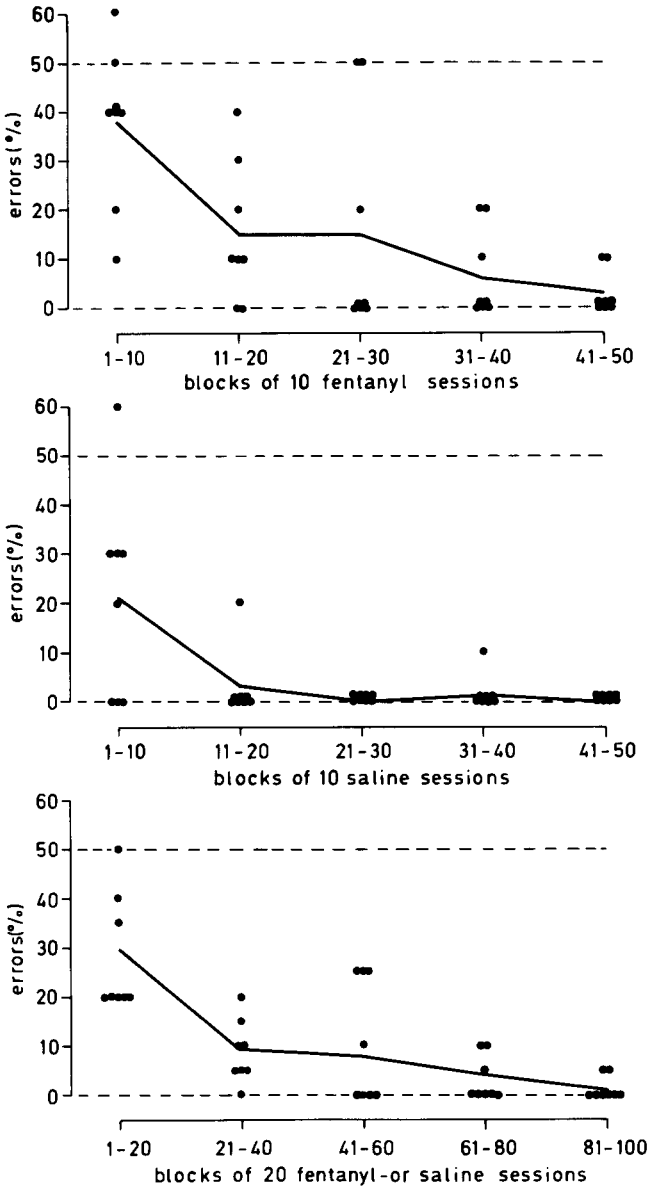

FIG. 2. Error rate as a function of training sessions in rats (n=8) trained to select the correct out of two levers with 0.04 mg/kg fentanyl and saline serving as a pair of discriminative stimuli. Each point represents 10 (top and middle sections) or 20 (bottom section) observations in one animal. The solid lines connect points of overall error rate (all rats combined).

drug lever, and 100% drug lever selection was obtained at the 0.02 mg/kg dose. This indicates that stimulus generalization of a narcotic training drug is a dose-dependent phenomenon, thus implying that detection of the DS produced by the narcotic is orderly related to its physical intensity. The data also demonstrate that, though all 12 animals were trained on the same dose of the training drug, marked interindividual differences may exist as regards their individual lowest effective, or threshold, dose for generalization.

The same data are also represented (Fig. 3, bottom section) as a stimulus generalization gradient. Such a gradient allows to infer [100] a dose which induces the discriminative

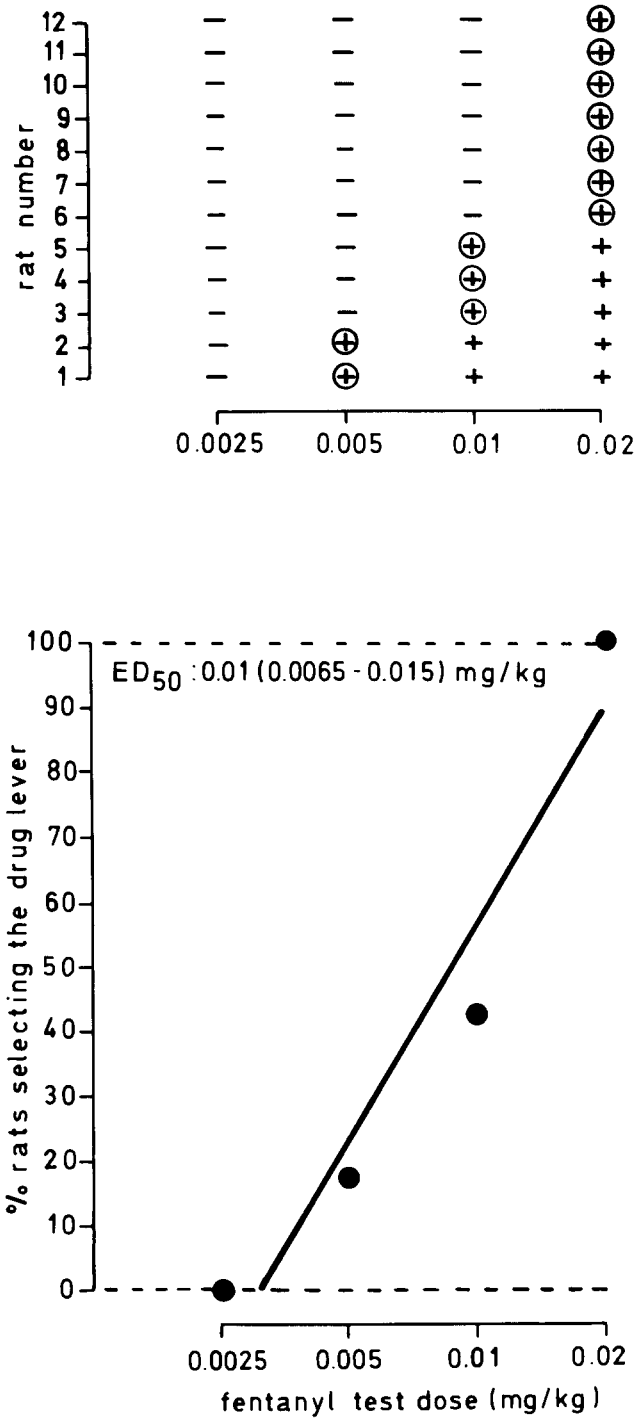

FIG. 3. Stimulus generalization of lower fentanyl doses with the training dose in rats (n=12) trained to discriminate 0.04 mg/kg fentanyl from saline. In the top section, lever selection data are presented for each rat individually (− refers to Saline Lever; + refers to Drug Lever); the individual lowest effective, or threshold dose is encircled. The bottom section represents the same data by a linear regression line on a log-linear plot.

response appropriate to the training drug in 50% of the animals tested (50% Effective Dose; ED_{50}). The ED_{50} is commonly used as an estimate of a drug's cuing potency, but can similarly be viewed as an estimate of the sensitivity of a group of trained subjects to the cuing properties of the drug. In the present case, the fentanyl ED_{50} is 0.01 mg/kg (95% confidence limits: 0.0065–0.015 mg/kg).

The phenomenon of stimulus generalization has been discussed quite extensively here because it constitutes the exclusive basis upon which drug discrimination studies are to be considered. A fact of particular importance is that generalization of a lower dose (e.g., 0.005 mg/kg in rat No. 1 in the above example) with the training dose indicates that the lower dose was equivalent to the training dose, but that this equivalence is valid only with reference to the discriminandum being applied. The equivalence thus is relative rather than absolute, and does not imply, for example, that these two stimuli would not be discriminable.

1.3 Specificity of the Narcotic Cue

The narcotic cue postulate proposes that this cue is associated with specific pharmacological action(s) of narcotic drugs, and at least four hypotheses amenable to empirical verification can be derived from this proposal.

1.3.1 Generalization of other narcotic drugs. The first hypothesis holds that narcotic analgesics exert distinct pharmacological actions which are characteristic of this class of drugs and that, if the DS produced by a narcotic is specific, then narcotics other than the training drug should induce stimulus generalization with the latter. The evidence originally corroborating this hypothesis was obtained in rats trained to discriminate 0.04 mg/kg fentanyl from saline; injections of 0.31 mg/kg phenoperidine, 0.63 mg/kg dextromoramide, 5 mg/kg piritramide or 10 mg/kg morphine were found to induce response selection appropriate to fentanyl in all animals tested [27]. The data indicated that chemically heterogeneous but narcotic compounds induce stimulus generalization with the training drug in rats trained to discriminate a narcotic from saline, and many similar instances of generalization have since been reported (Table 1). As the narcotic cue, by definition, relates to the agonist actions of narcotic drugs only, it is relevant to note that morphine also generalizes with pentazocine in rats trained to discriminate the latter from saline [98]. Pentazocine is a benzomorphan narcotic antagonist [7,94]. That the drug generalizes with fentanyl [33] and morphine [134], as well as the above-mentioned finding [98], is evidence that pentazocine exerts narcotic agonist activity as well.

Stimulus generalization involving narcotic drugs also occurs when the test drugs are administered *via* a route different from the one used during training. In rats trained to discriminate subcutaneously injected fentanyl, the administration of narcotics *via* the oral [29] or intracerebroventricular route [45] is similarly effective to induce stimulus generalization. The intracerebral injection route is also effective in rats trained on subcutaneous morphine [126,137]. This across-route generalization suggests that the animals utilize (a particular level of) a narcotic agonist effect of narcotics as a DS, and that secondary cues associated with the injection procedure contribute little, if at all, to the set of relevant stimuli presented by the drug administration.

1.3.2 Narcotic cuing and analgesic potency. The evidence cited above suggests that narcotic analgesic drugs have an action(s) in common which is characteristic of this class of drugs, and which may be instrumental in their generalization with a narcotic when the latter is applied as a DS. The first hypothesis relating to the specificity of the narcotic cue, may also be expanded so as to circumscribe the underlying action(s) more accurately. In rats, narcotic drugs produce several pharmacological effects such as mydriasis, catatonia, constipation and analgesia. However, the ability of narcotics to produce analgesia is commonly regarded as their most characteristic biological activity [102], and *in vitro* pharmacological [129,130] as well as biochemical studies [120, 139, 148] on narcotic drugs typically employ *in vivo* comparative analgesic activity as an external criterion to validate the assays being investigated. It can be hypothesized accordingly that if the narcotic cuing and analgesic activity of narcotics were associated with similarly specific pharmacological action(s) of these drugs, then a correlation might exist between their narcotic cuing and analgesic potency.

The hypothesis was first verified in a study [34] on nine narcotic and/or antidiarrheal compounds, in which a Spearman Rank Correlation Coefficient as high as $r_s=1.0$ ($p<0.01$; [138]) was obtained between the ED_{50} value of these drugs for their narcotic cuing activity, and their ED_{50} for analgesia. As more data have since become available, a more extensive analysis of the relation between narcotic cuing and analgesic potency of narcotic drugs is presented here.

The stimulus generalization gradient of a number of drugs was determined in rats trained to discriminate fentanyl from saline. Two compounds (sufentanil and piritramide) were tested 30 min after subcutaneous injection; 6 other compounds (bezitramide, difenoxin, diphenoxylate, methadone, codeine, pethidine) were tested 60 min after oral administration, and another 3 compounds (dextromoramide, fentanyl, morphine) were tested *via* both the subcutaneous and the oral route. Route and time of administration being equal, the analgesic activity of the same drugs in experimentally naive rats was determined with an analgesic assay described elsewhere [35].

The dose-effect gradients resulting from the stimulus generalization experiments are represented in Fig. 4. The statistical analysis of this data proceeded as follows [100]. After conversion of doses to logarithms, and of percentages (of rats selecting the drug lever) to probits, a straight line was fitted through the data points. The chi-square test was applied to assess goodness of fit. ED_{50} values and slopes (Table 2) were then computed, as were their 95% confidence limits. As a test for parallelism, the slope function ratio was determined for each of the 91 pairs of observations. This test revealed that, within experimental error, all curves (Fig. 4) could be considered parallel to one another, thus justifying computation of potency ratios. The latter revealed that the drugs spanned a 13,051-fold potency range relative to sufentanil (Table 3), which is probably the most potent narcotic analgesic available so far [117]. Finally, ED_{50} values were similarly computed for the analgesic activity of these compounds (Table 2). The ED_{50} values resulting from this analysis are graphically represented in Fig. 5. The data points appear to be scattered around the bisectre, and the correlation between narcotic cuing and analgesic activity in this set of narcotics amounts to $r_s=0.996$ ($p<0.001$). The bearing of this analysis on the hypothesized specificity of the narcotic cue, is two-fold. Firstly, it indicates that the typical slope of the generalization gradient of a narcotic with fentanyl is relatively steep, the slope varying between 1.14 (sufentanil) and 1.74 (pethidine; Table 2). As the steepness of

TABLE 1

DRUGS THAT INDUCE STIMULUS GENERALIZATION WITH THE TRAINING DRUG IN RATS TRAINED TO DISCRIMINATE A NARCOTIC AGONIST FROM SALINE. PARTIAL AGONIST-ANTAGONIST NARCOTICS ARE NOT INCLUDED. ALL DATA WERE OBTAINED IN RATS, EXCEPT FOR THOSE OBTAINED IN MONKEYS IN ONE STUDY [128]. THE ROUTES OF ADMINISTRATION BEING USED ARE SUBCUTANEOUS (SC), PER OS (PO), INTRAPERITONEAL (IP), OR INTRAMUSCULAR (IM)

Training Drug Condition	Test Drug	Approximate 100% Effective Dose		Reference
0.04 mg/kg Fentanyl (SC)	Dextromoramide (SC)	0.63	mg/kg	[27]
	Morphine (SC)	10	mg/kg	
	Phenoperidine (SC)	0.31	mg/kg	
	Piritramide (SC)	5.0	mg/kg	
0.04 mg/kg Fentanyl (SC)	Methadone (SC)	2.5	mg/kg	[28]
	Codeine (PO)	40	mg/kg	
	Diphenoxylate (PO)	20	mg/kg	
	Fentanyl (PO)	1.25	mg/kg	
1.25 mg/kg Fentanyl (PO)	Bezitramide (PO)	1.25	mg/kg	[25]
	Dextromoramide (PO)	5	mg/kg	
	Methadone (PO)	20	mg/kg	
	Morphine (PO)	40	mg/kg	
0.04 mg/kg Fentanyl (SC)	Sufentanil (SC)	0.0025	mg/kg	[29]
1.25 mg/kg Fentanyl (PO)	Pethidine (PO)	40	mg/kg	[32]
0.04 mg/kg Fentanyl (SC)	Pentazocine (SC)	10	mg/kg	[33]
1.25 mg/kg Fentanyl (PO)	Difenoxin (PO)	5	mg/kg	[34]
6 mg/kg Morphine (IP)	Levorphanol (IP)	1	mg/kg	[158]
10 mg/kg Morphine (IP)	Morphine (PO)	50	mg/kg	[65]
	Methadone (IP)	4.0	mg/kg	
10 mg/kg Morphine (IP)	Fentanyl (IP)	0.32	mg/kg	[66]
3.0 mg/kg Morphine (SC)	Oxymorphone (SC)	0.3	mg/kg	[134]
	Levorphanol (SC)	1.0	mg/kg	
	Methadone (SC)	3.0	mg/kg	
	Meperidine (SC)	30	mg/kg	
	Profadol (SC)	3.0	mg/kg	
	Pentazocine (SC)	10	mg/kg	
3.0 mg/kg Morphine (SC)	Etonitazene (SC)	0.003	mg/kg	[136]
	Fentanyl (SC)	0.03	mg/kg	
	Phenazocine (SC)	0.3	mg/kg	
	Heroin (SC)	1.0	mg/kg	
	Alphaprodine (SC)	3.0	mg/kg	
	Codeine (SC)	30	mg/kg	
	Propoxyphene (SC)	100	mg/kg	
3.0 mg/kg Morphine (IM)	Fentanyl (IM)	0.01	mg/kg	[128]
	Oxymorphone (IM)	0.1	mg/kg	
	Levorphanol (IM)	1.0	mg/kg	
	Methadone (IM)	3.0	mg/kg	
	Meperidine (IM)	30	mg/kg	

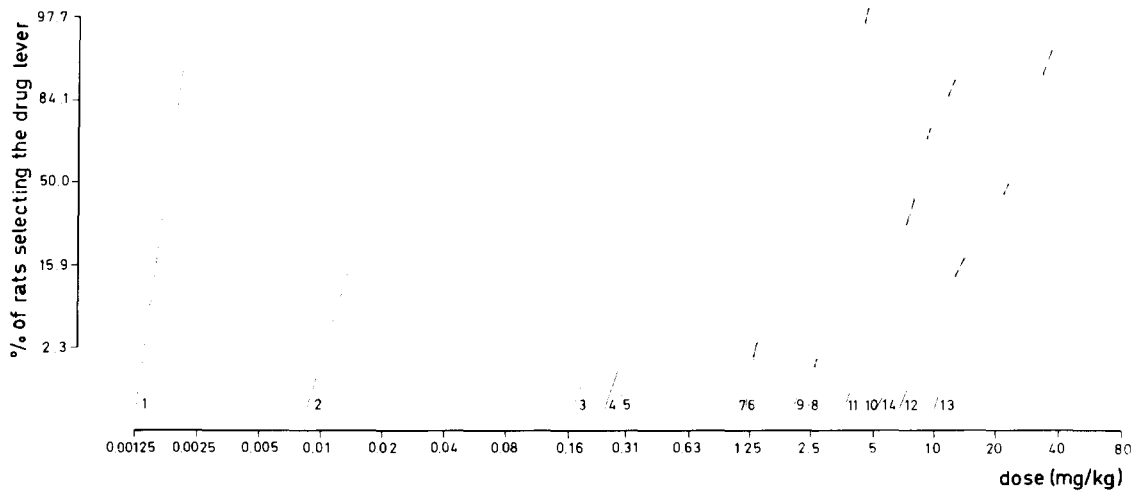

FIG. 4. Log-probit plot of the stimulus generalization gradients of narcotic drugs in rats trained to discriminate fentanyl from saline. The numbers at the right of the lines refer to the serial numbers of drugs as indicated in Table 3.

TABLE 2

NARCOTIC CUING AND ANALGESIC ACTIVITY OF NARCOTIC DRUGS*

Drug (Route)	Narcotic cue - ED_{50} in mg/kg (95% Confidence Limits)	Slope (95% Confidence Limits)	Analgesia - ED_{50} in mg/kg (95% Confidence Limits)
Sufentanil (SC)	0.00177 (0.00134–0.00234)	1.14 (1.03–1.27)	0.0010 (0.00054–0.0019)
Fentanyl (SC)	0.0182 (0.0131–0.0252)	1.33 (1.11–1.60)	0.0156 (0.012–0.021)
Dextromoramide (SC)	0.376 (0.276–0.513)	1.32 (1.04–1.68)	0.200 (0.154–0.260)
Bezitramide (PO)	0.570 (0.398–0.817)	1.34 (1.10–1.63)	0.381 (0.252–0.580)
Fentanyl (PO)	0.630 (0.499–0.796)	1.34 (1.17–1.53)	0.421 (0.275–0.644)
Dextromoramide (PO)	1.78 (1.31–2.42)	1.14 (1.02–1.28)	1.98 (1.52–2.57)
Difenoxin (PO)	2.50 (1.77–3.54)	1.36 (1.11–1.67)	2.57 (1.57–4.21)
Piritramide (SC)	3.55 (2.69–4.68)	1.14 (1.03–1.26)	3.13 (2.30–4.25)
Diphenoxylate (PO)	7.10 (4.90–10.3)	1.59 (1.14–2.21)	6.93 (3.34–14.4)
Morphine (SC)	8.27 (6.50–10.5)	1.24 (1.07–1.44)	5.50 (4.45–6.80)
Methadone (PO)	8.50 (5.86–12.3)	1.35 (1.09–1.67)	11.6 (8.16–16.5)
Morphine (PO)	20.0 (13.0–30.8)	1.47 (1.07–2.01)	13.5 (5.58–21.2)
Codeine (PO)	22.7 (15.9–32.5)	1.37 (1.10–1.70)	19.0 (13.3–27.7)
Pethidine (PO)	23.1 (14.7–36.3)	1.74 (1.09–2.78)	33.0 (22.9–47.5)

*Drugs were administered either subcutaneously (SC) 30 min before test, or orally (PO), 60 min before test. Their potencies are expressed in terms of ED_{50} values. The slope indicated pertains to narcotic cuing activity.

a generalization gradient is proportional to its specificity [122], these data suggest that the dimension along which stimulus generalization occurred in the present experiments, is highly specific. [In this particular context, the term specificity refers to the sensory distinctiveness ("uniqueness") of the DS with reference to the virtually unlimited variety of stimuli which the organism's sensory channels are able to process. Specificity so defined links to narcotic specificity through the fact that the DS being studied is actually produced by a narcotic. Due to this link, the above argument further supports the narcotic specificity of the narcotic cue.] The finding that the slope of each drug can be considered as essentially parallel to that of any other narcotic studied here, is consistent with the assumption that generalization always occurred along the same dimension. It also suggests, interestingly, that possible differences between the cuing properties of individual drugs have contributed little, if anything at all, to the generalization data, and that very similar results would probably have been obtained if a narcotic other than fentanyl had been applied as the training drug at a comparable training dose. Secondly, the correlation obtained here (Fig. 5) confirms the second hypothesis of narcotic cue specificity, asserting that the narcotic cuing and analgesic potency of narcotic drugs show a significant correlation.

1.3.3 Steric specificity. It has long been recognized [141] that the receptor sites to which narcotic drugs bind to produce their agonist and antagonist effects must be stereospecific. It can be hypothesized, therefore, that if the ability to produce the narcotic cue were a property that is specific to narcotics, then the requirement of steric specificity should

TABLE 3

POTENCY RATIOS BETWEEN NARCOTIC DRUGS AS REGARDS THEIR NARCOTIC CUING ACTIVITY

Drug (Route)	#	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Sufentanil (SC)	1	1	10.3	212	322	356	1006	1412	2006	4011	4672	4802	11299	12825	13051
Fentanyl (SC)	2	–	1	20.7	31.3	34.6	97.8	137	195	390	454	467	1099	1247	1269
Dextromoramide (SC)	3	–	–	1	1.52	1.68	4.73	6.65	9.44	18.9	22.0	22.6	53.2	60.4	61.4
Bezitramide (PO)	4	–	–	–	1	1.11	3.12	4.39	6.23	12.5	14.5	14.9	35.1	39.8	40.5
Fentanyl (PO)	5	–	–	–	–	1	2.83	3.97	5.63	11.3	13.1	13.5	31.7	36.0	36.7
Dextromoramide (PO)	6	–	–	–	–	–	1	1.40	1.99	3.99	4.65	4.78	11.2	12.8	13.0
Difenoxin (PO)	7	–	–	–	–	–	–	1	1.42	2.84	3.31	3.40	8.00	9.08	9.24
Piritramide (SC)	8	–	–	–	–	–	–	–	1	2.00	2.33	2.39	5.63	6.39	6.51
Diphenoxylate (PO)	9	–	–	–	–	–	–	–	–	1	1.16	1.20	2.82	3.20	3.25
Morphine (SC)	10	–	–	–	–	–	–	–	–	–	1	1.03	2.42	2.74	2.79
Methadone (PO)	11	–	–	–	–	–	–	–	–	–	–	1	2.35	2.67	2.72
Morphine (PO)	12	–	–	–	–	–	–	–	–	–	–	–	1	1.14	1.16
Codeine (PO)	13	–	–	–	–	–	–	–	–	–	–	–	–	1	1.02
Pethidine (PO)	14	–	–	–	–	–	–	–	–	–	–	–	–	–	1

Drugs are ranked according to decreasing potency. All potency ratios lying within the area circumscribed by the bold line, refer to pairs of observations whose members differ significantly ($p<0.05$) in potency.

TABLE 4

NARCOTIC CUING EFFECTS OF 0.63 MG/KG DEXTROMORAMIDE AND 10 MG/KG LAEVOMORAMIDE IN 6 RATS TRAINED TO DISCRIMINATE 0.04 MG/KG FENTANYL FROM SALINE. RESPONSE LEVEL REPRESENTS THE TOTAL NUMBER OF RESPONSES, EXPRESSED AS A PERCENTAGE OF TOTAL RESPONDING FOLLOWING SALINE (=100%). DRUGS WERE SUBCUTANEOUSLY INJECTED 30 MIN BEFORE TEST. SL: SALINE LEVER; DL: DRUG LEVER.

Rat No.	0.63 mg/kg Dextromoramide		10 mg/kg Laevomoramide	
	Selected lever	Response level	Selected lever	Response level
1	DL	20.0	SL	85.5
3	DL	83.9	SL	89.3
4	DL	35.5	SL	90.2
6	DL	91.4	SL	108.7
7	DL	34.4	SL	121.4
12	DL	6.3	SL	96.3

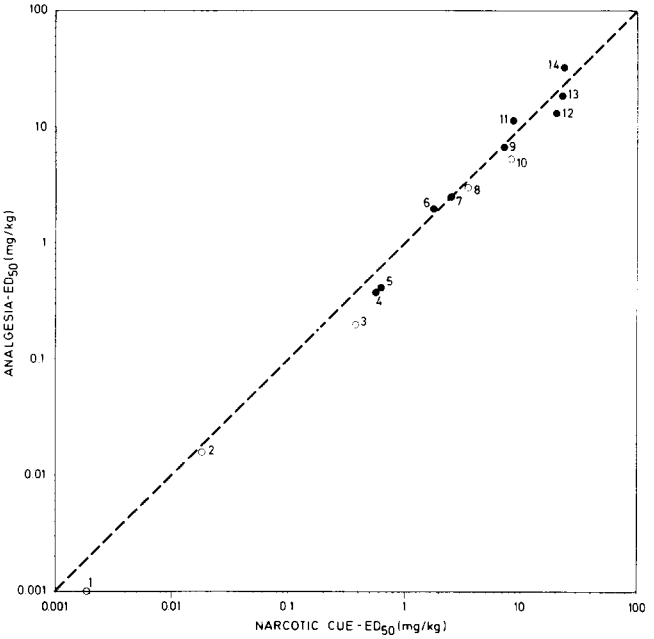

FIG. 5. Narcotic cuing and analgesic activity of narcotic analgesic drugs; log-log plot of ED_{50} values for stimulus generalization with fentanyl (abscissa) and for analgesia (ordinate). The numbers refer to the serial numbers of drugs as indicated in Table 3.

appear in comparative experiments with optical isomers.

The first evidence supporting steric specificity of the narcotic cue was obtained in a study by Winter [158] showing that, in rats trained to discriminate 6 mg/kg morphine from saline, levorphanol (effective dose: 0.25 to 0.44 mg/kg) is much more effective in inducing stimulus generalization with morphine, than its optical isomer dextrorphan (effective dose: 42 to 100 mg/kg). Shannon and Holtzmann [134] also reported that levorphanol (lowest effective dose: 0.3 mg/kg), but not dextrorphan (1 to 3 mg/kg) is generalized with morphine in rats trained to discriminate 3 mg/kg morphine from saline, and similar results were obtained in monkeys [128]. This finding thus accords with the fact that dextrorphan, unlike its optical isomer levorphanol, is virtually devoid of narcotic effects [88]. In a comparative experiment (unpublished) in rats trained to discriminate 0.04 mg/kg fentanyl from saline, it was similarly found that 0.63 mg/kg dextromoramide induces 100% stimulus generalization with fentanyl, whereas 10 mg/kg of its optical isomer laevomoramide [90] is entirely devoid of any such activity (Table 4). These data thus consistently support the hypothesis that steric specificity is required for drugs to induce stimulus generalization with the training drug in animals trained to discriminate a narcotic from saline.

1.3.4 Antagonism by naloxone. A fourth hypothesis that can be derived from the presumed specificity of the narcotic cue, is that this cue can be antagonized by naloxone and similar narcotic antagonists. Naloxone is a narcotic antagonist [11] that presumably acts by competitively occupy-

ing narcotic binding sites, thereby preventing access of agonists to these sites. As naloxone itself exerts little intrinsic effects [9,10], it competitively antagonizes the biological activity of narcotic agonists that is otherwise contingent upon their binding to specific narcotic binding sites.

Winter [158] found that 0.4 mg/kg naloxone antagonizes the DS induced by 6 mg/kg morphine. A similar single-dose experiment has also been carried out in rats trained to discriminate 0.04 mg/kg fentanyl from saline [36]. Other studies have shown that the antagonism of morphine's DS by naloxone is dose-dependent in rats [66,134] as well as in monkeys [128]. In an extensive series of experiments, Shannon and Holtzman [135] showed that naloxone and the similar antagonist naltrexone [10] antagonize both the morphine DS in rats and the generalization of methadone with this cue. Their time-effect experiments and comparative tests on the subcutaneous and oral route of administration appeared to correspond with clinical data on the relative antagonist efficacy of naloxone and naltrexone in man [135]. Fig. 6 presents data on the antagonist effects of naloxone on both the cuing and rate-depressant effects of 0.04 mg/kg fentanyl. It is shown that naloxone injection before 0.04 mg/kg fentanyl treatment antagonizes drug lever selection otherwise associated with the training drug condition. This antagonist effect is dose-dependent [ED_{50}: 0.026 (0.135–0.0487) mg/kg], as are the reversing effects of naloxone on the rate-depressant effects of the fentanyl training dose. Naloxone also antagonizes the DS produced by mixed agonist-antagonist drugs such as pentazocine [98], and cyclazocine and nalorphine [79] when these are applied as the training drug. It seems fair to conclude, therefore, that the narcotic cue also fulfills a fourth requirement for specificity, namely, that it is susceptible to the blocking effect of drugs known to occupy the specific binding sites for narcotic drugs. Along with its stereo-specificity, the reversibility of the narcotic cue by naloxone is unequivocal evidence that this cue is contingent upon the binding of narcotic drugs to specific opiate receptors.

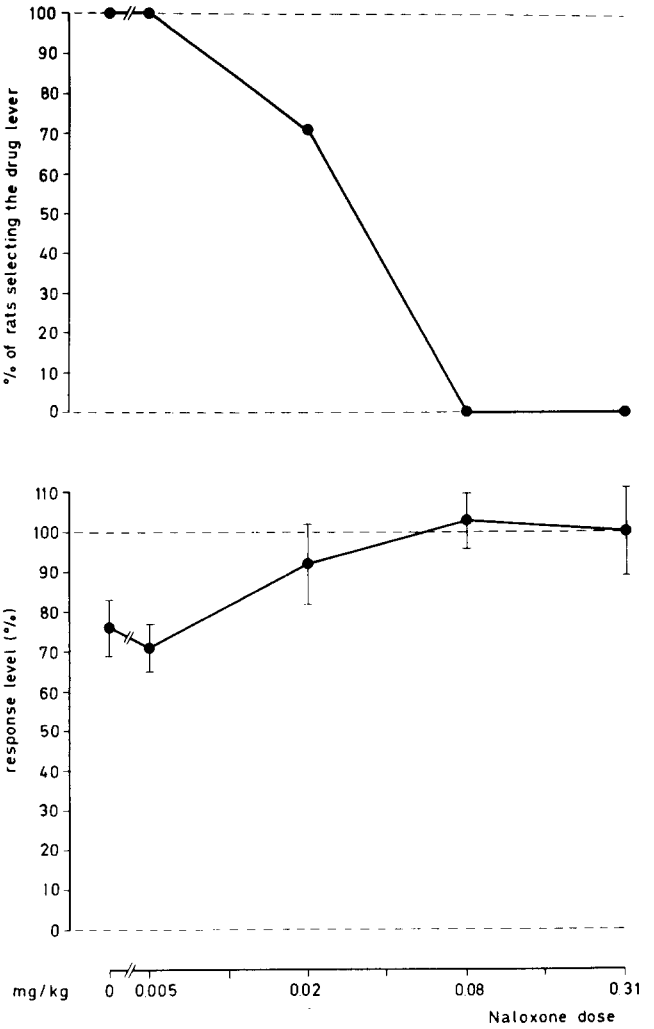

FIG. 6. Effects of naloxone on the cue produced by 0.04 mg/kg fentanyl in rats (n=7) trained to discriminate the latter drug from saline. Fentanyl was injected 30 min, and naloxone 60 min before test. All injections were subcutaneous. Response level as in Table 4.

1.4 Exclusive Cue

Where the narcotic cue postulate characterizes the narcotic cue as being exclusive to narcotics, it implies that drugs (or, for that matter, other stimulus sources) which do not possess typical narcotic properties, are not able to induce stimulus generalization with a narcotic when the latter is being applied as the training drug. This notion of exclusiveness cannot, of course, be understood as an absolute one, and the actual degree of exclusiveness of the narcotic cue is merely proportional to the amount of available evidence indicating lack of generalization of as broad a variety of non-narcotic drugs as possible. The postulate thus assumes that this degree will be relatively high, as very few, if any, non-narcotic drugs are expected to induce stimulus generalization with a narcotic.

Early attempts to demonstrate that non-narcotic drugs fail to induce stimulus generalization with a narcotic training drug, indicated that haloperidol [27], and a vast array of other centrally acting drugs [29] induce the discriminative response appropriate to saline in rats trained to discriminate 0.04 mg/kg fentanyl from saline. Table 5 summarizes the relevant data so far available; partial agonist-antagonist drugs are not included here, and will be considered elsewhere (section 4). It is shown that most drugs being tested induce no stimulus generalization whatsoever (0% of responding appropriate to the training drug condition) with either fentanyl or morphine. In some cases, however, partial generalization occurred, in particular in the data presented by Shannon and Holtzman [134,136]. There are several reasons to suggest that these partial generalization may not be wholly representative of the narcotic cue. Firstly, in all cases where generalization occurred, it never reached a quantitative level comparable to that of the training drug; if the latter is set as a criterion for the acceptance of stimulus generalization, then it is concluded that there is no stimulus equivalence between the test- and the training stimulus [134]. Secondly, the stimulus generalization with non-narcotic drugs, where it occurred, was not orderly related to dose. This is much unlike the case with narcotic drugs (e.g., [28]), and suggests that drug effects other than their stimulus properties act to contaminate the percentage of drug-appropriate responses as an index of possible stimulus generalization [22,31]. Many drugs exert behaviorally toxic effects which may disrupt discriminative stimulus control of behavior quite independently of the particular stimulus which is controlling

TABLE 5

SURVEY OF STIMULUS GENERALIZATION DATA OBTAINED WITH NON-NARCOTIC DRUGS IN RATS TRAINED TO DISCRIMINATE A NARCOTIC AGONIST FROM SALINE. THE ASTERISK DENOTES THAT GENERALIZATION DID NOT OCCUR IN AN ORDERLY DOSE-RELATED MANNER

Training Drug Condition	Dose	Test Drug	% of Responding Appropriate to Narcotic Drug	Reference
0.04 mg/kg Fentanyl	0.04–0.08 mg/kg	Haloperidol	0%	[27]
0.04 mg/kg Fentanyl	5–40 mg/kg	Loperamide	0%	[28]
0.04 mg/kg Fentanyl	10 mg/kg	Chlordiazepoxide	0%	[29]
	20 mg/kg	Pentobarbital	0%	
	0.04 mg/kg	Dexetimide	0%	
	0.08 mg/kg	Isopropamide	0%	
	0.16 mg/kg	Atropine	0%	
	0.16 mg/kg	Nicotine	0%	
	0.31 mg/kg	d,l-Amphetamine	0%	
	10 mg/kg	Cocaine	0%	
	20 mg/kg	Caffeine	0%	
	0.08 mg/kg	Spiperone	0%	
	0.63 mg/kg	Chlorpromazine	0%	
	0.08 mg/kg	Lysergic Acid Diethylamide	0%	
	10 mg/kg	Mescaline	0%	
	10 mg/kg	Desipramine	0%	
	40 mg/kg	Imipramine	0%	
1.25 mg/kg Fentanyl	0.04–160 mg/kg	Suprofen	0%	[32]
	160 mg/kg	Acetylsalicylic Acid	0%	
	10 mg/kg	Indomethacin	0%	
	160 mg/kg	Phenacetin	0%	
	160 mg/kg	Phenylbutazone	0%	
	160 mg/kg	Tolmetin	0%	
0.04 mg/kg Fentanyl	10–160 mg/kg	Naloxone	0%	[33]
0.04 mg/kg Fentanyl	0.16–0.63 mg/kg	Apomorphine	0%	[36]
0.04 mg/kg Fentanyl	350 mg/kg	p-Chlorophenylalanine	0%	[42]
	25 mg/kg	Tryptophan	0%	
	5 mg/kg	Cinanserin	0%	
	2.5 mg/kg	Cyproheptadine	0%	
	20 mg/kg	Methysergide	0%	
	10 mg/kg	Pizotifen	0%	
	40 mg/kg	Tryptamine	0%	
6 mg/kg Morphine	630–1260 mg/kg	Ethanol	7–79%*	[185]
10 mg/kg Morphine	2.5–10 mg/kg	Loperamide	0%	[65]
	0.16–1.25 mg/kg	Haloperidol	0–10%*	
3 mg/kg Morphine	1–30 mg/kg	Thebaine	0–10%*	[134]
	0.1–3 mg/kg	d-Amphetamine	5–61%	
	0.1–3 mg/kg	Chlorpromazine	0–15%*	
	1–17.5 mg/kg	Pentobarbital	5–15%*	
	1 mg/kg	Naloxone	0%	
10 mg/kg Morphine	0.8–3.2 mg/kg	Amphetamine	0%	[66]
	2–4 mg/kg	Pilocarpine	0%	
	0.32–0.64 mg/kg	Dexetimide	0%	
	0.32–0.64 mg/kg	Apomorphine	0%	
3 mg/kg Morphine	3–100 mg/kg	Mescaline	0%	[136]
	1–30 mg/kg	Ketamine	0–35%*	
	0.03–1 mg/kg	Physotigmine	0–15%*	
	0.01–1 mg/kg	Scopolamine	25–50%*	

performance; these disruptive effects produce a decrease of the percentage of drug-appropriate responses, and contaminate this percentage as an index of possible stimulus generalization [44]. This explanation probably accounts for much of the supposedly partial generalizations appearing in Table 5. Exception must be made for d-amphetamine which induced a dose-related generalization, with a maximum effect of 61% at the 3 mg/kg dose in rats trained to discriminate 3.0 mg/kg morphine from saline [134]. Subsequent experiments (Shannon, personal communication) revealed that maximal generalization of d-amphetamine with morphine varies between about 0% in rats trained on 5.6 mg/kg morphine, to nearly 100% in animals trained on 1.75 mg/kg morphine. Similar differential characteristics of different training doses have been encountered in studies where amphetamines were applied as the training drug [37,149]. It was found that a low amphetamine dose fails to produce the stimulus effects otherwise associated with the central actions of higher amphetamine doses. The discriminative response control by low training doses appeared to be based on amphetamine's peripheral effects, and the DS associated with these peripheral effects differed qualitatively from that associated with the central actions of the same drug. These findings suggest that, in general, the qualitative characteristics of the DS properties of drugs may vary according to the training dose at which they are applied. It seems likely, also, that the lower the dose of a training drug, the lower will be the strength and the distinctiveness of the DS it produces, and the more inclusive will be the dimension along which generalization proceeds. At the limit, subjects are likely to base differential responding upon a "drug *versus* no-drug" discrimination, rather than upon the specific DS properties of the training drug. The generalization of d-amphetamine with morphine may be viewed in this context, and demonstrates that a less-than-optimal exclusiveness may become apparent at training doses of narcotics which are too low to estabish their cuing properties at a level of distinctiveness and strength which, under other experimental conditions, appears so characteristic of this class of drugs.

With the above-mentioned limitations in mind, the data summarized in Table 5 are relevant to three issues. Firstly, they are evidence that the ability to induce stimulus generalization with a narcotic training drug is an exclusive property of narcotic drugs if the training dose is adequate in establishing the narcotic cue at its characteristic distinctiveness and strength. Secondly, the data may be instrumental in an elimination process through which those pharmacological effects of narcotics that constitute sufficient conditions for their cuing properties, can be isolated. For example, narcotics may exert mydriatic effects in rats, and the fact that peripherally acting anticholinergics (e.g., isopropamide; Table 5) fail to generalize with a narcotic training drug indicates that the mydriatic effects of narcotics in rats are not by themselves responsible for their cuing properties. A similar argument also applies to the many other pharmacological effects which are exerted by the drugs listed in Table 5. Among its more interesting applications is the one to the CNS stimulant and primary reinforcing action of cocaine (e.g, [59]). Resembling cocaine and the amphetamines to some extent, narcotics exert CNS stimulant effects (e.g., [15,142]) and can act as primary reinforcers in laboratory animals (e.g., [56,69]). The fact, then, that rats trained to discriminate a narcotic from saline, show no stimulus generalization with drugs such as cocaine, exemplifies to what extent the cuing properties of drugs may be drug-class specific despite the seeming similarity of their relevant biological activities. A third aspect of the data is that they testify to the degree of independence of the sensory dimensions along which the cuing properties of drugs are perceived. In discrete-trial two-response procedures (e.g., [27]), the application of a narcotic and its vehicle as a pair of discriminative stimuli appears to generate discriminative responding through which drug-produced stimuli become dichotomized into two categories, i.e., those which induce responding appropriate to the training drug, and those which induce responding appropriate to saline. The former category appears to consist uniformly of other narcotic drugs (Table 1). The second category, however, comprises a seemingly unlimited variety of drugs some of which also possess cuing properties. It appears, thus, that the narcotic *versus* saline discrimination defines a sensory dimension which one may refer to as the *narcotic dimension* and which assumes a position that is seemingly orthogonal with respect to all other possible sensory dimensions. Points along other drug class-specific dimensions are equivalent in yielding the saline response, though each of the dimensions may in turn relate differently to each other dimension. This set of sensory dimensions can be thought of as a *saline space*.

1.5 Site of Action

The approach we have adopted to investigate the possible central origin of the narcotic cue, consists of establishing differential quantitative relations between narcotic cuing activity on the one hand, further conditions being equal, other agonist effects of the same drug on the other [34]. This is a particularly valid approach in this case because narcotic drugs produce various specific actions of which some originate centrally and others peripherally. The two actions selected for this purpose were analgesia and constipation because analgesia undoubtedly constitutes a highly characteristic central action of narcotics [4, 17, 121], whereas constipation is probably their best documented peripheral action [115, 116, 150].

To this end, nine compounds were comparatively investigated for their narcotic cuing, analgesic, and constipating activity after oral administration in rats. The results of this study [34] are represented in Fig. 7. It is shown that, within the same group of compounds, there exists a very close correlation ($r_s=1.0$; $p<0.01$) between the narcotic cuing and analgesic activity of these compounds, but not between their narcotic cuing and constipating activity ($r_s=0.17$; $p>0.05$). That the narcotic cuing activity of narcotic analgesics correlates with their central as opposed to their peripheral activity, strongly supports the hypothesis that the bio-availability of a narcotic to the central nervous system is the principal quantitative determinant of the drug's potency in inducing the narcotic cue. Similar correlations between narcotic cuing and analgesic activity have later been reported for the time-effect characteristics of these actions upon systemic [46] as well as intraventricular administration [45] of narcotic drugs.

Other studies have investigated the cuing properties of intracerebrally administered narcotics. In rats trained to discriminate 3 mg/kg subcutaneous morphine from saline, Rosecrans and Krynock [126] found 4.0 μg of morphine injected into the periaquaeductal gray about equally effective as 3 mg/kg administered subcutaneously, and 14.4 μg naloxone into this area antagonized systemic morphine.

Using a similar training drug condition, Shannon and

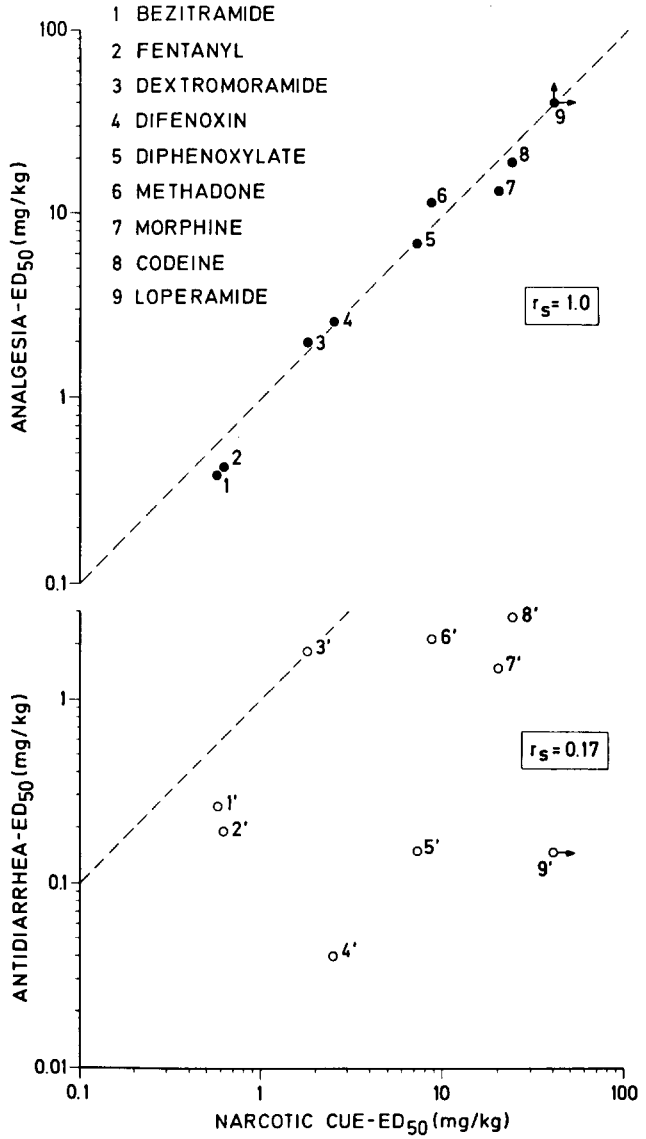

FIG. 7. Graphical representation of the differential quantitative relations between narcotic cuing activity on the one hand, and analgesic and constipating activity on the other. Log-log plot of ED_{50} values for stimulus generalization with fentanyl (abscissa), for analgesia (upper ordinate), and for constipation (lower ordinate).

Holtzman [137] obtained inconsistent results with 10 μg morphine into either the periaquaeductal gray, the lateral septum or dorsomedial thalamus, although morphine doses of 0.3 to 3.0 μg were generalized upon injection into the lateral ventricle. In the same study [137], 1 to 30 μg naloxone into any of these sites was required to antagonize systemically administered morphine. In rats trained to discriminate 0.04 mg/kg subcutaneous fentanyl from saline, 0.5 μg sufentanil, 4.0 μg fentanyl or over 250 μg morphine injected into the lateral ventricle generalizes to systemic fentanyl; systemic naloxone also antagonized intraventricular fentanyl [45]. Allowing for the potency difference between fentanyl and morphine upon either systemic [35] or intraventricular injection [45], the latter findings accord reasonably well with those of Shannon and Holtzman [137]. On injection into the nucleus magnus, a somewhat lower fentanyl dose (i.e., 2 μg) appears adequate to mimick 0.04 mg/kg subcutaneous fentanyl [153], suggesting that this area may represent a relatively sensitive site for narcotics to produce a DS.

Among the hazards associated with the study of the cuing properties of intracerebrally administered drugs, are differences in time-effect characteristics between drugs as well as between different routes of administration. The degree to which a drug is lipophylic, and the time-interval between its administration and testing are among the critical variables for an adequate appreciation of relative potencies. While the data so far available on intracerebrally injected narcotics are consistent with the presumed [27] central origin of the narcotic cue, no truly adequate evidence is currently available to denote a possible anatomically discrete site of action. In view of this, and considering the associative characteristics of narcotic cue and narcotic analgesia [46], it seems reasonable to entertain the possibility that, much like in narcotic analgesia [151], multiple brain sites rather than a single discrete area may be involved in the ability of narcotic drugs to produce the narcotic cue.

1.6 Stimulus Complex

The proposal [27] that the narcotic cue should be conceived as a stimulus complex allows for the possibility that drug-produced cues may be of a composite shape, rather than being defined by a particular value along a single pharmacological or physiological variable. In this context, drug-produced cues are thought [5, 22, 31] to be composed of pharmacologically and/or physiologically heterogenous components which may differ considerably as regards their relative significance to the thus composed entity, or complex.

Evidence for the complex shape of the narcotic cue has been obtained in a study [36] showing that 0.63 mg/kg apomorphine is not generalized with fentanyl in rats trained to discriminate 0.04 mg/kg fentanyl from saline; nonetheless, 0.04 mg/kg fentanyl appeared to induce stimulus generalization with apomorphine in rats trained to discriminate 0.16 mg/kg of this drug from saline. The latter generalization could be blocked by both haloperidol and naloxone. This case of asymmetrical generalization indicates that the second group of rats, while performing the (apomorphine *versus* saline) discrimination task, attends to a stimulus characteristic which fentanyl and apomorphine have in common. Presentation of this stimulus is not a sufficient condition for rats of the first group to select the drug-appropriate response, nor does its blockade by haloperidol entail a disintegration of the narcotic cue [36]. These data thus suggest that this stimulus constitutes a significant, but not a critical component of the cuing properties of narcotic drugs.

In another study (unpublished), a first group of rats (n=6) was trained to discriminate 0.04 mg/kg fentanyl from saline. Stimulus generalization experiments in this group revealed that 80 mg/kg mescaline (subcutaneous, 30 min before test) does not generalize with 0.04 mg/kg fentanyl, and that pretreatment with 20 mg/kg methysergide (subcutaneous, 60 min before test) fails to affect drug lever selection after 0.04 mg/kg fentanyl (30 min before test).

A second group of rats (n=5) was trained to discriminate 80 mg/kg mescaline from saline, and the data obtained in this group are summarized in Table 6. It is shown that, following training, stimulus generalization of mescaline proceeds in a dose-dependent manner; the ED_{50} value amounts to 17.3 (9.40–31.86) mg/kg, and it is noted that the slope of this gen-

TABLE 6

STIMULUS GENERALIZATION EXPERIMENTS IN RATS (N=5) TRAINED TO DISCRIMINATE 80 MG/KG MESCALINE FROM SALINE. DRUGS AND SALINE WERE SUBCUTANEOUSLY INJECTED AT STATED INTERVALS (IN MIN) BEFORE TEST. LEVER SELECTION DATA ARE REPRESENTED AS + (DRUG LEVER SELECTED) OR - (SALINE LEVER SELECTED) FOR INDIVIDUAL RATS. FRF REFERS TO THE TOTAL NUMBER OF RESPONSES EMITTED BEFORE 10 WERE MADE ON THE SELECTED LEVER, AND IS EXPRESSED AS THE MEDIAN. THE TOTAL NUMBER OF RESPONSES (TR) IS EXPRESSED AS THE MEAN (± 1 SEM), WHEREAS THE PERCENTAGE OF TR ON THE SELECTED LEVER IS EXPRESSED AS THE MEDIAN (AND LIMIT VALUES)

Treatment		Lever Selection					FRF	TR	% of TR on Selected Lever
t-60′	t-30′	1	2	3	4	5			
–	Saline	–	–	–	–	–	10 (10–10)	963 (± 90)	100 (99.8–100)
–	80 mg/kg Mescaline	+	+	+	+	+	10 (10–12)	633 (± 86)	99.7 (99.5–100)
–	40 mg/kg Mescaline	+	+	+	+	–	10 (10–12)	910 (± 55)	99.7 (94.5–100)
–	20 mg/kg Mescaline	+	+	–	–	–	10 (10–17)	918 (± 108)	98.9 (99.4–100)
–	10 mg/kg Mescaline	+	+	–	–	–	10 (10–13)	903 (± 115)	100 (84.6–100)
–	5 mg/kg Mescaline	+	–	–	–	–	10 (10–10)	982 (± 103)	100 (96.6–100)
–	2.5 mg/kg Mescaline	–	–	–	–	–	10 (10–10)	937 (± 219)	100 (51.8–100)
–	1.25 mg/kg Mescaline	–	–	–	–	–	10 (10–10)	1043 (± 112)	100 (99.9–100)
–	0.63 mg/kg Apomorphine	–	–	–	–	–	10 (10–13)	221 (± 93)	98.3 (87.9–100)
–	10 mg/kg Chlordiazepoxide	–	–	–	–	–	10 (10–11)	957 (± 168)	99.8 (80.6–100)
–	10 mg/kg Cocaine	–	–	–	–	–	10 (10–10)	1241 (± 137)	100 (100–100)
–	0.08 mg/kg Dexetimide	–	–	–	–	–	10 (10–10)	705 (± 199)	100 (100–100)
–	1.25 mg/kg d,l-Amphetamine	–	–	–	–	–	10 (10–12)	1192 (± 152)	100 (99.8–100)
–	0.31 mg/kg LSD	+	+	+	+	+	10 (10–13)	753 (± 70)	99.0 (98.5–99.5)
0.08 mg/kg Haloperidol	80 mg/kg Mescaline	+	+	+	+	+	10 (10–16)	200 (± 37)	92.3 (68.7–100)
1.25 mg/kg Naloxone	80 mg/kg Mescaline	+	+	+	+	+	10 (10–14)	772 (± 52)	99.7 (98.0–100)
20 mg/kg Methysergide	80 mg/kg Mescaline	–	–	–	–	–	10 (10–14)	905 (± 90)	100 (62.5–100)
Saline	0.04 mg/kg Fentanyl	+	–	+	–	–	10 (10–12)	725 (± 116)	99.8 (87.5–100)
0.08 mg/kg Haloperidol	0.04 mg/kg Fentanyl	+	–	+	–	–	10 (10–11)	80 (± 36)	98.1 (59.3–100)
1.25 mg/kg Naloxone	0.04 mg/kg Fentanyl	–	–	–	–	–	10 (10–15)	1062 (± 130)	100 (99.9–100)
20 mg/kg Methysergide	0.04 mg/kg Fentanyl	+	–	+	–	–	10 (10–10)	816 (± 101)	100 (99.9–100)

eralization gradient is relatively shallow (s=2.35). A second series of experiments (Table 6) was aimed at determining the specificity of the mescaline DS. It was found that the CNS stimulants apomorphine, cocaine and d,l-amphetamine, the benzodiazepine chlordiazepoxide, and the central anticholinergic dexetimide, induced saline lever selection in all rats tested; 0.31 mg/kg LSD, however, induced stimulus generalization with 80 mg/kg mescaline. The serotonergic receptor blocker methysergide, but not haloperidol or naloxone, antagonized the mescaline-DS. In a last series of experiments, 0.04 mg/kg fentanyl was found to consistently induce drug lever selection in 2 out of the 5 rats tested. Higher fentanyl doses were not submitted to test because of their behaviorally disruptive effect. In these 2 animals, the stimulus generalization of fentanyl with mescaline was antagonized by naloxone, but not by either haloperidol or methysergide. These data (Table 6) thus present a second case of asymmetrical generalization involving fentanyl, and reveal the existence of a second component of the cuing properties of narcotics. This second component differs pharmacologically from the first one in that it cannot be mimicked by apomorphine, nor blocked by haloperidol. Much like the first component, however, the mescaline-like stimulus produced by fentanyl constitutes a significant but, again, non-critical component of the narcotic's cuing properties. It should be pointed out, that the similarity of the cuing properties of fentanyl to the mescaline-DS is limited. Firstly, only 2 out of 5 rats showed generalization, and the data leave undetermined whether this is due either to the possibility that the fentanyl dose was too low to generate a 100% response, or to a possible divergence among mescaline-trained rats as regards the component of mescaline's cuing properties to which they attend. Secondly, the fentanyl generalization with mescaline, unlike the mescaline-DS itself, was not antagonized by a relatively high (20 mg/kg) dose of methysergide. This finding may serve to suggest that the mescaline-DS can be produced through neuronal activity which does not, unlike mescaline itself [99], depend critically upon serotonergic neurotransmission.

The data discussed above are evidence that the cuing properties of narcotics involve several pharmacologically distinct components. It is important to note, however, that the data do not provide evidence that these two components are actually involved in the narcotic cue; this is because it is left undetermined whether rats trained to discriminate a narcotic from saline, would actually attend to these components. In fact, the lack of generalization of either apomorphine [36] or mescaline (Table 6; [27]) with fentanyl, indicates that these two stimulus components may, at best, be involved in the narcotic cue as significant but certainly non-sufficient components. This distinction between the cuing properties of narcotics and the narcotic cue is no trivial exercise because there is suggestive evidence (Colpaert, unpublished data) that rats trained to discriminate the same

dose of the same training drug, may attend to pharmacologically distinct components of the drug's cuing properties. It can be concluded, therefore, that although the cuing properties of narcotic drugs are complex, the presumed complex shape of the narcotic cue has not been conclusively substantiated.

2. ROLE OF NEUROTRANSMITTERS IN THE DS PROPERTIES OF NARCOTIC DRUGS

Narcotic drugs are known to affect various central neurotransmission processes due to their interference either with the synthesis and/or metabolic degradation of different transmitter substances, or with their interaction with the transmitter's receptor sites. Consequently, alterations of neurotransmitter function are thought to mediate numerous pharmacological effects of narcotics, and among the neurotransmitters studied in this respect, dopamine, noradrenaline and 5-hydroxytryptamine are likely to play a significant role in narcotic drug actions [18,97]. It is these considerations that led to the investigation of the possible involvement of various neurotransmitters in the DS properties of narcotic drugs. The ultimate aim of this research is to uncover the neural processing through which a narcotic can act as a DS.

2.1 Dopamine

Apomorphine is presumed to mimic the intrinsic action of endogenous dopamine at dopamine receptor sites (for review, see [38]). The drug possesses DS properties [30] which are likely to be based on its direct dopaminergic activity [39]. We have found [36] that, in rats trained to discriminate apomorphine from saline, fentanyl is generalized with the training drug. The generalization of fentanyl with apomorphine may be suggestive of a dopaminergic effect of narcotics; this interpretation accords with considerable pharmacological and biochemical evidence (discussed in [38]) indicating that narcotic drugs may indirectly increase dopaminergic activity in some areas of the brain. Quite consistent with this interpretation, it was further found [36] that dopamine receptor blockade [3] by haloperidol, blocks this generalization. That naloxone also antagonizes fentanyl generalization with the apomorphine-DS can be explained by this drug's competitive occupation of the opiate receptor sites to which narcotics bind to generate the neural events upon which their dopaminergic activity is consequent.

The above suggests that the cuing properties of narcotics encompass a component that is contingent upon indirect dopaminergic activity. Further data seem to suggest that this component may not critically contribute to the narcotic cue. Firstly, apomorphine alone does not present a sufficient condition for eliciting the narcotic cue [36]. Secondly, haloperidol doses effectively blocking fentanyl generalization with apomorphine, fail to affect fentanyl's discriminability as determined in either a single-dose experiment [36] or in more sensitive dose-response experiments [44]. Higher doses of similar neuroleptic drugs (e.g., pimozide) may in some cases block the cue associated with fentanyl as the training drug [43]. In view of the deleterious effects of such doses on discriminative performance [44], the latter finding must be considered with much caution, and further research is required to determine the specificity of this antagonism. A third finding relating to this issue was obtained in an experiment in which trained rats were treated with α-methyl-p-tyrosine (α-MPT), and then tested for fentanyl discrimination 4.5 and 23.5 hr later [43]. α-MPT reduces catecholamine biosynthesis [52, 143, 154] by inhibiting tyrosine hydroxylase, and a critical involvement of dopaminergic neurotransmission in the narcotic cue would predict discriminative performance based thereon, to be markedly disturbed. However, α-MPT failed to produce any detectable effect on this performance [43]. It can be concluded therefore, that the evidence cited here fails to provide evidence that the dopaminergic component of the cuing properties of narcotic drugs contributes critically to the narcotic cue.

An interesting experimental design is presented in a recent paper by Spencer and Rosecrans [144]. Rats were chronically depleted of brain dopamine by intracisternal administration of 6-hydroxydopamine following desipramine injection, and then trained to discriminate 4 mg/kg morphine from saline. It was found that the dopamine-depleted animals acquired the morphine-saline discrimination more rapidly than controls; this effect can be attributed to the decreased susceptibility of the dopamine-depleted group to morphine's rate-depressant effects [144]. Surprisingly, however, haloperidol induced a dose-related increase in the percentage of morphine-appropriate responses with a maximum effect of 58.3% in the control, and of 67.6% in the dopamine-depleted group. Though the authors considered this as evidence that, in the dopamine-depleted group, "haloperidol (0.5 mg/kg) is perceived as similar to morphine" [144], the result must be considered in light of other data [44] indicating that high doses of neuroleptics may cause a non-specific deterioration of the percentage of drug-appropriate responding in the absence of any detectable effect on the DS condition otherwise controlling responding. For this and other [22] reasons, this percentage is probably not an adequate index of discrimination [31,44]. The study [144] is adequate, however, in showing that dopamine depletion does not to any detectable degree impair the ability of rats to discriminate morphine from saline, or to generalize methadone with morphine as the training drug. It is important to note that this study leaves undetermined whether the cue attended to by dopamine-depleted rats is entirely similar to the one attended to by normal rats similarly trained to discriminate morphine from saline.

2.2 Noradrenaline

The above-mentioned failure of α-MPT to disrupt discriminative responding based on a narcotic training drug also suggests that noradrenergic neurotransmission may not be critically involved in the narcotic cue. This interpretation is corroborated by further evidence [43] showing that drugs presumably blocking peripheral and central noradrenergic transmission do not detectably affect the narcotic cue.

2.3 Serotonin

In a study [42] on the possible role of 5-hydroxytryptamine (5-HT) in the narcotic cue, three experiments were reported. In the first experiment, p-chlorophenylalanine (p-CPA) was administered to rats trained to discriminate 0.04 mg/kg fentanyl from saline. p-CPA is known [96,112] to deplete 5-HT by inhibiting tryptophan hydroxylase, and its biochemical and behavioral effects in rats reach peak levels 2 to 4 days after administration. In this experiment, tests 1 to 6 days after p-CPA revealed that the drug produces marked behavioral disturbance (i.e., decreased total responding and overt excitation), but fails to affect discriminative responding after either fen-

tanyl or saline. The second experiment assessed the effects of drugs presumably blocking or stimulating 5-HT receptor sites, on fentanyl's discriminability. The drugs being used were cinanserin, cyproheptadine, methysergide, pizotifen, and tryptamine; each of these drugs decreased total responding, but none of them appeared to attenuate fentanyl-saline discrimination. In the third experiment, the stimulus generalization gradient of fentanyl (0.005 to 0.04 mg/kg) was determined under two conditions. One condition consisted of saline pretreatment before fentanyl injection, whereas in the second condition pretreatment consisted of the 5-HT precursor, l-tryptophan [72]. This tryptophan loading significantly increases brain 5-HT content [61], but does not affect the stimulus generalization gradient of fentanyl in rats trained to discriminate the latter from saline [42].

In an independent study by Winter [159], the effects of p-CPA and pizotifen were similarly determined in two groups of rats trained to discriminate 6 mg/kg morphine from saline in a one-level procedure. Quite consistent with the above findings, the results show that neither treatment had any detectable effect on discriminative performance based on the narcotic cue.

It seems fair to conclude from these data, that 5-HT is not critically involved in the narcotic cue.

2.4 Other Neurotransmitters

Research efforts aimed at defining the neuronal mechanisms subserving the narcotic cue are likely to be continued. Among the neurotransmitter substances whose possible involvement is worth of study are acetylcholine and γ-aminobutyric acid because cholinergic [58] and gabaminergic [83] neurotransmission may play a role in various pharmacological actions of narcotic drugs. However, no published data on the possible role of these substances in the narcotic cue are currently available.

3. THE NARCOTIC CUE: A SPECIAL CASE OF DRUG DISCRIMINATION

In this section, we will discuss a number of findings which relate to the DS properties of narcotics but which may also have some more general bearing on drug discrimination research.

3.1 Role of Training Dose

Figure 8 summarizes (unpublished) data from rats trained to discriminate different fentanyl doses from saline. It is apparent that speed of acquisition, as determined by sessions-to-criterion, rapidly increases as a function of training dose. Also, the ED_{50} value for stimulus generalization increases as a function of training dose, thus indicating that this dose co-determines the intensity of narcotic drug action required to induce stimulus generalization with the training drug condition. A more surprising finding is that the steepness of the slope of the stimulus generalization gradient is also proportional to the training dose. This may suggest that the distribution of individual sensitivities differs according to training dose, thus implying that the assumptions of normality and of equivariance of these distributions may be valid within a limited intensity range of the training drug only.

The role of the training dose in the apparent sensitivity of trained animals to the cuing properties of the training drug, is similarly apparent from cross-generalization experiments [84] involving narcotic agonist and mixed agonist-antagonist drugs in rats trained to discriminate morphine from saline. In addition, some data (Shannon, personal communication) indicate that the degree to which d-amphetamine induces stimulus generalization with morphine increases with decreasing morphine training dose. This observation suggests that this dose plays a prominent role in the determination of not only the quantitative, but also the qualitative aspects of the DS produced by narcotic drugs (Section 1.4).

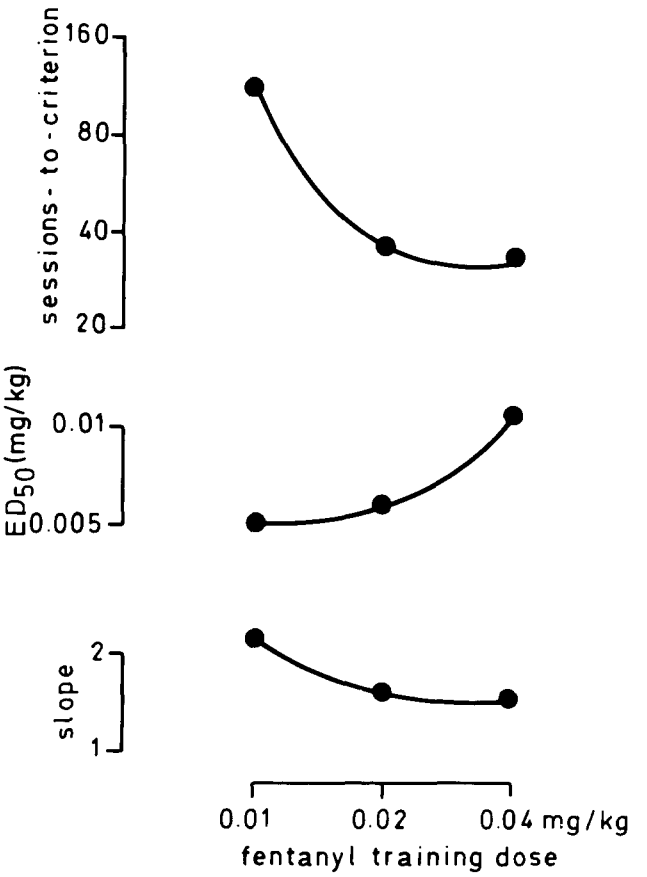

FIG. 8. Speed of acquisition (sessons-to-criterion), sensitivity (ED_{50} in mg/kg) and slope of the stimulus generalization gradient (in log-probit plot) as a function of training dose. Data were obtained from rats trained to discriminate different fentanyl training doses (n=6 per group) from saline.

3.2 Tolerance

Analgesia and other, though not all (see [38]) pharmacological actions of narcotic drugs have been reported to be subject to the development of tolerance (e.g. [19]). Tolerance often develops upon repeated administration of drugs, and is defined either as a decreased intensity of a response to the same amount of drug, or as the phenomenon that a greater amount of drug is required to obtain a response whose intensity is similar to that of the original response. The problem whether tolerance develops to the DS properties of narcotic drugs, is interesting for several reasons. First, the problem is of intrinsic significance to the narcotic cue itself. Secondly, the possibility that tolerance may have developed in the numerous groups of animals used in the studies discussed above, would seriously challenge some of the conclusions reached so far. This is because different levels of tolerance in different groups may have been as-

sociated with different degrees of susceptibility to the experimental conditions being investigated in these studies. Thirdly, elucidation of the tolerance problem is relevant to an interpretation of the possible relation between the narcotic cue and other actions of narcotic drugs (e.g., analgesia). Fourthly, the tolerance issue may make it possible to distinguish between the narcotic cue and state-dependent learning involving narcotic drugs (narcotic state). Finally, should the narcotic cue be subject to tolerance, then this would provide an explanatory basis upon which to discuss the effects of various conditions on (sensitivity to) the narcotic cue in terms of positive or negative accelerations of this process.

Hirschhorn and Rosecrans [80] originally reported that partial tolerance develops to what was referred to as "the stimulus effects" of morphine. In this study, responding in a two-lever task was brought under the control of morphine—as opposed to saline injections; following training, additional morphine injections were given as doses up to 16 times the training dose (10 mg/kg) during a period of continued exposure to the training conditions. It was found that additional injections of 40 or 80 mg/kg, but not of 8 or 160 mg/kg, decreased response control by morphine. While these data present evidence suggestive of tolerance development, a number of difficulties in interpretation seem to occur. One is that tolerance development was not clearly dose-related in that intermediate but not high doses were found effective [80]. Also, upon completion of the experiment, the subjects used in the latter study demonstrated several withdrawal symptoms following naloxone injection, and it is questionable whether similar results would be obtained in non-dependent rats. Finally, some of the experimental conditions in the study by Hirschhorn and Rosecrans [80] raise the possibility that morphine control over responding was at least in part due to state-dependency rather than being based upon morphine's DS properties.

Another experimental design was used in a study [35] with rats trained to discriminate 0.04 mg/kg fentanyl from saline. At different time intervals after discriminative responding had been established, the animals were subjected to stimulus generalization experiments with roughly equivalent dose-ranges of fentanyl (0.0025–0.02 mg/kg) and morphine (2.5–20 mg/kg). It was found that although contingent 0.04 mg/kg fentanyl injections were regularly continued throughout the experiment, the ED_{50} values of both compounds did not appreciably decrease over a period as long as four months. Nevertheless, significant tolerance to the rate decreasing as well as to the analgesic effect of fentanyl had developed but none of the subjects showed any sign reminiscent of physical dependence. These data were taken [35] as evidence that tolerance does not develop to those physiological effects of narcotic drugs which subserve their ability to function as a DS.

Conflicting findings, however, have been reported in experiments [111,134] using rats trained to discriminate morphine from saline. The experimental design was similar in both studies, and consisted of administering relatively high doses of morphine in a period during which the animals were withdrawn from daily exposure to the discriminative paradigm. It was found that, as compared with performance preceding this period of non-contingent exposure to morphine, the ED_{50} value for morphine had significantly increased. This result was considered [111,134] as evidence that tolerance develops to the narcotic cue, and Shannon and Holtzman [134] further concluded that this presumed tolerance development would represent further support for the specificity of the DS properties of narcotic drugs.

Two further studies are reported in a more recent paper [48]. In the first study, rats were given daily non-contingent exposure to 0.06 mg/kg fentanyl for 30 days before they were trained to discriminate 0.04 mg/kg fentanyl from saline. In contrast with the predictions which can be derived from the tolerance hypothesis it was found that, as compared with an appropriate control group, there was no increase in either the number of sessions-to-criterion, or in the ED_{50} for generalization of fentanyl doses lower than the training dose. In addition, the experimental group failed to show an increase of errors consisting of reporting saline in the presence of 0.04 mg/kg fentanyl (omission errors). The second study utilized rats with a long history of narcotic treatment; non-contingent exposure to increasing fentanyl doses in addition to regular contingent exposure, failed to increase the omission error rate, and had no measurable effect on the fentanyl ED_{50} for generalization. On the basis of these and other data [35,46] we concluded [48] that the decreased sensitivity in the aforementioned studies [111,134] probably results from partial extinction of the DS value of morphine due to non-contingent exposure to high doses of the drug. In fact, the approach used in these studies may be much similar to simply increasing the training dose and, hence, shifting the generalization gradient to the right.

The above discussion has pointed out the several approaches that have been used to investigate whether tolerance develops to the narcotic cue. While this issue is subject to considerable controversy, our current interpretation holds that there is no convincing evidence in support of the position that tolerance would develop to those physiological actions of narcotic drugs which subserve their ability to act as a DS. We wish to suggest, instead, that tolerance does not develop to the narcotic cue; elsewhere [24] we have formulated a more comprehensive proposal which describes in more detail the organism's regulation of sensitivity to the DS properties of drugs.

It is of interest to note that a similar controversy has arisen in studies on sensitivity to the cocaine cue. McKenna and Ho [110] found that, in rats that were given non-contingent exposure to cocaine, the sensitivity to the cuing properties of cocaine decreased in a manner that is similar to the decreased morphine sensitivity in the studies [111,134] discussed above. Using the approach of the Colpaert *et al.* [35] study, we found [49] that sensitivity to the cocaine cue remained constant for a period as long as 8 months. This discrepancy is thus very similar to the one encountered with narcotics, and is likely to be explained in a similar way.

3.3 Narcotic Cue and Narcotic Analgesia

One of the ways to gain more insight into the physiological action(s) which subserve the DS properties of drugs is to study the possible relation between these DS properties on the one hand, and other relevant pharmacological actions on the other. Analgesia being among the most characteristic effects of narcotic drugs, a number of studies have been undertaken to elucidate the relation between the narcotic cuing and the analgesic activity of narcotic drugs.

In a first study [34] relating to this issue, it was found that the potency of narcotics to induce stimulus generalization with a narcotic training drug, correlates highly if not perfectly with their analgesic potency in experimentally naive rats (Fig. 5); data suggestive of a similar correlation have also been obtained with intraventricularly, as opposed to

systemically administered drugs [45]. Secondly, it was found [33] that the dose-effect characteristics of both actions are similar, if not identical. Thus, as regards analgesia, fentanyl shows a simple, linear dose-effect relation, whereas cyclazocine and nalorphine yield inverted-U-shaped curves; at the same doses, similar curves are obtained for their cuing effects. Thirdly, the time-effect characteristic of fentanyl's cuing properties coincides perfectly with the time-effect characteristic of its analgesic action in experimentally naive animals [46]. These three findings converge to suggest that for both their cuing and analgesic actions, the bioavailability to the CNS and their intrinsic agonist activity constitute the major determinants of the *in vivo* activity of narcotic drugs. Furthermore, both the narcotic cue and narcotic analgesia demonstrate the requirement of steric specificity (section 1.3.3), and can be antagonized by naloxone (section 1.3.4), thus suggesting that the type of receptor interaction involved in both activities, must be largely similar.

Nonetheless, if observations are made within the same animals, data indicative of dissociative characteristics can be obtained. Within the same animals, tolerance appears to develop to the analgesic, but not to the cuing effect of narcotic drugs [35], and rats rendered highly tolerant to fentanyl-induced analgesia, are not detectably retarded in acquiring the fentanyl-saline discrimination [48]. The findings are consistent with the hypothesis [48] that the regulation of sensitivity to the cuing and analgesic effects of narcotic drugs is processed at least partly independent by the CNS, and indicate that the analgesic effect of narcotics does not *per se* actually constitute the narcotic cue. Furthermore, within the same animals, there is no correlation whatsoever between cuing and analgesic activity in terms of either the intensity [35,46] or the duration [48] of the response. This suggests that the dissociation between narcotic cue and analgesia is not solely due to differential tolerance development, and that an additional dissociative characteristic must be invoked to account for all data. One possibility [46] is that the neuronal populations mediating the two actions overlap less than perfectly.

To some extent, evidence similarly relating the cuing to other pharmacological actions of drugs is available for benzodiazepines and barbiturates [23,40], and it may be of interest to consider that the above-discussed approach may prove useful for the study of the cuing properties of drugs other than narcotics.

3.4 Narcotic Cue and ACTH

Adrenocorticotrophic hormone (ACTH) and its structural analogues interfere with the acquisition and maintenance of behavior in many experimental conditions [57], among which is the discrimination paradigm (e.g. [127]). As ACTH may effect the processing of stimuli long after their significance has been established through antecedent conditioning [114], we have investigated the possible effects of $ACTH_{4-10}$ in rats trained to discriminate 0.04 mg/kg fentanyl from saline. It was found [47] that $ACTH_{4-10}$ increases the incidence of errors consisting of reporting saline after fentanyl injection, while exerting no measurable effect on the other type of error. $ACTH_{4-10}$ also caused up- and downward shifts in the sensitivity of individual animals to fentanyl's cuing properties. These data thus indicate that this pituitary hormone may affect the relative efficacy with which narcotic drugs may exert DS control over behavior. As it is unlikely [47] that the results were due to a specific interaction of $ACTH_{4-10}$ with opiate receptors, it is possible that neuropeptides related to ACTH play a role in the DS properties of other drugs as well.

3.5 Conditional Establishment of the Narcotic Cue

The ability of narcotics to control (operant) discriminative responding in animals (Section 1.1) indicates that these drugs produce an internal stimulus which, through discrimination learning, can become a signal indicating which among several response alternatives is the more adequate one in a given set of environmental conditions. One question of major theoretical interest, then, is whether this DS control of behavior by narcotics can be made conditional to one set, as opposed to another set of environmental conditions. In a study [50] tackling this problem, rats were first trained to discriminate 0.04 mg/kg fentanyl in a two-lever procedure, and, thereafter, to discriminate 10 mg/kg pentobarbital from saline in an underwater maze. Stimulus generalization experiments following training on both discriminanda showed that, in the two-lever procedure, drug lever selection could be elicited by fentanyl and morphine; saline, but also pentobarbital and chlordiazepoxide, elicited saline lever selection. In the maze procedure, both pentobarbital and chlordiazepoxide induced drug-appropriate responding, whereas saline, fentanyl and morphine induced responding appropriate to saline. These data [50] thus indicate that it is possible to condition the DS control of behavior by drug-produced internal stimuli, to external stimulus conditions. This conclusion holds true for narcotics and barbiturates, and it is likely that it may apply to other drug-produced cues as well. It is also relevant to point out that the conditioning of drug-produced cues to external stimulus conditions offers an interesting research strategy with which to investigate different components of such cues within the same animals.

3.6 Narcotic Cue and Narcotic State

It has been proposed [31] that the ability of drugs to produce a DS on the one hand, and to generate a "state" upon which behavior can be made dependent on the other, are distinct phenomena. While this proposal is currently subject to much controversy, there is little doubt that narcotic drugs can produce both phenomena. Belleville [8] trained rats to press a lever for food while being injected with 3 mg/kg morphine. After the animals had acquired the response in the morphine state, it was found that the response transferred only partially to the saline state. This experiment thus presents evidence that narcotic drugs can produce a state ("narcotic state") upon which learning effects can be made at least partly conditional. As discussed above (section 1.1), narcotic drugs also possess DS properties, and the proposal [31] that drug-produced cues and states are distinct phenomena implies that they must be characterized by some distinctive features.

One line of evidence supporting this hypothesis is that, in rats trained to discriminate 0.04 mg/kg fentanyl from saline in our two-lever procedure, drug-appropriate responding is not conditional upon the narcotic [22]. After 0.04 mg/kg fentanyl injection, the animals typically make their first 10 responses on the drug-lever, thus indicating that fentanyl effectively controls response selection. However, if reinforcement does not follow these 10 initial responses, the animal typically starts responding on the saline lever. Such observations indicate: (1) that, in this procedure, lever selection is under

DS control by the training drug, whereas further responding is mainly controlled by the reinforcement contingencies, and (2) that responding on either lever is not conditional on either stimulus condition [22]. Also, the occurrence of errors during training as well as their disappearance following further training are difficult to interpret in terms of state-dependency. Thus, it may occur that after fentanyl-saline discrimination training, a rat incorrectly selects the saline lever. This suggests that not only the *responding* on-, but also the *selection* of either lever, is among the response alternatives that are available following narcotic injection. This being the case, the differential lever selection that is typically observed under those conditions can hardly be based upon a specific dependency of drug lever selection on the narcotic state, and of saline lever selection on the saline state. Rather, these observations suggest that the narcotic, as opposed to saline, provides a DS which allows the animal to predict which of the two available response alternatives will yield reinforcement.

A second line of relevant evidence derives from the discrepancy between different studies on tolerance. Thus, Hirschhorn and Rosecrans [80] found that partial tolerance develops to morphine-control of operant responding, whereas we found no evidence of tolerance in a study using a procedure that is felt to provide an uncontaminated measurement of DS control of behavior [35]. Among the possible explanations for this discrepancy is that the narcotic cue, unlike the narcotic state, is not subject to tolerance. However, subsequent developments in the study of the tolerance problem (Section 3.2) have generated other possible explanations of this discrepancy, and these data [35,80] can no longer be considered as compelling evidence dissociating the narcotic cue from the narcotic state.

Thirdly, Rosecrans *et al.* [125] have found that, in a shock-escape procedure, morphine control of responding is disrupted by p-CPA; the time course of this disruption closely resembled that of 5-HT depletion following p-CPA, thus suggesting that the disruption was consequential upon this depletion. Though these authors described their experiments in terms of both state-dependency and drug discrimination [125], later studies in our laboratory [42] have pointed to a state-dependent interpretation of these data. This followed the finding that p-CPA does not interfere to any detectable degree with discriminative responding based on either fentanyl [42] or morphine [159] as a cue. The inability of various 5-HT receptor blockers to affect differential responding in two-lever [42,81] or one-lever procedures [159] further supports that the integrity of serotonergic neurotransmission in the brain is not critically required for narcotics to produce a cue. We have proposed [42] accordingly, that the narcotic state, but not the narcotic cue, may be critically dependent upon the integrity of central serotonergic transmission.

The above indicates that there is some evidence that the physiological processes underlying the narcotic cue and those underlying the narcotic state, may indeed be partly distinct. However, definite conclusions cannot be drawn from the available data, and further research is required to deliniate the distinctive features of both phenomena. Our attempt to distinguish the narcotic cue from the narcotic state through the establishment of a differential susceptibility to p-CPA, has generated the working hypothesis "that, in general (i.e., irrespective of the drug or other instance which induces the state), the neural events responsible for the phenomenon of responses being dependent upon specific states of the organism might require, to a critical extent, the integrity of central 5-HT systems" [42]. Considering earlier data in retrospect, it is interesting to note that this hypothesis may account for discrepancies other than the one encountered with narcotics. Roffman and Lal [123], but not Schechter and Cook [132], found response control by amphetamine susceptible to p-CPA, and Schechter [131], but not Winter [159] found response control by ethanol susceptible to p-CPA. The serotonin hypothesis of state-dependency [42] thus would imply that state-dependency, whether associated with either amphetamine [123], morphine [125], or ethanol [131] can be disrupted by 5-HT depletion; further data, then, may serve to indicate that 5-HT is not critically involved in the cues produced by either amphetamine [132], fentanyl [42] and morphine [159], or ethanol [159].

3.7 Narcotic Cue and Endogenous Opioid Substances

The presence of opiate-like substances in the brain [85] has prompted us to investigate whether such substances would share the cuing properties of narcotic drugs. In a first study [45] 300 μg intraventricularly administered met-enkephalin was found not to be generalized with fentanyl in rats trained to discriminate 0.04 mg/kg subcutaneous fentanyl from saline. This negative finding may be due to the fact that this substance is only poorly active *in vivo*, even when administered directly into the brain [14], and it is possible that higher doses would have presented a more adequate test of met-enkephalin. In a recent study, however, we found [153] that the more potent [71] C-terminal fragment of β-lipotropin is generalized with fentanyl when administered at a dose of 2 μg. In this study, C-fragment and fentanyl were injected into the nucleus raphe magnus, a structure which is thought (e.g. [1]) to play a significant role in narcotic analgesia. Similar generalizations of endogenous opioid substances with the training drug have also been found [12,16] in rats trained to discriminate morphine from saline. The C-fragment was further found [153] to possess primary reinforcing effects when administered into the lateral ventricle. These findings thus indicate that an endogenous substance may share with narcotics those stimulus properties which enable narcotics to act not only as a reinforcer, but also as a DS. This further suggests [153] that C-fragment may be physiologically involved in the reinforcing and discriminative stimulus control of behavior and, hence, that the narcotic cue would be an endogenous phenomenon. It is noteworthy that this endogenous narcotic stimulus, much like other internal stimuli such as hunger and thirst, exerts both types of behavioral control through the occurrence of a single physiological event.

4. THE NARCOTIC CUE: A MODEL FOR OPIATE-LIKE SUBJECTIVE EFFECTS IN MAN?

We originally proposed [27,28] that the DS properties of drugs may be related to their subjective effects in man and, in particular, that the ability of drugs to produce the narcotic cue, may serve as a model for opiate-like subjective effects. This proposal originated from the contention that both the DS properties of drugs in laboratory animals and their subjective effects in man, pertain to those stimulus properties of drugs which can be overtly reported by the subject, whether animal or man. In both cases, the differential responding that is associated with different stimulus conditions is presumably based upon a covert discrimination of their sensory effects. Unlike many of the covert discriminations

which the organism is likely to make about other effects of the drug, the one covert discrimination which enables narcotics to act as a DS can, by definition, be reported overtly; the latter is achieved through the association of the outcome of the covert discrimination with differential reinforcement contingencies involving different operant responses. Albeit speculative, this contention seemed to provide an intriguing rationale for establishing a number of similarities between the narcotic cue and opiate-like subjective effects in man.

4.1 Formal Similarities

A first similarity between the narcotic cue and opiate-like subjective effects resides in the experimental conditions in which they are being studied. The clinical procedure typically consists of requiring subjects (by preference: former or actual opiate addicts) to evaluate whether the test solution produces the subjective effects they have formerly experienced with opiates [60, 64, 74, 75]. In essence, the clinical procedure thus proceeds as a discrimination procedure in which test substances can be assayed for stimulus generalization with the reference (opiate) experience [2].

A second line of argument is that the subjective effects of narcotics in man are characterized pharmacologically in a manner that is similar to the narcotic cue. Like the narcotic cue (Section 1), opiate-like subjective effects can be elicited by morphine, but also by a large variety of chemically heterogeneous narcotics [63, 64, 91, 104]. These subjective effects demonstrate the requirement of stereospecificity [88,146], and can be antagonized by naloxone [62,102] which is itself essentially devoid of such effects [62,92]. Also, opiate-like subjective effects can be elicited by narcotic drugs only, and other psychoactive but non-narcotic compounds produce markedly distinct subjective effects [77, 106, 107, 109].

The most characteristic component of the subjective effect of narcotics in humans is euphoria [64,104], and there is some circumstantial evidence [36] that the narcotic cue may possess an analogous composition. Unfortunately, few data are currently available on the possible involvement of the primary reinforcing action of narcotics, in the narcotic cue. It may nonetheless be worthwhile to note that, in rats, there is a close correlation between the narcotic cuing, analgesic, and primary reinforcing potency of narcotic drugs; while the narcotic cuing and analgesic potency of narcotic drugs correlate closely (Fig. 5; [34]), Fig. 9 suggests that a similar correlation may exist between analgesic and primary reinforcing potency. Thus, as both phenomena may occur at closely related dose levels, it is possible that the physiological drug effects underlying the narcotic cue and narcotic self-administration are in part similar. This is of some interest because much in the same way as there is no evidence of the narcotic cue being subject to tolerance development (Section 3.2), there is also no evidence that tolerance would develop to the primary reinforcing action of narcotic drugs. Thus, the operant response rate of laboratory animals that self-administer a particular unit dose of a narcotic, does not decrease upon long-term exposure to these conditions (J. H. Woods, personal communication). Extinction of drug-reinforced operant responding must be expected under the hypothesis that tolerance develops to the reinforcing action of the narcotic, and the seeming absence of this extinction is incompatible with the tolerance hypothesis. Few formally established clinical data are available on this issue, and this evidence too must be considered in view of the methodological difficulties outlined elsewhere (Section 3.2; [48]). The general consensus among clinical investigators is that tolerance develops to the euphoric and other subjective effects of narcotic drugs (J. Jaffe, personal communication), despite reported findings [108,113] indicating that part of these effects are considerably resistant to tolerance development.

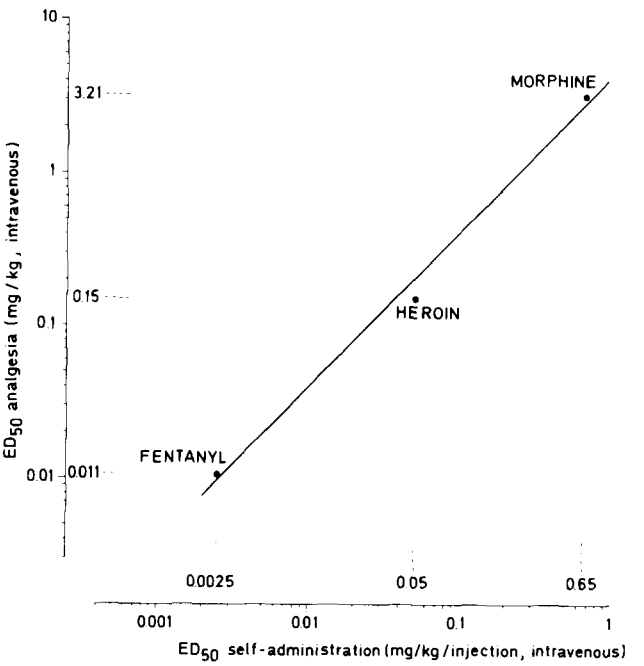

FIG. 9. Analgesic and primary reinforcing potency of intravenously administered fentanyl, heroin and morphine in rats. Log-log plot of ED_{50} for self-administration (abscissa) and analgesia (ordinate). The self-administration data are adopted from Van Ree, *et al.* [152]; the analgesia data are courtesy of Dr. C. J. E. Niemegeers (unpublished).

4.2 Empirical Verification

An explicit verification of the presumed [27] relation between the narcotic cue and opiate-like subjective effects has been sought by comparatively investigating the relative efficacy with which drugs with different narcotic agonist/antagonist effects induce stimulus generalization with a narcotic training drug. That is, the subjective effects of narcotic drugs vary according to their intrinsic activity; pure narcotic agonists produce typical opiate-like subjective effects in a manner that is directly proportional to dose [64], whereas pure narcotic antagonists are essentially devoid of such effects [62,92]. Mixed narcotic agonist-antagonists such as cyclazocine and nalorphine possess a peculiar profile in this respect [75]; the subjective effects induced by these drugs in humans are experienced as typically euphoric ("opiate-like") at low, and as sedative ("barbiturate-like") at comparatively high doses [105,156]. We hypothesized accordingly [26,33] that if the narcotic cue were related to opiate-like subjective effects in man, then its induction should closely parallel the agonist activity of drugs with different narcotic agonist/antagonist effects, and the following predictions should prove correct: (a) a pure narcotic agonist (e.g., fentanyl) should produce a regular dose-response stimulus

generalization, and the curve thus obtained should not decline at a supramaximal dose; (b) a pure narcotic antagonist (e.g., naloxone) should completely fail to produce the narcotic cue; (c) mixed narcotic agonist-antagonist drugs such as cyclazocine and nalorphine should produce the narcotic cue at comparatively low doses, but the generalization curve should decline at higher doses; (d) the dose-effect characteristics of the analgesic activity of fentanyl, naloxone, cyclazocine and nalorphine, should closely parallel those of their narcotic cuing activity. Using rats trained to discriminate 0.04 mg/kg fentanyl from saline, all four predictions have been confirmed in studies [33] indicating: (a) that fentanyl produces a stimulus generalization gradient that is a simple function of dose (0.005–0.04 mg/kg) and which does not decline at supramaximal doses (0.08 mg/kg); (b) that naloxone does not induce stimulus generalization with fentanyl, not even when tested at exceedingly high doses (10 to 160 mg/kg); (c) that cyclazocine (0.08 to 2.50 mg/kg) and nalorphine (10 to 160 mg/kg) induce a generalization gradient whose shape can be described by an inverted U; (d) that the analgesic effects of these four compounds closely parallel the shape of their dose-effect curves for generalization with fentanyl. It was found moreover, that the maximal cuing and analgesic responses to cyclazocine exceeded those to nalorphine by about 20%, and this result too is consistent with the clinical finding [105] that the maximal opiate-like subjective effects of cyclazocine are more intense than those of nalorphine. These data were interpreted [33] as evidence that within a specified dose-range, cyclazocine and nalorphine are generalized with a narcotic training drug.

Part of these data have been confirmed by similar experiments [134,136] in rats trained to discriminate 3 mg/kg morphine from saline. The latter studies revealed: (a) that morphine produces a generalization gradient that is linearly related to dose; (b) that 1 mg/kg naloxone produces no generalization with morphine, and (c) that 0.03 to 3 mg/kg cyclazocine [134] and 0.1 to 30 mg/kg nalorphine [136] produce an inverted U-shaped percentage of drug-appropriate responding. Also, the maximal effect of cyclazocine exceeded that of nalorphine by about 25%. As pointed out by Holtzman *et al.* [84], the accordance between their data in morphine-trained rats and ours in fentanyl-trained animals [33] is quite remarkable. Further data on narcotic agonist/antagonist drugs [82, 128, 134, 136] are consistent with the assumption that the stimulus generalization of these drugs with a pure agonist training drug, closely parallels their other narcotic agonist effects (e.g., analgesia) [33]. However, when applied as training drugs, mixed agonist/antagonists display DS properties which seem partly distinct from those of pure agonists. The evidence relating to this particular issue has recently been reviewed by Holtzman *et al.* [84], and is not further considered here.

In conclusion, the data discussed here seem to provide an empirical verification of the presumed relation between the narcotic cue and opiate-like subjective effects in man; it is shown that the occurrence of stimulus generalization of diverse narcotic agonist/antagonists with a narcotic training drug, is intimately associated with the narcotic agonist activity of these drugs. Their activity patterns for narcotic cuing activity, as those for their analgesic effects, closely resemble their activity patterns for opiate-like subjective effects in man. This conclusion, then, supports the hypothesis [27] that the narcotic cue may serve as a model for "subjectively experienced narcotic drug actions" in man.

4.3 Drug Abuse and Its Preclinical Evaluation

As part of their pioneering clinical work on the subjective effects of drugs in man, H. F. Frazer, H. Isbell, W. R. Martin and their associates have developed experimental procedures to ascertain the abuse potential of drugs (e.g. [64]). The predictive validity of these procedures rests, quite obviously, on the assumption that several classes of psychoactive drugs are being abused because of their ability to induce subjective effects which appear desirable to some subjects. This would apply in particular to narcotics, central nervous system stimulants, hallucinogens, and minor tranquillizers. Hence, the assessment and characterization of their subjective effects, should provide the primary evidence upon which the abuse potential of drugs can be evaluated. The above discussed relation between the narcotic cue in laboratory animals and opiate-like subjective effects in man, strongly suggests [28,41] that the occurrence as well as the nature of subjective effects can be predicted from drug discrimination studies in infrahuman species. The research strategy would consist of determining whether the drug being studied produces stimulus generalization in animals trained to discriminate a prototype of a drug-class with known abuse potential, from saline. The relative degree of generalization would then be predictive for the extent to which the drug being studied produces the type of subjective effects known to be produced by the training drug.

4.3.1 Loperamide

Loperamide is the first drug about which a preclinical prediction of subjective effects and, by inference, narcotic abuse potential, has been made on the basis of drug discrimination data. The case with loperamide provided an objective and unambiguous manner to test the predictive validity of drug discrimination data, because it presented an *a priori* prediction whose possible confirmation could have occurred at some later time only. Loperamide is a novel antidiarrheal possessing highly specific inhibitory activity at gastrointestinal sites [116]. Its possible narcotic cuing activity was investigated in a comparative study [28] involving codeine, diphenoxylate, and morphine. These three drugs exert narcotic agonist activity, and were selected for this purpose because their opiate-like subjective effects had been comparatively investigated by Fraser and Isbell [63]. The latter study had shown that, relative to its antidiarrheal potency, diphenoxylate produces markedly less opiate-like subjective effects than either codeine or morphine, though all three drugs were found capable of producing such effects at adequate oral doses [63,64]. In the comparative study, then, it was found that oral codeine (10 to 40 mg/kg), diphenoxylate (5 to 20 mg/kg) and morphine (10 to 40 mg/kg) induced a dose-dependent generalization with fentanyl in rats trained to discriminate 0.04 mg/kg fentanyl from saline. Loperamide, however, was found devoid of narcotic cuing properties at doses up to 40 mg/kg; higher doses were not tested because of apparent behavioral toxicity [28]. The data on the relative narcotic cuing and constipating efficacy of the four compounds being discussed here, confirm the study by Fraser and Isbell [63] in that they show (a) that relative to its antidiarrheal activity, diphenoxylate exerts far less narcotic cuing activity than codeine or morphine, and (b) that the absolute narcotic cuing potency of diphenoxylate exceeds that of both codeine and morphine. The data further indicate that oral loperamide does not possess narcotic cuing activity at up to behaviorally toxic doses; this result served to predict

[28] that oral loperamide would not produce opiate-like subjective effects in man, not even when administered at doses far higher than its therapeutic dose. As we regard the capacity to produce narcotic cuing activity as a necessary condition for a drug to possess narcotic abuse potential, it was concluded [28] that oral loperamide would not entail such a potential in man.

Clinical data specifically relating to this prediction have become available in a recent comparative investigation on loperamide and codeine in man [89]. These authors compared loperamide to a codeine dose which was only threshold for opiate-like subjective effects. It was revealed that oral loperamide, in doses (60 mg) up to 30 times the therapeutic dose (2 mg), does not produce opiate-like subjective effects equivalent to only a threshold dose of codeine. More convincing clinical confirmation would seem hardly feasible, and it may be reasonable to conclude that, until evidence to the contrary, the narcotic cuing activity of drugs in animals is intimately related to, and may serve as a model for opiate-like subjective effects in man.

4.3.2 Buprenorphine

Buprenorphine is an oripavine derivative exerting both narcotic agonist and antagonist activity in different animal species [53,54]. The drug reportedly [54,103] induces only a liminal degree of physical dependence and has been claimed [54] to be a non-psychotomimetic narcotic antagonist analgesic of low physical dependence potential.

In a series of (unpublished) comparative studies on fentanyl and buprenorphine, we found that the latter induces stimulus generalization with the training drug in all out of six rats trained to discriminate 0.04 mg/kg fentanyl from saline (Fig. 10a). Buprenorphine was about equipotent with fentanyl at the level of 50% effect, but only half as potent at the level of 100% effect; the slope of the buprenorphine gradient (s=1.65) is slightly shallower than that of fentanyl (s=1.33). These observations are thus consistent with the general case of pure agonists producing steeper slopes than partial agonists/antagonists [133]. Also, fentanyl (0.04 mg/kg) and buprenorphine (0.08, 0.16 and 0.31 mg/kg) reduced total responding in a dose-dependent manner. In the same animals, naloxone (0.02 to 0.31 mg/kg) was tested for possible antagonism of narcotic cue detection otherwise associated with the lowest fentanyl (0.04 mg/kg) and buprenorphine (0.08 mg/kg) dose producing 100% effect. We found (Fig. 10b) that naloxone antagonizes both drugs, but that the slope of its activity against buprenorphine (s: 3.67) is considerably shallower than that of its activity against fentanyl (s=1.69). At the level of 50% effect, naloxone was equiactive against both agonists; at the level of 100% effect, however, it was less potent against buprenorphine than against fentanyl. These data thus indicate that buprenorphine induces stimulus generalization with a narcotic drug, and that this generalization can be antagonized by naloxone. Estimation of relative potencies, however, appeared to be confounded by differences in slope not only for the agonist effects of fentanyl and buprenorphine, but also for naloxone's antagonist activity. Similar slope differences were also obtained in an experiment (not shown) on the analgesic effects of these two compounds in experimentally naive rats. Using the analgesia assay described elsewhere [35] it was found that buprenorphine is about 3.5 times less potent than fentanyl in producing analgesia; buprenorphine's dose-effect curve was shallower than that of fentanyl and, in the case of both fentanyl and buprenorphine, the steepness of the curve increased

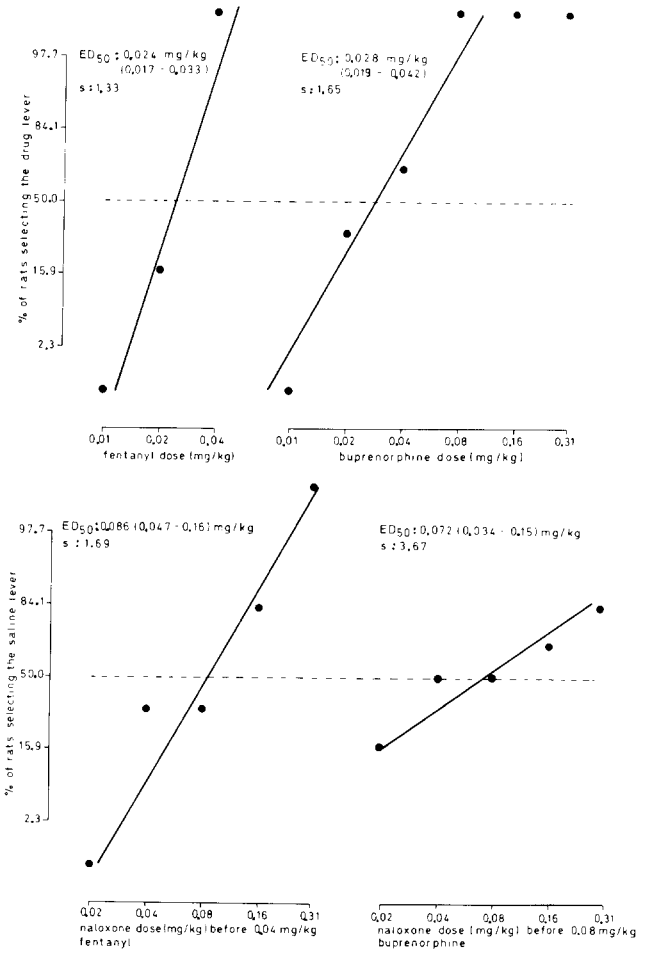

FIG. 10. (a) Fentanyl- and buprenorphine gradients in 6 rats trained to discriminate 0.04 mg/kg fentanyl from saline. Injections were s.c., 30 min before test. (b) Effects of naloxone on cue detection following fentanyl or buprenorphine in 6 rats trained to discriminate 0.04 mg/kg fentanyl from saline. Naloxone was injected s.c., 30 min before either agonist (60 min before test).

with increasing intensity of the effect required to meet the criterion. This relation between intensity of criterion and slope is thus consistent with the one found in drug discrimination experiments (Section 3.1; Fig. 8).

The data presented here (Fig. 10a) indicate that buprenorphine induces stimulus generalization with a narcotic training drug; according to the presumed relation between narcotic cue and opiate-like subjective effects in man, these data suggest that buprenorphine produces such effects and, hence, prossesses narcotic abuse potential in man. This suggestion is consistent with the recent observation [93] that buprenorphine does indeed produce opiate-like subjective effects in man.

4.3.3 Prediction of Drug Abuse Potential

The findings with loperamide [28] demonstrate that the absence of stimulus generalization with a narcotic training drug, validly predicts the inability of this drug to produce opiate-like subjective effects in man. The purported implication of this result is [28,41] that loperamide has no opiate-like abuse potential. The findings with buprenorphine set an interesting case of disparate predictions derived from different

psychopharmacological techniques. As judged from its reported [54,103] inability to induce physical dependence in laboratory animals, it would be inferred that the drug will not give rise to non-medical use. However, its generalization with fentanyl (Fig. 10a) would predict that the drug produces opiate-like subjective effects in man, and that it may be abused because of this property. This example thus resembles pentazocine in demonstrating that opiate abuse may occur with drugs that may nonetheless have no or little potential for physical dependence. The following is an outline of the differential utility of Drug Discrimination, Self-Administration and Physical Dependence liability assessing techniques in the prediction of the abuse potential of drugs. (1) Drug Discrimination studies may be uniquely suitable to assess the ability of drugs to produce subjective effects similar to those of different classes of reference drugs of abuse (e.g., hallucinogens, narcotics, CNS stimulants, minor tranquillizers). Both positive and negative findings have predictive value, and the principle may be applicable to all drugs producing subjective effects in man. (2) Self-Administration studies may detect primary reinforcing properties of drugs, and are likely to produce predictive positive results with some classes of drugs (e.g., narcotics, CNS stimulants). Negative findings with other classes of drugs are essentially inconclusive because some drugs (e.g., hallucinogens) are being abused in the seeming absence of primary reinforcing properties. (3) The utility of techniques assessing the physical dependence inducing capacity of drugs is limited to predicting this capacity quite irrespective of the abuse potential of drugs. Positive findings are probably predictive of continued intake following a history of drug use, but negative findings have no direct implication for potential abuse (as with hallucinogens). Thus, within this general framework, Drug Discrimination studies may play an important and unique role in the preclinical evaluation of the abuse potential of drugs. Examples demonstrating the utility of Drug Discrimination studies in this area, have been presented with narcotic [27,28] and CNS stimulant drugs [70], and applications involving other classes of drugs are similarly feasible.

5. GENERAL CONCLUSION

The first part of this review is concerned with our postulate [27] that the narcotic cue can be defined as the discriminative stimulus complex which is exclusively associated with the specific central action(s) of narcotic analgesic drugs. The evidence discussed here converges to indicate that narcotic drugs, when paired with their vehicle, can act as a discriminative stimulus. The discriminative stimulus properties of narcotics have been demonstrated with different narcotic training drugs, with widely differing discrimination procedures, and in various animal species. The discriminative stimulus complex produced by narcotic drugs is specific to narcotic drugs as a pharmacological class; this is substantiated by findings indicating (1) that other chemically heterogeneous but narcotic drugs induce stimulus generalization with a narcotic training drug; (2) that the narcotic cuing and analgesic potency of narcotic drugs correlate closely; (3) that the narcotic cue demonstrates the requirement of steric specificity, and (4) that it can be antagonized by naloxone and related narcotic antagonists. It is suggested, therefore, that the narcotic cue represents as much a specific action of narcotic drugs as is narcotic analgesia. To a large extent, the ability to produce the narcotic cue was found to be an exclusive property of narcotic drugs. There is compelling evidence that the narcotic cue originates centrally; efforts aimed at denoting anatomically discrete brain areas as the site of action for narcotics to produce the narcotic cue, have so far been indecisive, and it seems likely that multiple and diffusely organized brain sites rather than discrete brain areas are involved in the narcotic cue. Finally, there is evidence that the cuing properties of narcotics are complexly composed of a number of pharmacologically and/or physiologically distinct components; it is left undetermined, however, whether the components identified so far are actually incorporated in the cue to which trained subjects attend so as to discriminate a narcotic from its vehicle.

Studies concerned with the involvement of neurotransmitter substances in the narcotic cue, have revealed no significant role of noradrenaline or serotonin in the narcotic cue. There is suggestive evidence that increased dopaminergic activity in the brain may be associated with the narcotic cue, though the integrity of dopaminergic neurotransmission systems does not appear to be a prerequisite for animals to discriminate narcotics from vehicle. While the possible involvement of other neurotransmitter substances (e.g., γ-aminobutyric acid, acetylcholine) remains to be investigated, it seems unlikely at this stage that any single neurotransmitter would play a unique role in the narcotic cue.

The third section was concerned with the narcotic cue as a special case of Drug Discrimination learning. The findings are that the acquisition of and sensitivity to the cuing properties of a training drug, are proportional to its training dose; it was also found that the slope of stimulus generalization gradients of narcotic drugs, as well as other generalization phenomena, are co-determined by the training dose. Research on possible tolerance development has led to controversial interpretations; some of the methodological weaknesses of the research strategy commonly used in this context are outlined, and our conclusion is that the narcotic cue is not subject to tolerance development. Extensive studies on the relation(s) between narcotic cue and narcotic analgesia have arrived at the conclusion that these two phenomena possess a number of associative pharmacological and biochemical characteristics; the dissociative features characterizing narcotic cue and narcotic analgesia may result from the fact that they are subject to a differential functional processing by the central nervous system. It has also been found that $ACTH_{4-10}$ may affect discriminative performance based on the narcotic cue; this finding suggests that mechanisms of sensory gating play a significant role in discriminative performance based on drug-produced cues. Other data offer support for the contention that this performance can also be conditioned to environmental stimuli, thus indicating that (drug-produced) internal and (environmental) external cues can be superimposed so as to control behavioral output. This is the more interesting in view of the finding that the mammalian brain contains neuropeptides (e.g., lipotropin C-fragment) which are able to mimic both the reinforcing and the cuing properties of narcotic drugs or, conversely, that these drugs mimic these stimulus properties of C-fragment. Finally, some arguments are discussed which seem to argue in favor of a distinction between the narcotic cue and the narcotic state; perhaps most significantly, the serotonin hypothesis of state-dependency provides an explanatory framework within which seemingly divergent data on the effects of p-chlorophenylalanine on response control excerted by narcotics, CNS stimulants, and ethanol, can be understood.

The last section discusses evidence relating to the postulate [27] that the cuing properties of narcotic drugs relate intimately to opiate-like subjective effects in man. The supportive arguments are theoretical, methodological, and empirical. The relevance of such a relation is two-fold. At the therapeutic level, this relation has yielded a research strategy in the area of drug abuse which may provide a unique opportunity to study and predict the abuse potential of drugs with a perhaps unprecedented degree of accuracy and validity. At the theoretical level, it is of interest that drug-produced cues in animals and drug-produced subjective effects in man both pertain to those (internal) stimulus properties of drugs, which may gain discriminative stimulus control of behavior. It is this capacity which distinguishes these stimulus properties from the other internal physiological events that are contingent upon narcotic drug administration.

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