

**A Pharmacological Analysis of Processes Underlying Differential
Responding: A Review and Further Experiments with
Scopolamine, Amphetamine, Lysergic Acid
Diethylamide (LSD-25), Chlordiazepoxide,
Physostigmine, and Chlorpromazine¹**

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The results obtained in these experiments, and those of previous work with several active-passive avoidance tasks, show that (i) enhancements of locomotor responses to no go signals can occur after scopolamine and amphetamine, both with an extinction and with a passive avoidance contingency during compounds made up of the active avoidance signal and of a stimulus from a different modality; (ii) complex interactions between treatments, cues, and response-reinforcement relations can lead to marked differences between amphetamine and scopolamine hyperresponding in unsignaled portions of the schedules; (iii) a moderate LSD-25 disinhibition can take place in conditioned inhibition tasks, but not when the no go compound signals a passive avoidance contingency; (iv) a moderate disinhibition occurs also after chlordiazepoxide treatments; (v) the physostigmine facilitation of differential responding does not depend on the particular response-reinforcement contingency in no go trials; and (vi) the chlorpromazine depression of active responding is a nonselective one, and is not accompanied by any increase of low baseline responses.

The following main conclusions can be drawn on the basis of the above data and those of the literature. In the first place, the fact that the LSD-25 disinhibition depends on response-reinforcement relations in no go trials, and not on task difficulty *per se*, suggests that the mechanisms

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underlying response withholding with an extinction and with a passive avoidance contingency, respectively, are at least in part separated from each other, even when stimulus factors appear to make comparable contributions to the overall variance with different response-reinforcement relations (Frontali and Bignami, 1974). Second, the scopolamine syndrome consists mainly of high order interactions between treatment, sensory, and response factors given a particular reinforcement *background*, while response-reinforcement *relations* have importance mainly for compensation phenomena that allow to eliminate adverse consequences at the reinforcement level. Third, the definition of the amphetamine syndrome oscillates between a genuine motor bias (when responses of the preparatory type are used in alimentary tasks, or highly prepared motor responses are used in defensive tasks) and a genuine stimulation of reinforcement mechanisms (when other types of outputs are used, often allowing a facilitation of differential responding). Fourth, highly tentative alternative models are required to account for the benzodiazepine syndrome, since at least part of it cannot be ascribed to an attenuation of punishment suppression, nor to a reduction of fear. Fifth, the most parsimonious explanation of the chlorpromazine syndrome remains that of an overall psychomotor depression.

REVIEW SECTION

Drug Effects and Processes Underlying Differential Responding: Alternative Models and Tentative Predictions

A large body of data on discrimination behaviors indicates that the effects of "stimulant," "disinhibiting," and "antisuppressant" agents—e.g., the amphetamines, antimuscarinics, nicotine, LSD-25, 5-hydroxytryptamine (5HT) depletors, benzodiazepines, and barbiturates—are rarely amenable to explanations by simple unifactorial models. It is true that the ubiquity of the physiological-biochemical changes induced by most of these agents in the central nervous system (CNS) makes it unlikely that all behavioral effects of a particular drug can ever be explained by any given functional model. Nevertheless, with the present state of knowledge there is little agreement on the relative value of two basic types of explanations. The first one attempts to assign different components of a given syndrome to different biochemical changes induced by the same drug, or to similar changes taking place in different parts of the CNS, or to both (see, e.g., the section on Localization of Drug Effects in Bignami, 1976a). The second one attempts to test the validity of multifactorial models of drug action, thereby implying that at least part of the changes takes place in specialized structures that cannot be defined as serving mainly a particular function, but should rather be defined as interfaces between two or more systems.

Students of lesion effects have often pointed out that an insufficient understanding of altered patterns of behavior organization leads to the use of

responses merely as if they were convenient dependent variables (McCleary, 1961; see also the methodological discussion of treatment effects by Weiskrantz, 1968). The same happens in pharmacological studies emphasizing correlations between biochemical and behavioral events, while at the same time interpreting these correlations as causal relationships; and this, before a particular behavioral change (one or more symptoms) is understood as belonging to one, or to the other, of several possible syndromes. On the other hand, considerable efforts have been made to analyze particular drug-induced syndromes from a different viewpoint, i.e., starting from the assumption that fracture lines created by treatments can help understanding the processes involved in behavior modulation.

The work in the areas outlined above has shown that it is not sufficient to cope with the variability of drug-induced changes simply by extending the range of behavioral measurements. The problem is rather that most analyses underlining the interactions between a treatment factor and one or the other type of test factor have now been shown to be grossly inadequate. In fact, high order interactions have been found to prevail whenever they have been looked for, as indicated, e.g., by much literature on amphetamine to be discussed later, suggesting a predominance of motor changes with some combinations of cues, responses, and reinforcements, and a predominance of an effect on attention, or memory, or reinforcement mechanisms in other conditions. Furthermore, severe limitations have been encountered when attempting to define the profile and mechanism of action of a given drug or drug type *per se*. Much more information has usually been obtained in those studies that have employed two or more drugs from different classes, and have been directed to understand the conditions that allow the appearance of similar or, vice versa, dissimilar, treatment consequences.

The purpose of the present paper is to analyze, or reanalyze, a wide range of data on several drugs—scopolamine, amphetamine, LSD-25, chlor-diazepoxide, physostigmine, and chlorpromazine—and to confront two sets of working hypotheses, namely, those concerned with the mechanisms of action of the agents considered, and those concerned with the processes and mechanisms that underlie differential responding in various conditions. Since the emphasis will be on the role of particular combinations of test factors in determining the direction and size of drug effects (as well as analogies and differences between drugs), and on the theoretical inferences derived from the known interactions, some general considerations are in order here concerning possible types of changes induced by treatments.

By definition, an associative bias (e.g., a change in the rate, or probability, or both, at which transient neural events triggered by an experience lead to the permanent storage of retrievable information) should reflect itself on several aspects of the organism's "learning capacity"; and this, at least to some extent, independently of stimulus, reinforcement, response,

and several other factors, except for the role of "floor" and "ceiling" phenomena and of species-specific constraints on performance which can interfere with the assessment of learning abilities. In fact, the main effort in the literature on drugs and memory processes (see, e.g., the reviews by McGaugh and Petrinovich, 1965; McGaugh, 1973) is to show that a facilitating or, vice versa, an impairing, effect takes place (i) with different reinforcers, (ii) during critical acquisition phases, but not after an asymptote has been reached, (iii) with a wide variety of different responses, including go and no go requirements with regard to particular outputs (e.g., one-way active avoidance versus step-through or step-down passive avoidance), (iv) with a wide variety of different cue combinations (e.g., brightness relevant and position irrelevant in a two-choice situation, versus an opposite type of arrangement), and (v) with treatment schedules that apparently eliminate the confusion between learning and performance effects (e.g., post-trial and postsession treatments). If one is reminded of the amazing complexity of the controversy, about whether or not extinction (including response suppression during nonreinforced stimuli in a context of responding to reinforced stimuli) should be ascribed to an "active learning process," one can also understand why the literature on drugs and memory contains little information on still another point, namely, (vi) agreement, or disagreement, between pharmacological experiments on acquisition and extinction. (Part of the literature on drugs and frustrative nonreward will be discussed later, but it deals mainly with motivational-emotional explanations, rather than with possible associative changes.)

Table 1 uses the hitherto unverified assumption that the processing of information relevant for the "weeding out" of nonreinforced behavior has substantial elements in common with that relevant for the strengthening of reinforced behavior. Therefore, the expected consequences of an associative change such as "accelerated consolidation" include higher than control frequencies of a specified motor output both during acquisition of instrumental responding (e.g., active avoidance learning) and during extinction of instrumental response withholding (e.g., passive avoidance extinction), as well as lower than control frequencies both during acquisition of instrumental response withholding and during extinction of active instrumental responding. As concerns nonassociative changes, both an altered function of reinforcement mechanisms (in the case of Table 1, an assumed drive enhancement or disinhibition) and an altered function of motor control systems (hyperactivity or response disinhibition) should lead to response profiles different from one another and from that pertaining to the associative bias. Furthermore, all nonassociative changes should disappear upon treatment discontinuation—a prediction that should be easier to verify in the case of drugs than in the case of lesions—while the consequences of an associative change should be temporary in some instances (e.g., in the case of facilitated or impaired

TABLE 1

Response Changes Expected with Facilitating Treatments Acting either at the Associative Level (e.g., "Accelerated Consolidation"), or at the Motivational Level (e.g., "Drive Enhancement or Disinhibition"), or at a Motor Level (e.g., "Hyperactivity" "Response Disinhibition")^a

Type of change		Reinforcement of response		Extinction: Previous Reinforcement of response	
		Emission	Withholding	Emission	Withholding
Associative	Acquisition	increase	decrease	decrease	increase
	Performance	no change	no change	no change	no change
Motivational ^b		increase	decrease	increase	decrease
Motor ^b		increase	increase	increase	increase

^aIncrease, decrease, and no change are relative to the control rate of a specified response with a particular response-reinforcement contingency (or previous response-reinforcement contingency).

^bSimilar effects are expected on acquisition and performance, except for floor and ceiling phenomena (e.g., no further enhancement of a high rate of active avoidance, and no further reduction of a low rate due to an extinction or a passive avoidance contingency).

retrieval of information stored previously) and permanent in others (e.g., if consolidation is facilitated or impaired).

Nonassociative sensory changes are not amenable to a classification such as that used in Table 1, since the syndromes have been defined by various authors according to quite different criteria (see Table 2). A "stimulus hyperreactivity" as it is discussed in the literature on lesions (e.g., by Rosvold

TABLE 2

Representative Sensory Biases Hypothesized in the Literature, and Corresponding Cue Factors which Should Lead to Differential Treatment Effects

Biases	Interacting cue factors
Overall impairment of stimulus sensitivity ^a	No one in particular
Stimulus hyperreactivity	Few versus many irrelevant cues
Interference more with weak, than with strong stimulus control	Interceptive versus exteroceptive cues (in operant schedules); small versus large cue differences ^b

^aInferred on the basis of stimulus detection ("hits and false alarms") analyses; see, e.g., Warburton, 1972, 1976; Robbins and Iversen, 1973.

^bThis factor can be stretched to include different no go periods in a successive discrimination (e.g., in tasks such as those to be discussed later: CS-no CS difference larger than CS-CI-CS difference).

and Mishkin, 1961) is expected to induce behavior changes mainly as a function of the irrelevant stimuli in a given situation. A "treatment interaction with type of stimulus control," as referred to by several investigators working mainly with operant schedules, should have consequences depending on the strength of stimulus control which can be obtained with different categories of cues (e.g., interoceptive-weak, exteroceptive-strong in the work of the Rochester group recently summarized by Laties, 1975) or by using larger versus smaller differences between stimuli requiring different responses (e.g., Ksir, 1975). Finally, an "impairment of stimulus sensitivity" (or "generalized impairment of stimulus control") is defined by signal detection analysts on the basis of changes of response distribution which cannot be ascribed on a probabilistic basis to a simple response bias, at least to some extent independently of the category of the stimulus controlling behavior (Warburton, 1972, 1976).

After more than two decades of extensive work on drug-behavior interactions (Iversen, Iversen, and Snyder, 1976) the comparison of expected and observed changes on the basis of schemes such as those discussed above has entered a phase of diminishing returns. For example, the associative-nonassociative distinction has been blurred by the fact that response enhancements induced by several drugs in avoidance situations have been shown to be completely reversible, or partially reversible, or irreversible, depending on a variety of treatment and test factors. (Quotations can be limited here to those instances in which different results have been obtained by the same investigator(s) using different contingencies: for amphetamine see Barrett, Leith and Ray, 1972, 1973, 1974; Barrett and Steranka, 1974; for scopolamine see Barrett *et al.*, 1972, 1973, 1974; Bignami and Rosić, 1972; for nicotine see Morrison, 1974.) Even more important, much evidence to be discussed below indicates that drug profiles can fulfill the criteria for two or more nonassociative biases, depending on the combination of test factors in different series of experiments.

Two lines of evidence acquire special significance when attempting to cope with the problems mentioned above. The first can be found in the literature on so-called preparedness phenomena (or constraints on learning), which emphasize that most of the differences in the ability to acquire new behaviors can seldom, if ever, be ascribed to a predominant role of any given factor. More often than not, these phenomena appear to be a joint function of several factors—mainly, but not exclusively, stimuli, reinforcements, and responses—often with remarkable species-specificity (or even strain-specificity) of the resulting interactions (Bolles, 1970, 1972; Seligman, 1970; Seligman and Hager, 1972; Shettleworth, 1972; Hinde and Stevenson-Hinde, 1973). Within this area, special emphasis deserves to be placed on so-called auto-shaping phenomena. In fact, these show that depending on stimuli, reinforcements, and responses behavior outputs can be modulated either mainly by

stimulus-reinforcement relations (which understandably applies to sequences with high consummatory status), or mainly by response-reinforcement relations (which applies to sequences drawn from the appetitive repertoire), or by both (as shown by fine temporal and topographical analyses separating consummatory and appetitive components of a particular output) (see discussion and references in Jenkins and Moore, 1973; Boakes, Halliday and Poli, 1975).

The second line of work, to be considered in greater detail later on, has shown that the effects of several lesions on various types of differential responding can be quite specific for particular combinations of cues, reinforcements, and responses, at least to some extent independently of the relative easiness or difficulty of the tasks considered.

Both lines of evidence strongly suggest that a wide range of processes, and therefore of underlying functional mechanisms, should be taken into account when analyzing behavior changes observed in similar general paradigms (e.g., avoidance) with different combinations of test factors. In particular, the fact that several consequences of lesion or drug treatments appear to belong to one of the biases listed in Tables 1 and 2, when certain tests are used, and to a different bias, when other tests are used, has important methodological implications. In fact, it confirms the suspicion that critical functions in behavior modulation, and consequently, critical sites of action, should be sought for at the level of interfaces between physiological systems. Obviously, this is not to deny the need to understand the organization of different systems *per se* (e.g., of sensory analyzers, of homeostats such as those involved in the regulation of food and water intake and of temperature, of motor centers, and so forth) as well as the properties of physiological-biochemical mechanisms that allow behavior modification by experience (e.g., molecular processes responsible for information storage); nor to conclude that drugs and CNS stimulations or lesions cannot have a direct effect thereon. The provisional interface hypothesis is rather to emphasize that (i) since the relative hierarchical status of the innumerable "connections"—interfaces—between sensory, reinforcement, and motor systems which are theoretically possible appears to vary widely, depending on the "problem" with which the organism is faced (see the literature on preparedness phenomena and on autoshaping mentioned above), and (ii) since any given set of interfaces between two or more systems appears to include physiological mechanisms which are widely diversified (see some representative lesion evidence discussed below); then (iii) an attempt can be made to account for drug-behavior interactions in terms of possible effects on interfaces between systems, and eventually (iv) if reasoning along these lines has heuristic value, then pharmacological fracture lines can help explaining how particular "interfaces" are used in preference to others in given situations, and vice versa in other situations.

One may wonder at this point what can be the benefits of conceptualizing drug-behavior interactions in terms of assumed processes of increasing complexity, and in terms of physiological-biochemical mechanisms which encompass more than one system at a time, instead of limiting oneself to an accurate description of the interactions themselves. One reason is that the first of these approaches may have greater heuristic value than the second one, if experiments designed to falsify a particular working model based on a given set of interactions lead to the finding of still other critical interactions. A second reason is that the understanding of brain-behavior relations cannot rely exclusively on a descriptive (correlational) approach, since the latter cannot explain the frequent finding of correlations in opposite directions. Vice versa, a methodological and theoretical framework using both a wide variety of alternative assumed processes and an equally wide variety of block models for physiological organization, can ultimately reconcile the need for a description of the basic properties of physiological-biochemical units in the CNS with the need to understand how complex behavior changes in different directions can descend from apparently similar elementary changes.

With the present state of knowledge it would be premature to redraw Tables 1 and 2 so as to predict treatment changes on the basis of the numerous interfaces between systems which can be hypothesized *a priori*. A more useful approach is to discuss the available drug data and some of the relevant lesion data, so as to show that some of the possible interface explanations of drug-induced syndromes may have at least some heuristic value, while several of the simpler inferences on drug mechanisms of action can be definitely discarded.

Some Features of the Antimuscarinic Syndrome²

Both the scopolamine and the amphetamine syndrome have often been interpreted as being consequences of genuine motor biases, since the behavioral changes induced by these agents can be to some extent independent of response consequences at the reinforcement level. For example, the finding that a treatment leads to reduced shock frequencies in active avoidance tasks, and to increased shock frequencies in passive avoidance tasks, constitutes strong *prima facie* evidence against a wide range of sensory, associative, and motivational explanations. At the same time, however, it can

²The present section can deal with only a few of the many cue and response factors which have been shown to influence either the size, or the direction, of antimuscarinic effects. A more thorough analysis can be found in a recent review devoted mainly to this problem (Bignami, 1976a), which attempts to reconcile previous models emphasizing either motor changes or sensory changes induced by central cholinergic system drugs (Anisman and Waller, 1973; Bignami, 1967; Bignami and Rosić, 1971; Carlton, 1963, 1968a, 1968b, 1969; Carlton and Markiewicz, 1969; Leaf and Muller, 1967; Oliverio, 1968; Suits and Isaacson, 1968; Warburton, 1972, 1976).

also be shown that simple motor explanations, such as hyperactivity or response disinhibition (or perseveration), are grossly oversimplified.

With relatively few exceptions, antimuscarinics cause a disruption in tasks with complex response requirements, which is often more marked when treatments are given from the beginning of training, or to partially trained animals, than when they are given to well-trained animals (see, e.g., the well-known data on pole-climbing avoidance by Herz, 1960/1961, 1968). Therefore, it has often been hypothesized that central muscarinic blockade causes an associative deficit in combination with a response change (response disinhibition or perseveration). The latter bias has been used to account for the facilitation observed when the organism's ability to emit simple responses is reduced by contingencies that favor suppression, e.g., in two-way avoidance tasks (Bignami, 1967; Suits and Isaacson, 1968).

There is no doubt that the category of the response *per se* can have a considerable influence on direction and size of antimuscarinic effects, as was emphasized by some of the early reviewers (e.g., Longo, 1966; Bignami, 1967). For example, most active avoidance experiments with climbing and jumping response requirements have shown a response depression by antimuscarinics (for differential effects on acquisition and performance see above). Studies of lever-press avoidance have shown both stimulant and depressant drug effects, while the withholding of manipulatory responses in the presence of a punishment contingency was often unimpaired. Results on locomotor avoidance include several instances of facilitated active responding and impaired response withholding, however, with a wide variety of interactions between treatment and other factors—uni- versus bidirectionality of the response required, initial shock frequencies, duration of intertrial intervals (ITIs), presence versus absence of intertrial response (ITR) punishment, massed versus distributed practice, type of prior experience with an active avoidance CS, and so forth.

Most of the interactions observed in active avoidance tests have been interpreted as showing that the amount of punishment suppression interfering with the emission of the response required determines whether or not sufficient room is created for an antimuscarinic facilitation (Anisman, 1973; Anisman and Waller, 1973; Bignami, 1967; Bignami, Amorico, Frontali and Rosić, 1971; Carlton, 1968a, 1968b, 1969; Leaf and Muller, 1967; Suits and Isaacson, 1968). Moreover, these response changes have been clearly separated from other types of deficits (and particularly from sensory deficits) in studies such as those by Barrett *et al.* (1972, 1973, 1974). In fact, these investigators showed that marked enhancements of two-way avoidance can occur in rats without significant changes in the ability to discriminate between correct and incorrect compartments (see also the similar results obtained with hippocampal microinjections of scopolamine by Leith and Barrett, 1975; and the drug $\times$ strain interactions recently observed in mice by Anisman, 1975a). On

the other hand, however, the complex profile of antimuscarinic effects on passive avoidance has led to bitter controversies between supporters of associative explanations and supporters of motor explanations (see the discussions by Carlton and Markiewicz, 1971; Bignami, 1976a).

In recent years a considerable body of data has shown that the direction and size of antimuscarinic effects on avoidance, as well as the presence or absence of an interference with differential responding, can depend on factors other than task complexity, response requirement, or stage of training (Bignami, 1976a; Warburton, 1976), as could be shown by a detailed comparison of the results with the schemes of Tables 1 and 2. Alternative models, such as the ones emphasizing the sensory aspects of the deficit (Warburton, 1972, 1976; Laties and Weiss, 1966; Laties, 1972, 1975; Heise, 1975), have also been shown to lack generality. For example, the superimposition of relevant exteroceptive cues to interoceptive ones was sufficient to attenuate drug-induced changes in several situations (Laties and Weiss, 1966; Laties, 1972, 1975; Wagman and Maxey, 1969) but not in others (Heise and Lilie, 1970; Heise, Laughlin, and Keller, 1970; Ksir, 1974). The scopolamine disruption of discrete-trial discriminations was found to be inversely proportional to the difference between cues requiring different behaviors (Ksir, 1975) and to the salience of the relevant stimuli (Evans, 1975). However, the use of multiple exteroceptive cues led sometimes to an increase, and sometimes to a decrease, of antimuscarinic effects on discrimination, relative to the changes observed with a single cue controlling behavior (Warburton, 1974; Whitehouse, 1964, 1967). It has also been suggested that differential responding is affected by antimuscarinics when the control is exerted by brief exteroceptive stimuli to be used for response choice in discrete-trial tests (particularly go-no go "decisions"), but not when extended presentations of various stimuli correspond to different response-reinforcement contingencies in multiple operant schedules (Miczek, 1973a). This tentative classification exploited the contrast between a massive antimuscarinic disinhibition in some active-passive avoidance tasks (see later) and the minimal impairment of response withholding in punishment components of some tasks (Hanson, Witoslawski, and Campbell, 1967; Miczek, 1973a). However, several studies on go-no go avoidance discriminations to be discussed in some detail below indicated that the interactions between cue, response, and treatment factors are not amenable to this, or to other simple types of sensory deficits. Finally, the study of these interactions has been recently extended to behaviors emitted in the absence of specific reinforcement contingencies, showing the complexity of the changes in response tendencies in the scopolamine state (Stewart, 1975a, 1975b).

Some of the data so far obtained with active-passive avoidance tasks appear to be compatible with more than one type of explanation, at either the sensory or the response level. This applies to the results showing an

insensitivity to drug of tasks with simple go and no go signals of different modalities, and a much greater disruption when passive avoidance signals are made up of the active avoidance CS and of a stimulus from a different modality (Rosić and Bignami, 1970a). A sensory model can obviously account for these results on the basis of simple assumptions, e.g., the different "strain" imposed to analyzers in the two types of situations. On the other hand, a motor model can assume that, in the presence of adverse consequences of hyperresponding, the size of the deficit caused by a motor bias depends on the "strain" imposed on the mechanisms which are responsible for motor act modulation. When such strain is high, "other behavior" seems to acquire an important role in the withholding of a specified response, as has been observed in schedules with differential reinforcement of low rates (DRL) in the absence of relevant exteroceptive cues (Laties, Weiss, Clark, and Reynolds, 1965; Laties, Weiss, and Weiss, 1969), as well as in the more difficult active-passive avoidance task (Carro-Ciampi and Bignami, 1968). Therefore, a particular version of the response disinhibition hypothesis could be that a scopolamine-treated animal maintains or, vice versa, loses response control, depending on the type of balance between a specified response and other behaviors that have taken up a role in fulfilling reinforcement requirements (see also the motor-act differentiation model proposed for go-no go discriminations with symmetrical reinforcement contingencies; Konorski, 1967, and later in the present review).

The use of active-passive avoidance tasks, however, has also pointed out a joint role of cue and response factors, which makes it impossible to ascribe drug effects to either sensory or motor changes *per se*. For example, a marked scopolamine disinhibition was repeatedly observed in the more difficult task with a nondirectional light stimulus as the active avoidance CS and a noise-light stimulus complex as the passive avoidance CS (Light/go, noise-light/no go = L^+NL^- ; Bovet, Robustelli, and Bignami, 1965; Bignami, 1967; Carro-Ciampi and Bignami, 1968). Vice versa, the changes were much slighter with the opposite type of stimulus arrangement (N^+LN^- ; Rosić and Bignami, 1970a). Furthermore, several manipulations of the pretraining procedures, which cannot be discussed in detail here, led to a modification of drug effects on active avoidance and on go-no go avoidance suggesting a perseveration of response tendencies (perseveration of set), rather than a perseveration of responses *per se* (Carro-Ciampi and Bignami, 1968; Rosić and Bignami, 1970a; Bignami and Rosić, 1971). As a consequence, it became increasingly difficult to account for the antimuscarinic syndrome on the basis of either sensory, or motor, deficits. Interestingly enough, a recent discussion by Heise (1975) shows that a similar conclusion can be drawn on the basis of antimuscarinic data in a wide variety of discrete-trial discrimination tasks with positive reinforcement.

The Main Features of the Amphetamine Syndrome

An analysis of the data concerning amphetamine encounters difficulties which are at least as remarkable as those created by results on antimuscarinics. In the case of the latter agents, the main problem is to achieve a satisfactory classification of the factors which allow, or vice versa prevent, a facilitation in tasks with active response requirements of a simple kind (e.g., locomotor and lever-press avoidance), a disruption in tasks with more complex response requirements (e.g., vertical avoidance), a disruption of response withholding in tasks using highly prepotent sequences (e.g., step-down and step-through passive avoidance), and a disruption of various types of differential responding. In the case of amphetamine and similar agents one must explain not only several results which bear a close similarity to those obtained with antimuscarinics (e.g., hyperactivity, facilitation of one-way and lever-press avoidance, and disruption of differential responding in many studies which made direct comparisons of the effects of the two types of compounds), but also an impressive series of results showing a facilitation in tasks with complex response requirements, as well as a facilitation of differential responding in a wide variety of maze and discrimination tasks (e.g., Breda, Carlini, and Sader, 1969; Calhoun, 1974; Calhoun and Jones, 1974; Domino, Caldwell, and Henke, 1965; Falk, 1969; Glick, 1971; Kulig and Calhoun, 1972; Kulkarni, 1968, 1972; Peel and Yehle, 1969; Porsolt, Joyce, and Summerfield, 1971; Rahmann, 1961; for facilitation by post-trial or postsession treatments see later).³ These data and many others are obviously incompatible with any kind of explanation based on a sensory or on a motor deficit. Therefore, attentional, associative, and motivational models are often proposed in the amphetamine literature, only to be denied again whenever new data show the predominance of a response bias in particular situations (see, e.g., the conclusions of Calhoun and Jones, 1974, and of Kulkarni, 1972, on the one side; and those of Robbins and Iversen, 1973, and of Warburton, 1976, on the opposite side).

Several caveats are in order here, before the discussion is extended to high order interactions observed with amphetamine treatments. In fact, no attempt can be made to analyze those differences in drug effects which can be clearly ascribed to nonmonotonic dose-response functions, such as the attenuation of locomotor enhancements that often accompanies the appearance of stereotypies after higher doses of several stimulants. These non-monotonic effects on particular responses are known to reflect themselves on

³A facilitation of discrimination has also been found after scopolamine treatments. This effect, however, is rather exceptional, e.g., it has been observed in studies using opportunity to explore as the reinforcer and particular combinations of stimuli and responses (Leaton, 1968, 1969). One of the studies mentioned in the previous section when dealing with the role of sensory factors in the antimuscarinic syndrome also showed a scopolamine facilitation when exteroceptive cues were available, contrasting with the disruption observed in the absence of such cues (Wagman and Maxey, 1969).

treatment consequences in various tasks, as exemplified by the inverted U-shaped dose-response curve of errors and of trials to criterion in a recent passive avoidance study by Seliger (1975). Second, some important differences in the interactions between reinforcement and other factors (mainly response factors), depending on the type of reinforcer, will be underlined below. No attempt, however, can be made in the present context to relate these differences to one or the other of several neural events caused by particular combinations of reinforcers, schedules, and treatments (see recent discussions by Anisman, 1975b; Sparber, 1975; Seiden, MacPhail, and Oglesby, 1975). Third, several data are now available concerning the relative roles of different biochemical events in mediating one or the other behavioral event (e.g., in the case of amphetamine, changes of dopamine and of noradrenaline metabolism with regard to changes of activity and exploration). The extension of such analysis to interactions of higher order between treatment and test factors does not appear to be justified with the present state of knowledge, since even the mechanisms underlying simpler types of response changes have not been sufficiently clarified (see, e.g., a discussion of hyperactivity, impaired alternation, and genuine perseveration, in a recent paper by Anisman and Kokkinidis, 1975). Furthermore, any attempt to beat this path should consider a large body of data concerning analogies and differences between amphetamine and related compounds, as well as differential modifications of the amphetamine syndrome as a joint function of test factors and of concurrent treatment with several types of compounds which influence monoamine metabolism.

Several hypotheses based mainly or exclusively on an activation of reinforcement mechanisms by amphetamine and its congeners have received considerable attention in the past decade. This is shown by several papers concerning self-stimulation and avoidance by Stein and coworkers (review by Stein and Wise, 1970), by the work with conditioned reinforcers (Hill, 1970; Bond, Sanger, and Blackman, 1975; Robbins, 1975), and by longitudinal analyses of amphetamine effects on various components of a particular response output as a function of reinforcement factors (Grilly, 1975). The lack of general validity in such models, however, is shown by at least three types of data, namely, (i) those indicating that amphetamine hyperresponding can lead either to a reduction of positive reinforcement frequencies (see, e.g., the DRL data reviewed by Weiss, 1970; Weiss and Laties, 1964, 1967; for exceptions see later), or to an increased punishment frequency (e.g., in a difficult go-no go task: Bovet *et al.*, 1965; in some conflict tasks: McMillan, 1975); (ii) those indicating that at least part of the amphetamine facilitation of shuttling responses to discrete signals can be obtained in the absence of stimulus-response and of response-reinforcement contingencies (pseudoconditioning experiments by Izquierdo, 1974a; Vásquez and Izquierdo, 1970); and (iii) those pointing out a peculiar kind of proactive amphetamine effect (Anisman and Waller, 1971, 1973). In the latter experiments drugged rats

were exposed to shocks which were both inescapable and unavoidable. This led to faster active avoidance learning and to slower passive avoidance learning at a later time, when the animals were exposed to different response-reinforcement contingencies in the no-drug state.⁴

When turning to motor-bias explanations of the amphetamine syndrome, one quickly discovers that treatment-response interactions must be handled separately for situations with positive (alimentary) reinforcement and for situations with negative reinforcement. As concerns the former, it has been known for several decades that amphetamine and similar agents can have enhancing effects on instrumental and operant responses (i.e., preparatory or appetitive outputs in the ethological language), and depressant effects on consummatory responses (Skinner and Heron, 1937; Wentink, 1938; see also the review by Dews and Morse, 1961). Furthermore, the experiments conducted mainly with operant schedules of intermittent reinforcement, and using most of the time either manipulatory responses of rats and monkeys or pecking responses of pigeons, have shown some interesting analogies and differences between the data obtained in various conditions. In fact, most studies using schedules without adverse consequences of hyperresponding (or moderate hyporesponding) on reinforcement frequency have yielded fairly uniform results, consisting of an enhancement of low to moderate baseline rates, and of a reduction of high baseline rates.⁵ Vice versa, the studies using schedules with

⁴A discussion of the learning facilitation repeatedly obtained with post-trial or postsession amphetamine treatments is outside the scopes of the present review. A close analysis of this phenomenon must separate situations with positive reinforcement (e.g., Hall, 1969; Krivanek and McGaugh, 1969) from situations with negative reinforcement (e.g., Doty and Doty, 1966; Evangelista, Gattoni, and Izquierdo, 1970; Evangelista and Izquierdo, 1971; James, 1975; Mah and Albert, 1975). As concerns the latter, one should consider both the well-known response changes due to incubation phenomena which take place after exposure to aversive events, and the proactive facilitation in the amphetamine studies by Anisman and Waller (1971, 1973), which have been mentioned in the text. As a consequence, it appears difficult to discriminate between a genuine learning facilitation due to associative changes from a response change caused by nonassociative effects (see also the data of Bauer and Duncan, 1971, showing facilitated avoidance learning after repeated treatments administered prior to the beginning of training).

⁵For a closer analysis of rate-dependent effects see Kelleher and Morse (1968). Several authors have supported the view that the reduction of high rates by stimulant or disinhibiting agents is due to intrusion of other activities enhanced by the treatments. In the case of amphetamine this explanation is supported by the fact that responding at a high rate in a FR-30 schedule by rats can be further enhanced, instead of reduced, by amphetamine doses too small to induce sizeable changes of overall activity (Glick and Muller, 1971). Furthermore, rate enhancements in a FR-100 schedule after small amphetamine doses were obtained both in a chimpanzee in which the high ratio maintained a relatively low response rate, and in another animal showing a much higher control rate (Byrd, 1973).

adverse consequences of hyperresponding on reinforcement frequency (mainly, but not exclusively, DRL) have shown a discrepancy between the data obtained in different species and/or with different responses. In rats and monkeys an enhancement of response rates and a reduction of reinforcement frequencies were observed in most studies after low to moderate doses of the drug, while a parallel reduction of responses and reinforcements followed the administration of higher doses (reviews by Weiss, 1970; Weiss and Laties, 1964, 1967; for recent analyses using different requirements of response withholding see MacPhail and Gollub, 1975; Smith and Clark, 1975; for stimulus factors and tolerance phenomena see below). Conversely, in pigeon studies the reinforcement reduction due to hyperresponding has been either absent, or slight, or limited to some of the subjects, while parallel reductions of responses and reinforcements have varied widely between individuals, doses, and studies (Hearst and Vane, 1967; McMillan and Campbell, 1970; MacPhail and Gollub, 1975).

One should consider at this point that manipulatory responses of mammals, although they can take place in conjunction with consummatory patterns, belong mainly to the preparatory (appetitive, instrumental) repertoire, while pecking responses of pigeons have been shown to contain both preparatory and consummatory components. (Brief mention has already been made of the work on autoshaping and automaintenance phenomena, showing basically that the two components can be identified on the basis of topography and of the way in which they come under the control respectively of response-reinforcer and of stimulus-reinforcer contingencies.) This leads to hypothesizing that instrumental (operant) responses drawn from the appetitive repertoire are uniformly enhanced in the amphetamine state—except after high doses, and when a high baseline creates room for competition by intruding responses such as locomotion—while outputs with mixed preparatory and consummatory properties can show a wide variety of changes as a function of response-reinforcement relations. In fact, the latter outputs are (i) depressed by the drug, when they have not been previously trained in an instrumental or operant paradigm (e.g., in food consumption tests), (ii) enhanced by the drug, when their emission, but not their withholding, is, or has been, instrumental to meet reinforcement requirements (for the reduction of high rates see above), and (iii) appropriately modulated in spite of drug treatment, when both their emission and their withholding are required by the schedule.

The analogies and differences between data on rats and data on pigeons appear even the more striking, if one considers that the spacing of pecking responses is a more difficult task than the spacing of lever-press responses (see, e.g., the different control values for the S3 groups in Figs. 2 and 6 in the paper by MacPhail and Gollub, 1975). This, *per se*, is quite understandable, given the high degree of consummatory "automatism" of the pigeon's

pecking.⁶ One must also assume, however, that the bird can "rely" both on the enhancing effect of amphetamine on the instrumental component of its pecking output, and on the depressant action of the drug on the consummatory component of the same output, depending on the contingencies imposed by the experimenter. In this context, it can also be recalled that several data on amphetamine show not only a depression of consummatory outputs or an enhancement of instrumental outputs, but also remarkable shifts in the balance between the two. For example, the drug is able to alleviate the "conditioned suppression" of operants which is induced by stimuli paired to gratis food (Miczek, 1973b). Furthermore, operant licking responses emitted at low rates by rats during periods of nonreinforcement in an operant schedule can be either unaffected or depressed by amphetamine, which is in sharp contrast with the stimulation observed with more conventional response requirements (see the data on the early portions of fixed intervals reported by McKearney, 1973a).

Since a triggering of consummatory responses by an alimentary US or by a classical alimentary CS inhibits instrumental behavior, while an instrumental CS does not have a direct inhibiting action on consummatory activation mechanisms (see the evidence discussed by Soltysik, 1975) it should be provisionally concluded that either the opposite effects of amphetamine on the two types of outputs take place independently from each other, or that instrumental activation is a consequence of consummatory suppression. (In fact, the third possibility—consummatory depression as a consequence of instrumental activation—seems to be in direct contrast with the data on the organization of alimentary behaviors; see Soltysik, 1975.) In any event, independently of the mechanism by which amphetamine might produce the changes emphasized above, one must underline the fact that the type of output studied exerts a profound influence on response modulating abilities in the amphetamine state, particularly (but not exclusively) when both response activation and response withholding are made instrumental to meet reinforcement requirements.

The separation of preparatory and consummatory outputs cannot be made as clearly in the case of situations with negative reinforcement, as in the case of situations with positive reinforcement (Konorski, 1967). As suggested by some evidence which has already been mentioned, another distinction seems to have considerable explanatory value for amphetamine effects in

⁶In fact, response withholding in a DRL schedule is known to be difficult for rats when licking, instead of lever-pressing, is the operant (Kramer and Rodriguez, 1971). Vice versa, the use of a treadle-press response requirement greatly facilitates spaced responding by pigeons (Hemmes, 1975). Unfortunately, factorial experiments to assess amphetamine effects on DRL in different species, and with different responses within each species, have not been carried out.

animals exposed to punishing events, namely, the one that separates motor suppression components (freezing) and motor activation components (running, jumping, biting) of the species-specific defensive repertoire. In fact, it appears that in the drug state the latter are regularly enhanced at the expense of the former even in the absence of a response-reinforcer relation, and sometimes even in the presence of adverse consequences of hyperresponding (see the review by Anisman and Waller, 1973). Furthermore, one should also separate situations requiring a response withholding from those requiring a choice between different active responses. In fact, the amphetamine enhancement of active avoidance and disruption of passive avoidance in the former type of task (Bovet *et al.*, 1965) is paralleled by an enhanced responding without impairment of choice in the latter type of task (Barrett *et al.*, 1972, 1973, 1974).

When the motor activation induced by amphetamine in aversive situations is examined more closely, a further distinction appears possible. At one extreme, response enhancements in the absence of response-reinforcement contingencies, and in the presence of adverse consequences of hyperresponding, have been described mainly in the case of outputs with an intrinsically high defensive status, such as locomotion.⁷ At the opposite end, the effects of amphetamine on motor responses with an intrinsically low defensive status (e.g., lever-pressing by rats; for monkeys see later) seem to be quite variable, depending on response-reinforcement relations. For example, it is well known that both discrete-trial and continuous lever-press avoidance are regularly enhanced by amphetamine treatments, while the withholding of the same response in punishment components of multiple schedules or in CER tests is largely unimpaired, or even facilitated (review by Kelleher and Morse, 1968; for exceptions see McMillan, 1975, and later in the present discussion). Such maintenance of the ability to modulate responses as a function of response-reinforcement contingencies is further illustrated by the studies that show a facilitation of discriminated avoidance behavior, both with regard to responding

⁷It is only fair to emphasize that such effects consist simply of a further enhancement of the amphetamine action on locomotion, which takes place independently of the reinforcement background. Actually, locomotion can be viewed as a response with high preparatory status with regard to several reinforcement systems, including those that may be responsible for the effects of stimulus events not leading to genuine consummatory behaviors. Although the present discussion cannot be extended to all aspects of amphetamine action, it should be noted here that responses such as lever pressing, which are relatively insensitive to the drug in the absence of response-produced changes, are enhanced by amphetamine not only when they are (or were previously) instrumental to obtain food or to avoid shock, but also when they lead to other types of stimulus changes (e.g., Carlton, 1966; Glow and Russell, 1973a, 1973b; Gomer and Jakubczak, 1974). The study by Grilly (1975) should also be viewed in this context, since it shows that various components of a lever-press operant can be selectively modified by amphetamine as a function of reinforcement factors.

on reinforced and nonreinforced levers, and with regard to responding during reinforced and nonreinforced signals (Kulkarni, 1968, 1972).⁸

A study by Heise and Boff (1971) acquires considerable significance in this context, since it points out competition phenomena between nonreinforced responses with an intrinsically high defensive status and reinforced responses with an intrinsically low defensive status. In fact, amphetamine was less effective in raising lever-press avoidance responses in a large, than in a small testing compartment, and the size of this difference correlated with the dose-dependent locomotor enhancement in the larger box (see also the data of Lyon and Randrup, 1972, who compared lever-pressing and lever-holding avoidance, and other activities). Finally, a classical study by Teitelbaum and Derks (1958) seems to confirm the validity of the above criteria of classification. In fact, these investigators showed that licking responses of rats, which are normally depressed by amphetamine in water-consumption tests, were enhanced by the drug when they were used as active avoidance responses. When licking at a low rate was made instrumental to avoid shock (with punishment both for nonresponding and for hyperresponding) successful response modulation was maintained after doses which were moderate, although sufficient to induce marked enhancements in the schedule mentioned previously. A breakdown of response withholding followed the administration of a high dose (5 mg/kg of DL-amphetamine).

The above discussion has attempted to show that amphetamine changes can be influenced either mainly by reinforcement background, or mainly by response-reinforcement relations, depending on the response studied. In fact, both motor responses with a high preparatory status with regard to the alimentary drive, and motor responses with a high status in the defensive repertoire, have been found to be enhanced to some extent independently of response-reinforcement relations. Vice versa, motor responses having consummatory status with regard to the alimentary drive, as well as motor responses with low defensive status, have been shown to be reduced, or unchanged, or

⁸The reader must be warned that the conditions used by Kulkarni (1968, 1972) are different from those prevailing in the studies on continuous lever-press tasks with superimposed warning signals, in which amphetamine caused marked increases of presignal responses (e.g., Gatti and Bovet, 1963). In the first place, facilitation of differential responding in the Kulkarni studies took place after a certain amount of training in the drug state, including a period of generalized responding. Conversely, most data on discriminated Sidman avoidance showing a disinhibition of presignal responses concern the effects of treatments preceded and followed by control sessions in pretrained animals. Furthermore, presignal responses in the latter situations, although not required to avoid shock, postpone both CS and shock by resetting the apparatus, and therefore cannot be defined as being nonreinforced; vice versa, conditioned reinforcement contingencies cannot operate in discrete-trial tasks with no effect of ITRs on the next CS presentation. As a matter of fact, one could speculate that "punishment" of ITRs by the next CS presentation might counteract the amphetamine hyperactivity in discrete-trial avoidance tasks with ITIs paced by the experimenter, similar to what happens in some CER and conflict situations in which suppression of manipulatory responses can be enhanced by amphetamine.

enhanced by the drug, depending on response consequences. The obvious, although provisional, conclusion is that any model that considers either reinforcement or response systems (and treatment effects thereon) as separable from each other is bound to failure. To this one can add that interactive (interface) working models are also made necessary by other lines of evidence, e.g., the data showing that the effects of amphetamine and those of satiation on operant behavior are not superposable (Carey, Goodall, and Procopio, 1974), and the studies that found a dissociation of amphetamine effects on lever pressing for food and for intracranial stimulation, at doses lower than those which can induce a response perseveration (Brown and Seiden, 1975).

Other types of results appear, at first glance, to contradict the tentative scheme outlined above, therefore they need to be considered in some detail. Several studies conducted in primates, while confirming that amphetamine can be without effect on punishment suppression in situations with concurrent positive and negative reinforcement (e.g., Hanson *et al.*, 1967), also showed an enhancement of punished manipulatory responses which either had been previously trained in an active avoidance paradigm (McKearney, 1973b, 1974; Orloff and Stretch, 1975), or served as active avoidance responses in a different component of the multiple schedule (McKearney and Barrett, 1975). This leads to focusing the attention on a particular component of the defensive repertoire, i.e., the aggression patterns triggered by painful or by fearful stimuli; and also, on the fact that the greater preparedness of primates, than of rats, to acquire lever-press avoidance responses may depend on species differences in the defensive status of manipulatory outputs. At this point, one should conclude that in primates the withholding of these outputs in the presence of a punishment contingency is facilitated by prior alimentary training which lowers the defensive status of the response (hence the absence of amphetamine hyperresponding in Geller-type conflict schedules), and opposed by active avoidance training which exploits the species-specific defense and aggression patterns (hence the amphetamine enhancement of punished lever presses with a previous or a concurrent active avoidance contingency). This appears to be confirmed by the apparently paradoxical finding that pecking responses of pigeons, which are part both of the alimentary repertoire and of the defensive-aggressive repertoire, are easily withheld in the amphetamine state when hyperresponding reduces the frequency of alimentary reinforcement (see the DRL data discussed above), while being amenable to moderate disinhibition in tests with punishment (McMillan, 1973, 1975; Foree, Moretz, and McMillan, 1973). A recent study by Griffiths and Wahlsten (1974) on rats confirms that a thorough understanding of amphetamine effects requires an analysis of interactions between treatment and other factors which can affect the balance between various components of the species-specific repertoire. In fact, handling of amphetamine-treated rats required to learn a two-way avoidance task led to much struggling and squealing, and to a disappearance of the usual facilitating effect on avoidance.

A second line of apparently contrasting evidence is the one that regards the role of stimulus factors in the amphetamine syndrome, which appears to be an important one in certain situations, while being absent in others. For example, the drug-induced hyperresponding in a DRL schedule has been shown to be attenuated by relevant exteroceptive stimuli signaling the end of the nonreinforced period (Carey and Kritkowsky, 1972; Glick, Cox, and Greenstein, 1975). Several experiments by Calhoun and coworkers (Calhoun, 1974; Calhoun and Jones, 1974; Kulig and Calhoun, 1972), also on rats, have shown a facilitation of differential responding in discrete-trial go-no go tasks with positive reinforcement.⁹ The data by Heise and co-workers point out an attenuation by exteroceptive stimuli of the amphetamine disruption of a complex discrimination habit in the rat (Heise and Lilie, 1970), but not of the drug-induced hyperresponding during reinforcement withdrawal periods (Heise *et al.*, 1970). A recent experiment by Ksir (1975) showed an attenuation of the amphetamine disruption in a discrete-trial discrimination when larger differences between go and no go signals were used. Studies with switching schedules have indicated that exteroceptive cues signaling the completion of the first one of two successive response requirements can attenuate the drug-induced perseveration in key-pecking pigeons (Laties, 1972, 1975), but not in lever-pressing rats (Scheuer and Moore, 1974). The latter difference seems to confirm that pecking outputs of amphetamine-treated pigeons are modulated to obey positive reinforcement requirements more efficiently than manipulatory responses of treated rats (see above). On the other hand, the discrepancy between data obtained in rats with cued DRL and discrete-trial discriminations, respectively, and with switching schedules, seems to indicate that the role of cue factors in the amphetamine syndrome might depend to a considerable extent on reinforcement factors. In fact, in the former situations the exteroceptive stimulus changes have the function of simple instrumental CS, signaling that a particular response must be emitted, rather than withheld, in order to meet reinforcement requirements. Even more important, such stimulus events are scheduled so as to allow their becoming conditioned positive reinforcers of behavior other than the specified response. Conversely, in switching schedules the exteroceptive stimulus change is located farther away from the consummatory stimulus, and also, it can become a conditioned reinforcer for active responses which are appropriate in the first, but not in the second part of the required sequence. Therefore, any strengthening of conditioned reinforcement mechanisms by amphetamine might summate its effects to those of hyperactivity in the latter situations, while working in the opposite direction in the former situations.

⁹Calhoun and coworkers have used a postponement of the presentation of trials by responses during ITIs. This procedure constitutes one out of several ways for introducing adverse consequences of hyperresponding at the reinforcement level, thereby creating remarkable analogies between go-no go tasks such as those used in the above studies and cued DRL tasks.

In conclusion, it appears that the interactions between treatment and stimulus factors can lend themselves to a different interpretation in the case of the amphetamine syndrome, as compared with the scopolamine syndrome.¹⁰ In fact, cue factors seem to act mainly by modifying the balance between two main effects of amphetamine, namely, between a direct stimulation of responses having a particular status and a stimulation of reinforcement mechanisms activated by response-reinforcer relations. At this point, the tentative inferences so far drawn deserve to be confronted with some data and interpretations in the neuropsychological literature, which have recently led to interesting working models of the mechanisms that may underlie differential responding.

Provisional Conclusions on Scopolamine and Amphetamine, and Tentative Models from the Nonpharmacological Literature

The analysis of interactions between treatment, cue, response, and reinforcement factors which has been conducted above has underlined both analogies and differences between the amphetamine and the scopolamine syndromes. In fact, behavior changes induced by antimuscarinics appear to be to a larger extent dependent on stimulus factors, and independent of response-reinforcement relations, than those caused by amphetamine. Vice versa, specific reinforcement factors—those referred to as depending on response-reinforcement relations, as opposed to those referred to as depending on reinforcement background—can allow a remarkable selectivity of response changes in the amphetamine state, provided that the output studied does not belong to those components of the repertoire which have a particular status with regard to a given drive system.

Assuming that the provisional inferences on scopolamine can be translated into physiological terms, one should hypothesize (i) that a variety of sensory-motor interfaces are responsible for the activation and suppression of various response outputs, as a joint function of the particular drive which is activated (reinforcement background) and of the stimulus setting; (ii) that a

¹⁰A more thorough discussion of these problems should consider the differences between scopolamine and amphetamine effects on habituation (e.g., Carlton, 1969), and also the differences between perseverative tendencies created by the two agents in alternation tests. For example, it is well known that scopolamine-treated animals tend to alternate at chance levels in most situations (see the reviews quoted in a previous footnote). Vice versa, both the enhanced spatial preference observed in several situations (e.g., Glick, 1973; Glick, Levin, and Jarvik, 1970), and the genuine perseveration observed in alternation tests (Anisman and Kokkinidis, 1975) suggest that the amphetamine effects may be ascribed at least in part to an increased reward value of the emission of a "preferred" response (see also the analyses of amphetamine effects in several operant schedules as a function of spatial preferences; Glick and Jerussi, 1974; Glick *et al.*, 1970).

selective interference with some of these interfaces can alter the hierarchy of response prepotencies which would be observed in the absence of treatment, and (iii) that the "facilitating" or "impairing" effects of treatment depend on how particular interfaces work for, or vice versa against, successful coping in particular situations. (According to this view, the interactions between anti-muscarinic treatments and response-reinforcement relations should be ascribed mainly to the greater or lesser efficiency of compensation mechanisms that can cope with adverse consequences of inappropriate responding at the reinforcement level; see later.) Vice versa, the interactions between amphetamine and test factors which have been emphasized above indicate that there might exist different types of interfaces between the reinforcement and the response levels. In fact, one must be able to account for shifts in the balance between two types of response modulation—overall strengthening of some outputs given a particular reinforcement background and fine modulation by response-reinforcement contingencies. A more detailed analysis could turn these problems the other way around, and arrive at similar conclusions by placing greater emphasis on areas of overlap between the scopolamine and the amphetamine syndrome (e.g., stimulation of locomotor outputs in fearful situations) and areas of nonoverlap (e.g., presence versus absence of facilitating or disrupting effects on various types of differential responding).

At this point, however, an alternative approach based on data and models from other fields appears to have greater heuristic value. In fact, several studies of brain lesion effects have repeatedly underlined that the roles of cue, response, and reinforcement factors in a treatment bias cannot be readily separated from each other. In some instances relatively simple explanations have been provided by performing critical experiments. For example, septal lesions exert almost constantly a marked facilitating effect on two-way avoidance, while their influence in one-way situations has ranged from an absence of effect to a marked depression. The discrepancy between two-way and one-way data has generally been ascribed to differences in suppression phenomena, creating room for a facilitation by "disinhibition" in the former, but not in the latter type of task (e.g., McCleary, 1966). Vice versa, little information has been available until recently concerning the variability of the lesion effect in one-way tasks. Based on the data of Thomas and McCleary (1974) it appears now that the discrepancies should not be ascribed to the type of task (or response) *per se*, nor to the animal species or strain, nor to any one of several test factors which are usually emphasized under similar circumstances, but to a peculiar interaction between cue and response factors. In fact, one-way avoidance in septal rats was depressed when an acoustic stimulus was used as the warning cue, but not with door opening as the CS. It was also observed that the former signal elicited in frightened septal animals a response that was incompatible with the one which met reinforcement requirements.

The interactions between cues, reinforcements, and responses, as well as those between treatments (lesions) and these factors, are known to be even more complex in situations with differential response requirements. For example, several studies conducted at the Nencki Institute in Warsaw have shown two main types of differences between go-no go differentiations using reinforced and nonreinforced signals with only one type of response requirement (the instrumental equivalent of Pavlovian or classical differentiations; "drive differentiations") and discriminations requiring different responses to various reinforced signals (e.g., CS1-go left-food; CS2-go right-food; "motor-act differentiations"; for a discussion and literature see Konorski, 1967). In the first place, opposite types of stimulus nonequivalences were found in the two types of tasks, with nondirectional cues allowing a quick development of differential responding in the former, but not in the latter situations, and vice versa in the case of directional cues. Furthermore, the effects of medial frontal lesions in dogs were limited mainly to a reappearance of responses to nonreinforced signals in drive differentiations, without genuine perseverative phenomena. Vice versa, dorsolateral frontal lesions affected mainly the motor-act differentiations (although studies with restricted lesions showed different localizations as a joint function of cue and response factors; see below), while their disinhibiting effects on drive differentiations, when present, could be clearly ascribed to a perseverative change (e.g., they disappeared with long intertrial intervals; see also Brutkowski, 1965; Dąbrowska, 1972; Konorski, 1972). These and other related data led to the tentative inference that signaling systems serving mainly drive differentiation—i.e., drive activation by a reinforced CS⁺ and drive inhibition by a nonreinforced CS⁻, or by a conditioned inhibitor (CI)—and signaling systems serving mainly motor-act differentiation under a given drive operation are, at least in part, separated from each other.

It must be underlined here that go-no go tasks with symmetrical reinforcement contingencies, i.e., with reward both for emitting a specified response during one signal and for nonresponding (or rather, for behavior other than a specified response) during another signal, belong to the category of motor-act differentiations under the same drive operation (Konorski, 1967; see, however, the alternative explanation outlined in a previous discussion by Konorski, 1961).

A further step in these studies was to analyze in greater detail the features of motor-act differentiations with either directional or nondirectional cues, and either directional or nondirectional response requirements (mainly CS1-go left, CS2-go right, versus CS1-go, CS2-no go, with reward for both types of correct behaviors). These studies also showed stimulus nonequivalences, as well as differential effects of localized dorsolateral frontal lesions, as a function of both sensory and response factors (see discussion and literature in Konorski, 1972; Dąbrowska, 1972). The tentative conclusion was that "we

cannot be sure which factor is responsible for the localization of the motor-act differentiation control, whether only the category of the cue... or the category of the response, ... or else, both the category of the cue and that of the response. So far the last supposition seems to be most probable..." (Konorski, 1972, pp. 605-606).

The above statement can also be viewed as an attempt to "physiologize" those preparedness models which emphasize the interactions between sensory and motor factors. In reality, however, Konorski's emphasis was on high-order interactions between species, cue, reinforcement, and response factors, as shown by the fact that the Nencki group was quite active in the analysis of similarities and differences between alimentary and defensive tasks. Some of the critical data on avoidance discriminations have now been published by Dąbrowska (1975; see also the summary of other published and unpublished results provided by this paper). These suggest that when a dog pretrained in an active avoidance paradigm shows a tendency to respond to a nonreinforced stimulus (generalization), differential responding in an active avoidance-extinction task is not acquired simply by a drive differentiation (fear enhancement by the active avoidance signal and fear inhibition by the differentiated or extinction signal). In fact, stimulus factors and treatment factors (lateral versus medial frontal lesions) were found to exert a similar influence on the performance of both active avoidance-extinction tasks and active-passive avoidance tasks. This led Dąbrowska (1975) to underline the possible role of a punishment mechanism not only with a passive avoidance, but also with an extinction contingency. In other words, she suggested that generalization of fear from a reinforced to a nonreinforced signal and nontermination of the latter by an active avoidance response can lead to a response suppression similar to that obtained by a passive avoidance contingency.

Several other lines of work could be discussed here to show that drug syndromes have seldom been the object of in-depth analyses comparable to those that can be found in the literature on lesions. As a consequence, experiments with drugs allowing a fine discrimination of alternative working hypotheses are difficult to plan at the present stage, since some broad predictions still remain to be verified. However, it was felt that some tentative inferences of considerable relevance could be put to a test by extending drug experiments from active-passive avoidance tasks to active-avoidance extinction tasks with different stimulus arrangements. Therefore, the rest of the present review section will discuss, in the first, place, some alternative predictions concerning amphetamine and scopolamine effects in avoidance discriminations with asymmetrical reinforcement and then deal with a series of complementary problems and predictions regarding other important drug syndromes.

Tentative Predictions on Scopolamine and Amphetamine Effects in Active Avoidance-Extinction Tasks

The extension of experiments on discrimination from active-passive avoidance tasks with compound no go signals and different stimulus arrangements to the equivalent active avoidance-extinction tasks (conditioned inhibition paradigms) went not without difficulties. In fact, preliminary shuttle box experiments carried out several years ago had shown that when an active avoidance CS is not reinforced in the presence of a stimulus of a different modality, rats respond to both CS and CI-CS for extended periods of time (Bridger and Bignami, unpublished observations).

A recent acquisition study, while confirming that differential responding develops much more slowly with an extinction than with a punishment contingency in no go trials, also pointed out a stimulus nonequivalence in active avoidance-extinction tasks at least as marked as the one previously observed in active-passive avoidance tasks (slower discrimination learning with the L^+NL^- , than with the N^+LN^- stimulus arrangement; Frontali and Bignami, 1974). This analogy clearly favored the hypothesis of a major influence of preparedness phenomena descending from interactions between sensory factors, response factors, and some of the reinforcement factors (the active avoidance contingency during the simple stimulus, since the literature on classical differentiations does not show comparable nonequivalences). On the other hand, the same data made it difficult to understand the role of response-reinforcement contingencies during no go compound signals. In other words, no inference could be drawn on possible analogies or, vice versa, differences, in the way in which cues are used with an extinction and with a passive avoidance contingency, respectively.

If response suppression is a consequence of punishment both with a passive avoidance and with an extinction contingency, as hypothesized by Dąbrowska (1975), then the problem of unity, or vice versa diversity, of signaling systems serving, respectively, drive and motor-act differentiations would not apply to avoidance discriminations. A second and a third possibility, however, are that rats do learn active-passive avoidance tasks and active avoidance-extinction tasks in different ways—by a motor-act differentiation under the same drive operation and by a genuine drive differentiation, respectively—but either (i) the two types of signaling systems postulated by Konorski are marked by similar nonequivalences (a hypothesis indistinguishable from that of a nonseparation of the systems themselves in this particular instance), or (ii) the two types of signaling systems are separated, but any differences in the way in which cues are used tend to be overshadowed by the above-mentioned preparedness phenomena.

In any event, marked response enhancements were obviously expected both with scopolamine and with amphetamine, since active avoidance responses of a locomotor kind were known to be enhanced by both drugs and punishment by shock for responding to no go signals was eliminated. At the same time, however, it was felt that an accurate analysis of response distribution in drugged animals might have provided additional evidence concerning whether or not the scopolamine syndrome is more dependent on sensory-motor interactions than the amphetamine syndrome, particularly by comparisons between response increases during CI-CS extinction periods and during unsignaled extinction periods (intertrial intervals, ITIs). In fact, with a response easily enhanced by both agents, and with a low cost of hyperresponding, it might have been difficult to account by purely motor explanations for a smaller increase of intertrial responses (ITRs) after scopolamine than after amphetamine, given similar response enhancements in signaled no go trials.

For the same reasons indicated above it was also felt that other interactions between treatments and cues (i.e., those involving symmetrically opposite CS and CI arrangements— L^+NL^- versus N^+LN^-), if any, should be more marked with scopolamine than with amphetamine. However, the alternative finding of a disappearance of those interactions between scopolamine and stimulus arrangement, which had been shown in active-passive avoidance tasks, was not deemed to be directly amenable to a satisfactory explanation. In fact, no appropriate model was available to account for possible analogies or differences in the use of cues as between active-passive avoidance tasks and active avoidance-extinction tasks (see above). Furthermore, a reduction of response cost, by allowing higher levels of hyperresponding in general, might have blurred the differences between drug effects in the L^+NL^- and the N^+LN^- conditions simply by a ceiling phenomenon. Since the first prediction concerning intertrial activity data was confirmed by the results to be reported below, while interactions between treatments and CS and CI arrangements were not significant, alternative explanations of the latter finding and the resulting testable predictions can be postponed until the discussion.

The LSD-25 Syndrome: Drive Changes Suggested by Interactions between Treatment and Response-Reinforcement Relations

Additional information concerning the processes hypothesized in previous sections can be provided on the basis of available data on the indole hallucinogen LSD-25. Small doses of this drug have often been shown to induce response enhancements in a variety of different situations (see data and references in Appel, 1968). Furthermore, these mild stimulating effects have led to an interference with discrimination performance in some situations in which hyperresponding was devoid of adverse consequences at the reinforcement level (Lindsley, Carpenter, Killam, and Killam, 1968; Key, 1961, 1964a;

Halasz and Marrazzi, 1965, 1966; Miller, Drew, and Wikler, 1973; see, however, the basically negative results obtained in generalization tests by Dykstra and Appel, 1970, 1972; and the mixture of depressant and disinhibiting effects observed in the go-no go task used by McGaugh, De Baran, and Longo, 1963). On the other hand, an LSD-25 facilitation of differential responding has often been found with discrimination tasks in which errors (including ITRs which postpone the presentation of the next reinforced trial) have adverse consequences at the reinforcement level (Becker, Appel, and Freedman, 1967; Blough, 1957; King, Martin, and Melville, 1974; Meltzer, 1965; Rosen and Buga, 1973; Schechter and Winter, 1971). These data are obviously incompatible with any single hypothesis based either on sensory, or associative, or motor changes, while they support the view that the drug acts on reinforcement mechanisms, i.e., that it induces a drive enhancement or disinhibition (Bignami, 1972; Bignami and Rosić, 1971).

Several other changes that have been observed after LSD-25 treatment, such as interference with habituation in some experiments (Key and Bradley, 1960; Miliareassis and St. Laurent, 1974; but not in others: Davis and Sheard, 1974), enhanced interference by irrelevant stimuli with responses to relevant stimuli (Key, 1964b), and reduction of Y maze alternation (Swonger and Rech, 1972; Drew, Miller, and Baugh, 1973) cannot be readily interpreted as being either in favor or against a motivational explanation. This depends on the relations between mechanisms responsible for habituation phenomena, and mechanisms responsible for extinction of responses to nonreinforced stimuli in a context of previous or concurrent reinforced responding, which are far from being clarified and cannot be discussed further. It should also be emphasized that the contrast between motor explanations of amphetamine and scopolamine effects (although with the reservations descending from the discussion above) and drive explanations of LSD-25 effects (Bignami, 1972; Bignami and Rosić, 1971) can be made to coincide with the dual inhibition model proposed by Swonger and Rech (1972), except for the different terminologies.¹¹ In fact, Swonger and Rech (1972) concluded that LSD-25 interferes with a serotonergic inhibitory system (placed "upstream" with regard to a muscarinic inhibitory system), which opposes the general facilitation induced by enhancement of adrenergic tone, "in order that arousal does not produce a state of confusion due to cross-talk between the plethora of possible inputs and outputs." This view can be easily reconciled with the one that considers separate functions for response-reinforcement interfaces

¹¹These differences derive mainly from the fact that the drive and response disinhibition hypotheses were based on comparisons between LSD-25, amphetamine, and scopolamine effects in situations with different response-reinforcement relations, while the conclusions of Swonger and Rech (1972) were based mainly on drug interactions in activity and alternation tests without a response-reinforcement contingency. Given these differences, one is surprised that the two types of models are compatible to the point which is illustrated in the text.

(affected by amphetamine), for stimulus-drive "filters" (affected by LSD-25; see also a recent analysis of the changes in stimulus sensitivity caused by this drug in a note by Brown and Cooper, 1975), and for sensory-motor interfaces with a response-modulating function (see above discussion on muscarinic blockers).

Previous studies on go-no go avoidance discriminations, which have been conducted in different laboratories on cats and on rats, have suggested that an LSD-25 disinhibition of responses to no go signals can be obtained when the animals are trained with an extinction contingency in no go trials, but not when they are trained with a passive avoidance contingency (Key, 1961; Bovet *et al.*, 1965; Bridger and Bignami, unpublished observations extending the work on an active-passive avoidance task reported by Bovet *et al.*, 1965, to a few animals trained in the corresponding active avoidance-extinction task). It was deemed at this point that a more thorough analysis of LSD-25 effects on the performance of active avoidance-extinction tasks by rats could provide useful information. In fact, the finding of widespread disinhibitory phenomena, contrasting with the absence of hyperresponding in active-passive avoidance situations, might have confirmed that the LSD-25 profile should not be ascribed to sensory or motor changes *per se*, and supported further the hypothesis of an influence on drive modulation. As a corollary, one could have inferred that an explanation like that proposed by Dąbrowska (1975) in order to account for the features of defensive differentiations in the dog should not be extended to the rat and/or the situations used in the Rome laboratory.

No additional explanations would have been necessary in case the L^+NL^- and the N^+LN^- tasks were found to be equally sensitive to the drug. Vice versa, the finding of an interaction between LSD-25 treatments and stimulus factors might have meant either (i) that a physiological-biochemical specialization of the interfaces between sensory analyzers and reinforcement mechanisms can lead to differential treatment effects; or (ii) that the punishment mechanism postulated by Dąbrowska (1975) to account for response suppression in nonreinforced trials plays a variable role as a function of more than one type of stimulus factor, that is, not only depending on whether or not nonreinforced signals are originally responded to (Dąbrowska, 1975), but also depending on stimulus arrangement in situations in which nonreinforced signals are originally responded to (in this instance, different conditioned inhibition paradigms). Since no substantial differences were found between LSD-25 effects in the two tasks, the above possibilities and the resulting testable predictions will not be discussed further. It is felt, however, that they should be kept in mind, since the fact that an interaction between drug and cues was not found in a particular type of situation does not exclude that it can surface in other types of situations.

Some Other Problems

(1) *Attenuation versus maintenance of response changes induced by scopolamine and amphetamine.* The statement that response-reinforcement relations in no go trials have been found to influence the effects of LSD-25 in locomotor avoidance tasks, but not those of scopolamine and amphetamine, represents an oversimplification. Sooner or later, response enhancements caused by the latter drugs become attenuated when they have adverse consequences at the reinforcement level, while they are maintained over a much longer series of treatments when they have either a favorable, or no influence on the organism's ability to meet reinforcement requirements (for amphetamine see Schuster and Zimmerman, 1961; Schuster, Dockens, and Woods, 1966; for scopolamine, see Carro-Ciampi and Bignami, 1968; Bignami and Gatti, 1969). As a further check on the validity of the above distinction, rats performing in one of the active avoidance-extinction tasks (L^+NL^-) were given a series of daily treatments with either amphetamine or scopolamine, which was known to suffice for a substantial desensitization to scopolamine in the presence of a passive avoidance contingency (see the difference between the first and the ninth day of treatment in Bignami and Gatti, 1969, Fig. 1B).

(2) *Physostigmine facilitation of differential responding.* It is well known that the cholinergic stimulant physostigmine can facilitate the acquisition, or the performance, or both, of various types of discriminations (see discussion and references in Bignami and Gatti, 1967; Bignami, Rosić, Michałek, Milošević, and Gatti, 1975; Carlton, 1963, 1969; Warburton, 1972; and the recent studies by Cox, 1974; Cox and Tye, 1973, 1974). In particular, a previous study conducted with the more difficult active-passive avoidance task (L^+NL^-) had shown a response reduction in both active and passive avoidance trials. The latter change was somewhat larger than that of the former one, therefore the overall result was a slight facilitation of discrimination learning (Rosić and Bignami, 1970b). The finding of a similar facilitation of differential responding in the presence of an extinction contingency might have provided additional evidence that the response control exerted by muscarinic systems is at least to some extent independent of response-reinforcement relations. Vice versa, a discrepancy between the results obtained, respectively, with and without a passive avoidance contingency might have introduced a contradiction into part of the framework discussed in previous sections.

The most economic approach to the above problem was to use animals that showed little or no differential responding in spite of extensive pretraining in the more difficult task (L^+NL^-). Since a facilitation similar to that found with the corresponding active-passive avoidance task was obtained in this experiment, no attempt was made to carry out a genuine acquisition study.

(3) *Contrasting interpretations of the disinhibitory effects of tranquilizers (benzodiazepines).* The barbiturate and benzodiazepine disinhibition of responses suppressed by contingent punishment is well known, and needs not to be commented upon¹² (reviews by Bignami, 1976b; Cook and Sepinwall, 1975a, 1975b; Gray, 1976; Kelleher and Morse, 1968; McMillan, 1975; Millenson and Leslie, 1974; Randall and Schallek, 1968; Randall, Schallek, Sternbach, and Ning, 1974; Schallek, Schlosser, and Randall, 1972; see also the controversies on the biochemical substrates of the anticonflict effect in the volumes edited by Garattini, Mussini, and Randall, 1973; Costa and Greengard, 1975). This effect is often ascribed either to an overall attenuation of emotional changes, or to an attenuation of the consequences of aversive experiences at the response level (antipunishment action). Furthermore, similar explanations have been used to account for (i) the avoidance enhancements observed mainly in situations in which suppression phenomena can interfere with the emission of the response required, (ii) the drug facilitation of discrimination learning or performance after experiences which lead to "fixated behaviors", and (iii) the attenuation of some of the consequences of non-reward, based on the hypothesis that aversive stimuli and nonreception of anticipated rewards have similar emotional consequences (see the above reviews).

In recent years the specificity of the antiemotional or antipunishment action of benzodiazepines has been often questioned. In fact, disinhibition has not been obtained as consistently in situations with noncontingent punishment (Conditioned Emotional Response (CER) tests), as in those with contingent punishment (conflict tests; for contrasting explanations of these discrepancies see Kelleher and Morse, 1968; Millenson and Leslie, 1974; Huppert and Iversen, 1975; and later in this section).

The literature on frustrative nonreward is also somewhat contradictory. On the one side, drug treatments have been shown to induce several of the changes expected on the basis of the Fear = Frustration hypothesis, and of an antiemotional model of drug action (for the retardation of extinction see

¹²Benzodiazepine effects bear a close similarity to those of subhypnotic doses of barbiturates in most situations discussed here, while it is impossible to extend the present analysis to the differences between the two types of compounds. This discussion and the tests reported in the Experimental section deal with the effects of benzodiazepine tranquilizers, and not with those of barbiturates, mainly because with the former compounds it is easier to separate muscle-relaxant and "tranquilizing" effects, on one side, from general sedative and hypnotic effects, on the other. Therefore, one does need to deal in considerable detail with nonmonotonic dose-response relations, which is unavoidable in the case of barbiturates. Furthermore, previous work has shown that the close qualitative analogies between benzodiazepines and subhypnotic doses of barbiturates in tests with conflict and with frustrative nonreward can also be extended to avoidance enhancements observed in particular situations (see, e.g., Bignami, De Acetis, and Gatti, 1971; Bignami and De Acetis, 1973; reviews by Bignami, 1976b; Gray, 1976).

Iwahara, Nagamura, and Iwasaki, 1967; Tessel and Lash, 1968; for the attenuation of performance depression in experiments with incentive reduction see Rosen and Tessel, 1970; Vogel and Principi, 1971; for the prevention of the partial reinforcement acquisition effect see Iwahara *et al.*, 1967; Tessel, Freedman, and Rosen, 1968; for a more detailed analysis of the above and of related phenomena see Gray, 1976). On the other hand, benzodiazepine influences on the partial reinforcement extinction effect have been at least inconsistent (Iwahara *et al.*, 1967; Tessel *et al.*, 1968), while runway studies have also pointed out other changes which are not easily amenable to an antiemotional explanation. For example, several of the above studies showed an elevation of running speeds in early trials (i.e., when control baselines were still low), while asymptotic speeds were generally reduced. (However, given the type of response used and the high control speeds at the end of training, the latter change might well be ascribed to the muscle relaxant properties of the drugs.)

It should be underlined at this point that insufficient attention has been so far given to alternative explanations of partial reinforcement effects which are based on changes in the balance between consummatory and preparatory (appetitive, instrumental) outputs, rather than on emotional consequences of nonreception of an anticipated reward (Sol'tysik and Gasanova, 1969; for a thorough analysis of the relations between consummatory and instrumental activation see the review by Sol'tysik, 1975). In fact, benzodiazepine data often show parallel enhancements of both instrumental and consummatory behaviors of the alimentary type (see, e.g., the study of food consumption and of lever-pressing for food by Wise and Dawson, 1974; the effects on adjunctive consummatory responses, however, have been far from uniform, as shown by the data of McKearney, 1973a; Sanger and Blackman, 1975; Smith and Clark, 1975). Furthermore, some recent data have shown that the enhancing effects of benzodiazepines on alimentary behaviors take place without disruption of the normal inhibition of instrumental outputs by strong consummatory activation. In fact, "conditioned suppression" of ongoing operant behavior by stimuli previously paired to gratis food was not modified by treatment (Miczek, 1973b). Besides contrasting with the opposite effects of amphetamine on the two categories of responses, and confirming that strong consummatory activation can block appetitive outputs, while the converse is not true (Sol'tysik, 1975), these data appear to be compatible both with a conventional explanation of benzodiazepine effects (release of the alimentary drive from inhibition by emotional responses) and with a direct action on the mechanisms underlying alimentary behaviors.

Additional difficulties arise when considering a wider range of data on extinction and on discrimination. In fact, an antiemotional explanation which can account for hyperresponding or perseverative responding in extinction and discrimination tasks with positive reinforcement (see runway studies

mentioned above, and Hasegawa, Ibuka, and Iwahara, 1973; Molinengo and Ricci-Gamalerio, 1969; Nicholson and Wright, 1974; Schallek, Kuehn, and Kovacs, 1972; Wedeking, 1969)¹³ cannot be extended to disinhibition of behavior suppressed by nonreception of a negative reinforcer (Hidalgo, Tarleton, Di Leo, and Thompson, 1968; Iwahara and Matsushita, 1971; Kamano, 1972; Kumar, 1971; Yamaguchi and Iwahara, 1974; Ziskind, Amit, and Baum, 1974). Obviously, this does not mean that the above data showing an interference with extinction or with differentiation in situations with negative reinforcement, or those showing a paradoxical increase of suppression in particular CER tests (Stein and Berger, 1969) must be ascribed to an emotional enhancement. It simply means that neither an antiemotional explanation *per se* (including models based on an attenuation of punishment suppression), nor the opposite type of model (fear enhancement or disinhibition) can account for the complex profile of benzodiazepine effects. It is true that either symmetrical or asymmetrical dissociation of learning has often been reported with these compounds. It appears difficult, however, to ascribe all antipunishment, antifrustration, and antiextinction effects observed in some situations to an attenuation of emotional changes, and all effects which apparently point in different directions to a state dependence.¹⁴

Kelleher and Morse (1968) have attempted to show that benzodiazepine effects in CER tests are similar to those observed in conflict tests when the contingencies allow adventitious reinforcement phenomena (noncontingent punishment "perceived" as if it were response-contingent). This hypothesis has considerable interest, since it implies that the drug-induced disinhibition appears when feedbacks of a specified response and feedbacks of other behaviors become part, respectively, of fear-enhancing and of fear-inhibiting

¹³An apparently remarkable exception is represented by the data of Geller, Hartmann, and Blum (1971), showing a chlordiazepoxide facilitation of discrimination in a go-no go alimentary task with food reward for responding to a light-tone complex, and "punishment" by total inactivation of the chamber for responding to light alone. The study, however, was conducted with rats which did not show differential responding after an extended period of training, which means that the results should be compared to the facilitation of discrimination learning impaired by "fixations," rather than to the disinhibition or perseveration in well-learned discrimination tasks (see discussion and references at the beginning of this section).

¹⁴This analysis could be extended to other aspects of the benzodiazepine profile. For example, the literature on social behaviors shows that treatments with doses smaller than those endowed with antiaggressive effects can enhance aggression, provided that a high control baseline does not lead to ceiling phenomena preventing the demonstration of further enhancements (reviews by Krsiak, 1974; Miczek and Barry, 1976; see also the human data briefly discussed in a recent Editorial, 1975). Furthermore, some recent studies of the adrenocortical response have shown that benzodiazepine effects can be in opposite directions depending on dosage levels. The lower doses prevented the changes induced by stress, while higher doses had a stress-like effect of their own (Lahti and Barsuhn, 1975).

compounds, while with classical contingencies perceived as such both "danger" and "safety" are signaled exclusively by exteroceptive cues (for a more thorough discussion of classical and passive avoidance paradigms see Huppert and Iversen, 1975). This type of analysis could be extended to other instances of behavioral disinhibition, in order to show that independently of the particular motivational events which lead to response attenuation, one should examine drug effects in relation to general suppression phenomena, and in relation to selective suppression of specified outputs, which must rely on an appropriate use of the informational value of feedbacks.¹⁵ This type of approach has so far led to contrasting conclusions, as shown by the analysis of CER changes carried out by Millenson and Leslie (1974), which is in disagreement with that by Kelleher and Morse (1968). Furthermore, all explanations discussed above appear to be weakened by the disinhibiting effects which have been found in classical differentiation tests measuring heart rate changes after stimuli paired or unpaired to shock (Hidalgo *et al.* 1968; Yamaguchi and Iwahara, 1974). In fact, not only was the drug action at the level of a classical response, but also, it took place in a direction opposite to that expected—enhancement of changes caused by signals not paired to aversive events, instead of reduction of changes caused by signals paired to aversive events.

Given the many problems encountered with the explanations discussed so far, it appeared obvious that experiments with active avoidance-extinction tasks using a conditioned inhibition paradigm could not provide clear-cut answers concerning the mechanism of action of benzodiazepines. In fact, the information available on these tasks did not allow to separate the role of an

¹⁵The above general statements should not lead to a confounding of several types of inhibition phenomena, which have been clearly separated from each other at a behavioral level. It is known, for example, that there are marked differences between the genuine drive inhibition caused by a nonreinforced stimulus presented in a context of reinforcement, and not responded to, and the complex phenomena occurring when the response is to a nonreinforced stimulus. When the paradigm is a classical or Pavlovian one, relatively simple tests can clearly distinguish between the properties of the "primary inhibitory stimuli" and those of stimuli with mixed excitatory and inhibitory functions (Konorski, 1967; see also Rescorla, 1971, for additional differences between a primary inhibitory stimulus and a signal having lost part of its salience by exposure in a "latent inhibition" paradigm). When the paradigm is an instrumental (or operant) one, the nonreception of an anticipated positive reinforcer (including the nonreinforcement of a response generalized from a CS⁺ or SD to a CS⁻ or S^Δ), leads to a rebound increase of the instrumental drive which parallels the inhibition of the consummatory drive system (Konorski, 1967; Sol'tysik and Gasanova, 1969; for the relations between nonconsummatory and consummatory activation see also Sol'tysik, 1975). Furthermore, little is known about retroactive response inhibition phenomena triggered by nonobtention of an anticipated positive reinforcer, which may account for particular consequences such as peak shift (Bignami, 1968). Finally, one should keep in mind possible differences between alimentary and defensive tasks, which have been emphasized when discussing the results reported by Dąbrowska (1975).

inhibition of fear responses by a CI (same as in a classical test) from that of a specific inhibition of a response not terminating CS in the presence of CI, with the latter hypothesis clearly favored by the data of Dąbrowska (1975), which, however, were obtained in a different species and in different testing conditions. In spite of these uncertainties chlordiazepoxide was included in the experiments reported below both in order to obtain additional normative data on this agent, and on the basis of the following considerations. An absence of changes in responding to CI-CS after treatment might have denied the generality of the disinhibiting action with regard to behavior suppressed by nonreception of a negative reinforcer, and therefore prompted further research on the factors which allow, or vice versa prevent, a reappearance of "paradoxical" fear responses to nonreinforced stimuli after benzodiazepine treatment.

Vice versa, the finding of a drug enhancement of responses to CI-CS would have confirmed and extended the data showing a disinhibition both in the presence of formal punishment contingencies (expected) and in the presence of extinction contingencies (unexpected in the case of negative reinforcement). Therefore, this finding might have further emphasized the need for an in-depth analysis of the mechanisms that underlie response withholding during nonreinforced stimuli in aversively motivated tasks, particularly as concerns the relative role of fear inhibition and of punishment by stimulus nontermination (Dąbrowska, 1975). It goes without saying that any data showing that an antipunishment model of benzodiazepine action lacks generality already in the case of changes in situations with negative reinforcement would make it even more necessary to explore alternative explanations to account for other types of changes, e.g., the attenuation of some nonreward consequences.

(4) *Chlorpromazine: Psychomotor depression and loss of stimulus control.* In spite of some early claims to the contrary, the depressant effects of phenothiazine neuroleptics are now known to be basically similar with widely different combinations of test factors (stimuli, reinforcements, responses, and so forth). As a consequence, the term "psychomotor depression" is often used to define the neuroleptic syndrome. Some investigators, however, still give either direct or indirect support to the hypothesis that response changes observed in negatively reinforced tasks are due at least in part to an antiemotional action (see, e.g., the discussion by Millenson and Leslie, 1974). Furthermore, in some operant situations the effects of chlorpromazine consist of a rate-dependent mixture of response enhancements and response reductions (review by Kelleher and Morse, 1968). Finally, some of the available data have been interpreted as showing a drug interference with stimulus control of behavior (e.g., Johnson, 1970, 1971).

Previous studies in this laboratory yielded results which were against a fear reduction hypothesis, and also against an explanation based on loss of

stimulus control. In fact, chlorpromazine changes in the more difficult active-passive avoidance task (L^+NL^-) were exclusively in the direction of an active avoidance suppression, without response enhancements during passive avoidance signals (Bovet *et al.*, 1965; Bignami and Carro, 1967). However, the consequences of an impairment of stimulus control, or of a genuine motivational change, might have been attenuated by the high cost of responding outside the active avoidance signal. Therefore, the above experiments were replicated in rats performing in the active avoidance-extinction task with the L^+NL^- stimulus arrangement, and showing sufficiently low rates of responses to CI-CS to allow a change in stimulus sensitivity to reflect itself in a response enhancement.

Some experiments in few rats with poor differential responding in the L^+NL^- paradigm had previously shown similar depressant effects of chlorpromazine on responses avoiding shock and on responses punished by shock (Gatti and Bignami, 1966). This work was extended to animals with high rates of responding to both CS and CI-CS, so as to obtain further information on the specificity, or nonspecificity, of the chlorpromazine response suppression.

EXPERIMENTAL SECTION

Methods

Subjects

Subjects were male albino rats of a Wistar-derived strain maintained at Istituto Superiore di Sanità. The animals were about 80-100 days old at the beginning of discrimination training.

Apparatus

The apparatus consisted of six 490 × 270 × 225 mm shuttle boxes without central partition or barrier, placed inside cork-lined wooden containers providing sound insulation. Each box was equipped with two 10-W bulbs at the center of the ceiling, which served as a source of nondirectional light stimuli. A 4-in. loudspeaker connected to a Grason-Stadler generator (Model 901B) was located behind the shuttle box in a central position, so as to provide a nondirectional acoustic signal (speech noise of 90-dB intensity, as measured by a Bruel & Kjaer sound level meter, Type 2203, placed inside the box at floor level). Scrambled shock of 1.5 mA was given through the grid floor, using a 105-V source with a 70 k Ω resistance in series. Each box was connected to a programming unit made up of conventional circuitry, and to event recorders.

Discrimination Schedules

Each training and testing session consisted of 50 trials at 30-sec intervals, with 25 active avoidance (AA) and 25 extinction (EX) trials given according to the sequence (AA-EX-AA-EX-EX-AA-EX-AA;AA...) repeated six times, plus one AA and one EX trial. Active avoidance trials started with the turning on of the appropriate CS (see later), followed 5 sec later by grid shock (US). A crossing response during the CS-US interval terminated the CS and avoided shock, while a response after shock onset terminated both CS and US at the same time. Shock was terminated after 10 sec if an animal did not respond. Extinction trials consisted of the presentation of the CS for 5 sec, preceded by 1 sec and accompanied for its whole duration by a stimulus of a different modality (conditioned inhibitor, CI). The duration of this no go stimulus complex was fixed. In other words, the CS was terminated by a response when presented alone to signal an avoidance contingency, while it was unaffected by the animal's response when presented with the CI. No shocks were scheduled outside AA trials, i.e., both responses to no go signals and intertrial responses (ITRs) were not punished. Two varieties of this go-no go discrimination with asymmetrical reinforcement were used, one with light as the CS and noise as the CI (L^+NL^-), and the other with the opposite stimulus arrangement (N^+LN^-).

Procedure

As indicated in a previous paper (Frontali and Bignami, 1974) crossing responses to go signals (conditioned avoidance responses, CARs) can be established fairly rapidly in the absence of punishment of ITRs and of responses to no go signals (responses to the CI-CS extinction signal, ESRs). On the other hand, differential responding develops slowly over a period of several weeks in the N^+LN^- schedule, while most rats need a much longer period of training in order to achieve a satisfactory discrimination criterion in the L^+NL^- schedule. Therefore, pretraining was carried out in two or more steps, starting with several subgroups of animals which were given a first series of 12-18 learning sessions either in the L^+NL^- or in the N^+LN^- condition.

After two sufficiently large pools of partially trained animals had been formed, it was realized that any attempt to carry on further training, and then drug testing, with both schedules at the same time would have led to pharmacological experiments with an insufficient number of well-performing L^+NL^- rats. Therefore, except for a partial replication to be mentioned later, all experiments in the L^+NL^- paradigm were carried out first, with a series of controls for order and other effects. As soon as a first group of rats showed stabilization of CARs above 80% and of ESRs below 40%, drug tests were started with a series of LSD-25 doses (0.01, 0.02, 0.03, 0.05, 0.075, 0.10 mg/kg; for other details on treatments, see below), followed by a first

series of amphetamine doses (0.50, 0.75, 1.0, 2.0 mg/kg), then by a series of scopolamine doses (0.01, 0.02, 0.05, 0.10, 0.20, 0.50, 1.0 mg/kg), and then by a second series of amphetamine doses (0.5, 1.0, 2.0 mg/kg). A second group of animals showing little or no differential responding was used for a cross-over experiment with repeated physostigmine treatment. The procedure in this experiment differed markedly from that of the others, therefore it will be described in the section on Results that deals with physostigmine effects.

The extended period of training received during the physostigmine treatment and during the post-treatment control period made that several rats with originally poor discrimination performance eventually reached the above criterion. Therefore, it was possible to create a second group of rats with 80% or more CARs and less than 40% ESRs, which was treated with scopolamine and amphetamine as indicated above (in the case of amphetamine, see second series). After a period of rest, followed by some retraining, several rats from both original pools were given a series of chlordiazepoxide treatments (2.5, 5, 10, 20, 40, 80 mg/kg). Afterwards, a check was made for the consistency of the changes induced by LSD-25 (single-dose treatment with 0.075 mg/kg). This was followed by another check for the consistency of changes induced by scopolamine (0.5 mg/kg) and by amphetamine (1 mg/kg), leading to the subdivision of the available animals into two subgroups. One of these was given nine consecutive daily sessions, each preceded by an amphetamine treatment (1 mg/kg), while the second went through a similar series of scopolamine treatment sessions (1 mg/kg). (It should be noted that the above replications of LSD-25, amphetamine, and scopolamine experiments were carried out when rats were about 1 1/2 years old. Considering the consistency of the results obtained in various replications, it appears unlikely that some variable differences between L⁺NL⁻ and N⁺LN⁻ data regarding exclusively ITR levels in amphetamine-treated animals, could be ascribed to the age factor; see later.) The final step in the L⁺NL⁻ experiments was a series of chlorpromazine tests (0.5, 0.75, 1.0, 1.5, 2.5, 3.5 mg/kg). By drawing from the original pools it was also possible to treat a number of animals with this drug with fairly high ESR rates.

Given the consistency of the results obtained in the L⁺NL⁻ animals, tests in the N⁺LN⁻ condition were carried out with fewer doses per drug, and with fewer controls for order and other effects. A series of LSD-25 treatments was given first (0.01, 0.02, 0.05, 0.075, 0.10 mg/kg), followed by chlordiazepoxide (5, 10, 20, 40 mg/kg). The animals were then subdivided into two subgroups, the first of which received a series of amphetamine doses (0.5, 1.0, 2.0 mg/kg), followed by a series of scopolamine doses (0.1, 0.2, 0.5 mg/kg), while the other one was treated similarly, but in a reverse order.

All drugs were dissolved in distilled water and administered subcutaneously 30 min before testing. In the case of DL-amphetamine sulfate, scopolamine hydrobromide, chlordiazepoxide hydrochloride, chlorpromazine

hydrochloride, and physostigmine salicylate the doses refer to the weights of the salts, and not to those of the respective bases. It should also be noted that a DL-amphetamine preparation was used, instead of D-amphetamine, which is about two times more active. This was to facilitate comparisons with the data obtained in previous research in the same laboratory.

Besides the treatment series so far described, yielding data for routine analyses carried out as indicated below, several additional data were collected. First, scopolamine and amphetamine effects were reinvestigated in two additional groups of animals which were run simultaneously with the L^+NL^- and the N^+LN^- stimulus arrangements, respectively, and with a procedure that allowed to make direct statistical checks on main effects and interactions involving stimulus arrangements (for the details, see the section on Results which deals with scopolamine and amphetamine effects). Second, some of the rats from the original pools were used to assess the effects of LSD-25 doses higher than 0.1 mg/kg. Third, several tests were carried out with animals that could not be assigned to either the criterion group or to those with high ESR levels. Most of these rats, belonging to an intermediate category with fairly high CAR levels and fluctuating ESR levels, showed drug-induced changes similar to those observed in well-performing animals. Therefore, the results obtained in these animals will not be mentioned further. Finally, a few rats exhibited low CAR frequencies with little or no responding in no go trials. Since changes of CAR frequencies by response enhancing drugs were obviously limited by a ceiling effect in well-performing animals, brief mention will be made in the next section of the data obtained in low avoiders.

Data Analysis

All data, except those from the factorial replication comparing scopolamine and amphetamine with both stimulus arrangements, and those on physostigmine (see Results), were subjected to separate drug-by-drug ANOVAs for each response category. These analyses used a $2 \times N$ design, with control versus treatment as one factor, and doses as the other factor, while subjects were treated as blocks. In several instances significant treatment $\times$ doses interactions were obtained, therefore dose-by-dose t tests for paired observations were also carried out. In all instances in which the effects were mainly in the direction of ESR enhancement (after scopolamine, amphetamine, LSD-25, and chlor-diazepoxide) additional data analyses using discrimination indexes proved to be redundant. Furthermore, no attempt was made to use data obtained with different drugs, or with the same drug but in different tasks, for more complex factorial analyses, which might have been biased by the design used.

Only a few illustrative examples of the consistency of drug effects in various replications will be given in the section on Results. Therefore, it should be added here that a series of preliminary calculations showed that the changes induced by LSD-25, amphetamine, and scopolamine in the L^+NL^-

task and in the treatment series described above were not affected by order nor by "type" of animal. ("Type" applies to rats assigned to treatments with response enhancing agents from the start versus rats showing a slower acquisition of discrimination and having received a series of physostigmine treatments; for the variability of ITR data in amphetamine treated animals, see later). Only the latter one of these possible sources of variance was controlled for in the cases of chlordiazepoxide and chlorpromazine, which were tested in a mixed group made up of rats from both L^+NL^- pools. Finally, the cross-over procedure used to assess amphetamine and scopolamine effects in the N^+LN^- test will be ignored in the section on Results, since order effects were absent.

Results

Most of the results obtained with amphetamine, scopolamine, LSD-25, chlordiazepoxide, and chlorpromazine are presented as averaged difference scores, i.e., as deviation of CARs, ESRs, and ITRs from control levels (Figs. 1-7). Except in the physostigmine experiment, and in the chlorpromazine experiment using rats with high ESR rates, the range of control baselines averaged dose by dose was 20.3-24.0 CARs, 1.3-6.9 ESRs, and 0.5-2.8 ITRs. As concerns the latter, the figures refer to frequencies corrected so as to allow direct comparisons of response rates in extinction periods marked, respectively, by the absence of discrete stimuli and by no go signals (CI-CS). All ANOVAs but one showed a significant effects of blocks (subjects) which will not be mentioned further. Vice versa, a main effect of doses in the absence of a treatment $\times$ doses interaction was obtained only in a few instances,¹⁶ therefore the presentation of statistical results can be limited to significant treatment or treatment $\times$ doses effects, corresponding to deviations from control levels, respectively, without and with differences between doses.

Scopolamine and Amphetamine (Figs. 1-4)

The L^+NL^- data in Figs. 1 and 2 refer mainly to the results obtained in rats of the first group (those which achieved stable differential responding in relatively fewer sessions), while limited data from animals used after the physostigmine experiment are given in the upper right section of the respective graphs. Data on amphetamine are from the second series of treatments given in the first group (see procedures). In fact, average ESR

¹⁶Given the ANOVA design used, a main effect of doses in the absence of a treatment $\times$ doses interaction does not constitute evidence for a dose-dependent difference in treatment effects. It rather points out similar deviations from the overall mean of both control and treatment scores at different doses, i.e., essentially, a fluctuation of the control baseline.

baselines during this series were practically identical to those observed during the scopolamine series, while those measured during the first amphetamine series were slightly higher.

Deviations from high CAR baselines were apparently negligible after scopolamine and amphetamine, but in opposite directions. As concerns the former drug, statistical evidence of a slight dose-dependent depression was obtained both in the L^+NL^- and in the N^+LN^- condition (L^+NL^- : treatment $\times$ doses interaction $F(6, 91) = 2.30$, $P < 0.05$; N^+LN^- : $F(2, 70) = 4.39$, $P < 0.05$). Statistical evidence for a CAR enhancement after amphetamine was limited to the N^+LN^- condition (treatment $F(1, 70) = 6.48$, $P < 0.05$). The slowness or absence of CAR changes after the latter drug was obviously due to a ceiling effect. In fact, response enhancements were constantly obtained in a few rats with low CAR baselines in control conditions.

Both scopolamine and amphetamine caused highly significant enhancements of ESR and ITR frequencies, which in most instances were clearly dose-dependent. The apparent exceptions (see statistical results below) can be ascribed to the fact that sufficiently low doses were not included in particular treatment series. In the case of scopolamine, ESR and ITR enhancements were practically the same in the L^+NL^- and N^+LN^- conditions (L^+NL^- : ESR treatment $\times$ doses interaction $F(6, 91) = 15.75$, $P < 0.01$; ITR treatment $\times$ doses interaction $F(6, 91) = 14.38$, $P < 0.01$; N^+LN^- : ESR treatment $F(1, 70) = 201.28$, $P < 0.01$; ITR treatment $\times$ doses interaction $F(2, 70) = 11.47$, $P < 0.01$). In the case of amphetamine, the data seemed to point out a lower sensitivity to the drug in the N^+LN^- , than in the L^+NL^- task, as suggested, e.g., by the finding of treatment $\times$ doses interactions only in the former situation (L^+NL^- : ESR treatment $F(1, 35) = 433.33$, $P < 0.01$; ITR treatment $F(1, 35) = 79.53$, $P < 0.01$; N^+LN^- : ESR treatment $\times$ doses interaction $F(2, 70) = 18.79$, $P < 0.01$; ITR treatment $\times$ doses interaction $F(2, 70) = 14.05$, $P < 0.01$). As concerns drug-induced changes in animals used previously in the physostigmine experiment the results were practically identical to those reported above, both at the doses shown in the figures and at other doses. This applies also to other checks for the consistency of scopolamine and amphetamine effects in the main treatment series, which have been mentioned in the section on Methods.

The data so far illustrated, while showing a substantial analogy of scopolamine and amphetamine effects on ESRs and pointing in the direction of a lower overall sensitivity to drug with the N^+LN^- than with the L^+NL^- stimulus arrangement, also suggested that given similar ESR enhancement (i) ITRs were more markedly elevated after amphetamine than after scopolamine, and (ii) ITR enhancements in amphetamine-treated animals were more marked in the L^+NL^- , than in the N^+LN^- task. Since no direct statistical test of these tentative inferences could be performed on the basis of

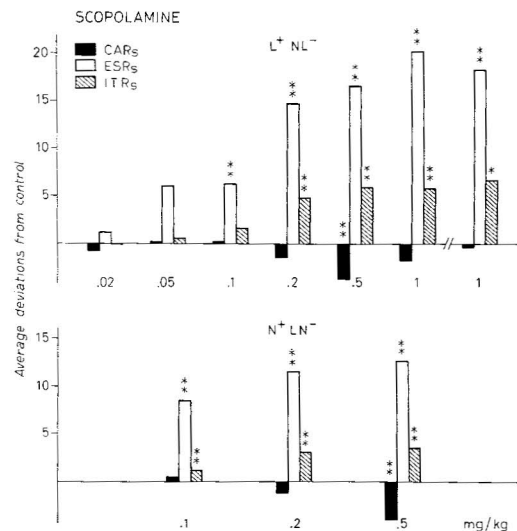


Fig. 1. Changes in CAR, ESR, and ITR frequencies induced by scopolamine hydrobromide in active avoidance-extinction tasks with different stimulus arrangements (L^+NL^- , $n = 8$; N^+LN^- , $n = 15$). All treatments were given sc 30 min before testing. The last group of bars to the right in the upper graph refers to part of a replication using a different group of animals, which took a much greater number of sessions to reach the discrimination criterion ($n = 10$, see text). Control and treatment values at each dose were used for ANOVAs (see text), followed by paired t tests within doses (* $P < 0.05$; ** $P < 0.01$). The L^+NL^- graph does not include the 0.01 mg/kg dose, which was without effect like the lowest dose shown in the figure (0.02).

the above data, still another replication of the scopolamine and amphetamine tests was carried out after all experiments described below had been completed. For this purpose, two additional groups of L^+NL^- and N^+LN^- rats were trained as indicated in the section on Methods, until animals in each group reached the usual criterion. These animals were then treated at weekly intervals with ascending doses of amphetamine (0.25, 0.5, 1, and 2 mg/kg) and of scopolamine (0.05, 0.1, 0.5, and 2 mg/kg). (The criteria for selecting these doses are obvious if one considers the data of Figs. 1 and 2.) The design was balanced to allow a measurement of between-group task effects and within-group order effects. The latter, however, were controlled by a procedure different from that used in previous experiments, since each animal received ascending doses of the two drugs in alternate weeks (scopolamine in odd tests and amphetamine in even tests, or vice versa). Order effects were absent and will not be mentioned further.

Within-drug ANOVAs pertaining to the data illustrated in Fig. 3 were carried out on difference scores, with L^+NL^- versus N^+LN^- as the two levels of one factor, and doses as the four levels of the other factor. The results of

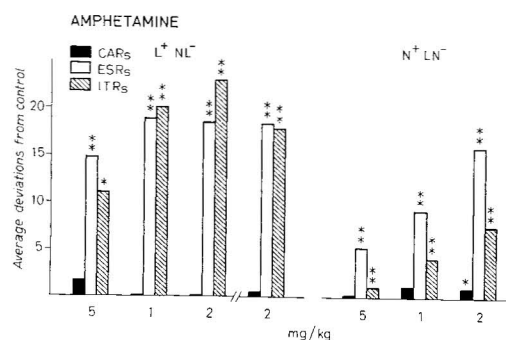


Fig. 2. Effects of DL-amphetamine sulfate in active avoidance-extinction tasks (L^+NL^- , $n = 8$; N^+LN^- , $n = 15$). The group of bars to the right in the L^+NL^- graph refers to part of the replication carried out with "slow learners" ($n = 10$; see text). For other indications see the legend of Fig. 1.

these analyses need not be reported in detail since they confirmed a dose-dependent reduction of CARs after scopolamine and dose-dependent enhancements of both ESRs and ITRs after both amphetamine and scopolamine. No statistical evidence was obtained for a difference in sensitivity to drug treatments due to stimulus arrangement.

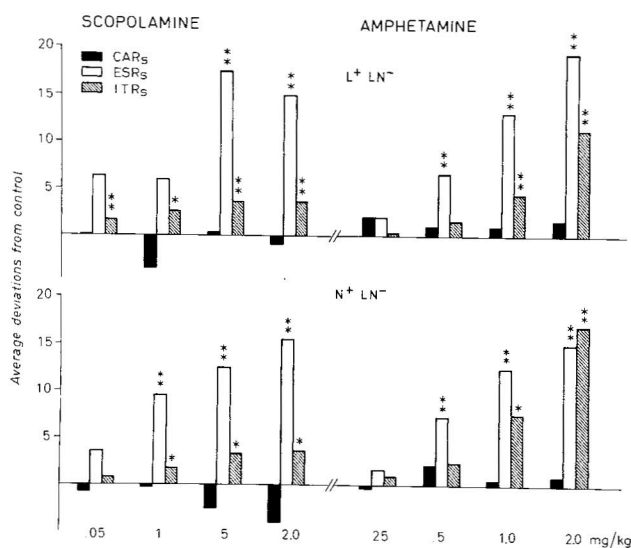


Fig. 3. Replication of scopolamine and amphetamine experiments by a cross-over design allowing a direct measurement of possible differences due to stimulus arrangement (within drugs), and an assessment of the relative size of ESR and ITR enhancements (between schedules and drugs; see text). Each subject ($n = 7$ in each schedule) received all doses of both drugs.

Since the different doses of amphetamine and scopolamine could not be handled as equivalent levels of a dosage factor in a comparison of the effects of the two drugs, the latter was carried out so as to provide an answer to the remaining question—whether or not similar elevations of ESRs were accompanied by different elevations of ITRs after amphetamine and scopolamine. For this purpose, ratios between ITR and ESR difference scores were calculated for each animal on the basis of the data pertaining to the 2 mg/kg doses of the two drugs, i.e., to treatments which on the basis of the available data were known to induce asymptotic response enhancements. These scores were used to perform a 2×2 ANOVA, which yielded a highly significant effect of the drug factor, $F(1, 24) = 9.99$, $P < 0.01$, with no significant effect of the task factor and no significant interaction. In other words, this analysis provided definite evidence that a significantly larger proportion of the hyperresponding during CI-CS periods should be ascribed to an overall hyperactivity in the case of amphetamine, than in the case of scopolamine.

Brief mention must also be made of the results obtained with daily scopolamine and amphetamine treatments (Fig. 4). The effects of these drugs were again similar to those observed in previous treatment series, and showed little or no attenuation with repeated exposure. This was confirmed by the

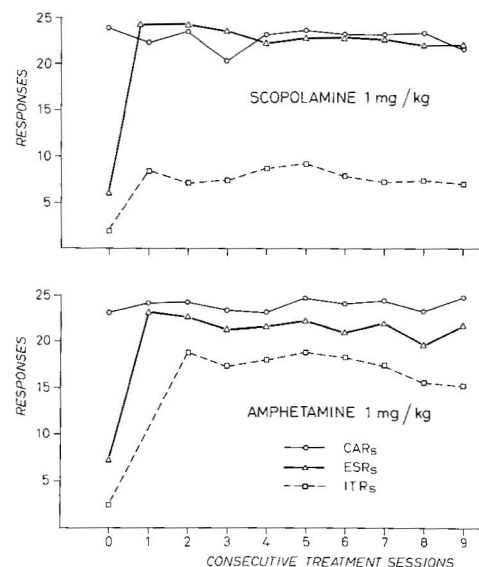


Fig. 4. Effects of daily treatments with scopolamine hydrobromide and DL-amphetamine sulfate on response frequencies in the L^+NL^- task ($n = 8$ in each group). 0, last pretreatment session; 1 to 9, successive treatment sessions.

absence of significant results of paired *t* tests confronting CAR, ESR, and ITR frequencies in the first and in the last of the treatment sessions.

LSD-25 (Fig. 5)

Slight CAR enhancements were observed after most LSD-25 treatments, but statistical confirmation of this phenomenon was obtained only in the N^+LN^- condition [treatment $F(1, 99) = 9.95$, $P < 0.01$]. A few tests on animals with low CAR baselines showed that the drug was able to enhance avoidance responding in the absence of a ceiling effect, although this action was less marked than that of amphetamine and scopolamine.

LSD-25 also caused significant elevations of ESR rates in both tasks, which however were not comparable to the marked disinhibition induced by scopolamine and amphetamine [L^+NL^- : treatment $F(1, 99) = 17.22$, $P < 0.01$; N^+LN^- : treatment $F(1, 99) = 26.50$, $P < 0.01$]. Besides the relatively low disinhibition asymptote, two other factors may have contributed to the absence of a significant dose-response relation. The first was that a significant deviation from control was obtained already at the lowest dose tested (0.01 mg/kg). The second was that the main testing series did not include doses higher than 0.1 mg/kg. Additional tests carried out in the L^+NL^- condition with doses up to 0.6 mg/kg showed a disappearance of the enhancing effects on ESRs and ITRs. No attempt to obtain depressant effects with still higher doses of the drug was made.

A slight ITR enhancement was observed in the L^+NL^- condition

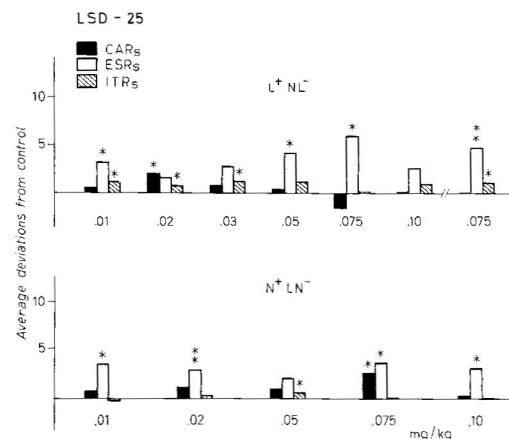


Fig. 5. Effects of LSD-25 in active avoidance-extinction tasks (L^+NL^- , $n = 10$; N^+LN^- , $n = 12$). The last group of bars to the right in the upper graph refers to a replication carried out with a group of rats including part of the animals used for the main treatment series, and some of the "slow learners" ($n = 13$; see text and legends of Figs. 1 and 2). For other indications see the legend of Fig. 1.

[treatment $F(1, 99) = 9.76$, $P < 0.01$]. In any event, paired t tests comparing ESR and ITR rates after drug treatment showed that the former were constantly more elevated than the latter. Furthermore, Fig. 5 shows the results obtained by replicating the .075 mg/kg treatment in a group made partly of rats which achieved stable differential responding during or after the physostigmine experiment, and partly of the same rats used above. These data showed that neither order effects, nor "type" of animal influenced the changes induced by LSD-25.

Chlordiazepoxide (Fig. 6)

The effects of chlordiazepoxide on CAR frequencies differed in the L^+NL^- and N^+LN^- conditions, inasmuch as no changes were observed in the former, while a dose-dependent depression appeared in the latter task [treatment $\times$ doses interaction $F(3, 84) = 3.72$, $P < 0.05$]. Statistically significant elevations of ESR frequencies were observed in both situations, with no evidence for dose-dependence [L^+NL^- : treatment $F(1, 154) = 78.83$, $P < 0.01$; N^+LN^- : treatment $F(1, 84) = 13.01$, $P < 0.01$]. The data reported in Fig. 6 suggest that ESR disinhibition was more marked in the L^+NL^- than in the N^+LN^- task. As discussed in the section on Methods, however, the design used did not allow a statistical evaluation of this difference. A slight increase of ITRs reached significance in the L^+NL^- task [treatment $F(1, 154) = 17.61$, $P < 0.01$]. Paired t tests, however, showed that ESR rates after treatment were constantly higher than ITR rates.

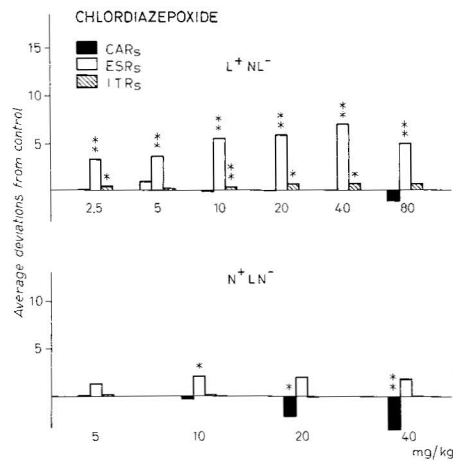


Fig. 6. Effects of chlordiazepoxide hydrochloride in active avoidance-extinction tasks (L^+NL^- , $n = 15$; N^+LN^- , $n = 13$). For other indications see the legend of Fig. 1.

Chlorpromazine (Fig. 7)

The main effect of chlorpromazine in animals with high discrimination performance in the L^+NL^- task was a dose-dependent reduction of CARs [treatment $\times$ doses interaction $F(5, 143) = 19.36, P < 0.01$]. The drug caused also a significant reduction of ESRs (treatment $\times$ doses interaction $F(5, 143) = 2.58, P < 0.05$) and of ITRs [treatment $F(1, 143) = 18.43, P < 0.01$]. The smaller size of these changes, compared to CAR changes, was obviously due to a floor effect, i.e., to the low ESR and ITR baselines. In fact, the tests carried out in rats with high ESR control rates (range of CAR averages 22.2-23.7, range of ESR averages 14.4-18.6) showed a marked reduction of both CARs and ESRs. Since the main purpose of these tests was to assess whether or not chlorpromazine had different effects depending on the two types of responses, an ANOVA using discrimination indexes ($DI = [CARs / (CARs + ESRs)] \cdot 100$) was carried out according to the same design used previously. This analysis showed no significant effects of treatment and no treatment $\times$ doses interaction, confirming the nonspecificity of the drug-induced depression.

The data reported in the two graphs of Fig. 7 suggest a lower sensitivity of CARs to chlorpromazine in animals with high ESR baselines, as compared

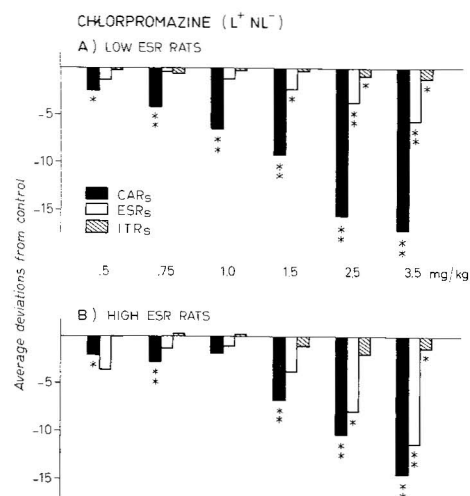


Fig. 7. Effects of chlorpromazine hydrochloride in an active avoidance-extinction task (L^+NL^-). The upper graph shows deviations from control baselines in animals with high discrimination performance ($n = 14$), while the data in the lower graph refer to animals with high CAR and ESR rates ($n = 8$). For other indications see the legend of Fig. 1.

to animals with low ESR baselines. Since the tests in the two types of animals were carried out in parallel, CAR difference scores were used in an ANOVA for repeated measures, which showed no influence of animal "type" on the size of CAR depression.

Physostigmine (Fig. 8)

The main problem when studying physostigmine effects on discriminations is the narrow range between the threshold dose for a facilitating effect (in those situations that allow such an effect) and the threshold dose for overall behavioral depression. Based on the information in the literature and on previous experience in the same laboratory, and considering also the limited number of animals available in experiments like the one reported here, no attempt was made to establish dose-response relations. Sixteen rats with high CAR and ESR frequencies were subdivided into two equal groups. The first of these was given subcutaneous physostigmine daily for 4 weeks, while the second one received injections of water. In the following 4 weeks the treatments were reversed. In each of these treatment series the animals were initially injected with 0.05 mg/kg of physostigmine salicylate sc 30 min before testing. Since after 6 days most animals of the first group showed a slight facilitation of discrimination with no change in CAR frequencies, subsequent treatments used a 0.075 mg/kg daily dose. When the treatments were reversed the same treatment schedule was started. However, after six sessions with 0.05 mg/kg three rats of the second group showed a slight CAR depression,

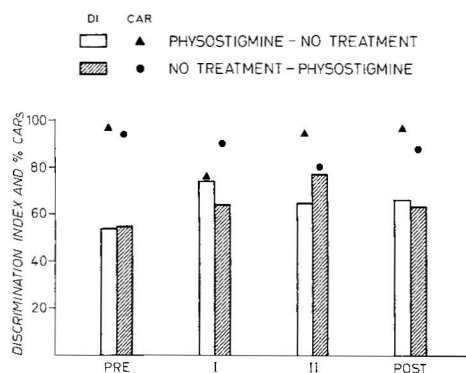


Fig. 8. Facilitation of differential responding by repeated treatment with small doses of physostigmine salicylate (0.05-0.075 mg/kg, sc; see text) in rats with high CAR and ESR baselines ($n = 8$ in each group). The data refer to CAR frequencies and discrimination indexes (DIs) during the last three days in the pre- and post-treatment periods (PRE, POST), and at the end of the first and second part of the cross-over experiment (I, II).

similar to that induced by 0.075 mg/kg in previously treated animals. Therefore it was decided to maintain the dose at the 0.05 mg/kg level in these animals, while raising it to 0.075 mg/kg in the others. This allowed to obtain a slight and balanced CAR depression in both groups, thereby avoiding at least one of the possible biases in the evaluation of the effects of response-depressing treatments on discrimination performance. In fact, the main question was whether or not a reduction of ESRs reliably larger than that of CARs could lead to a facilitation of differential responding. Further testing was carried out for two more weeks after all treatments had been discontinued.

Only the essentials of the results are presented in Fig. 8, showing CAR levels and DIs right before the beginning of the treatment (PRE), at the end of the first (I) and of the second (II) treatment period, and at end of the first week after discontinuation of all treatments (POST).

The reversible physostigmine depression of CARs was confirmed by a Latin square ANOVA on the data from periods I and II [treatment $F(1, 14) = 15.89$, $P < 0.01$]. An ANOVA on DIs showed a facilitation of differential responding which was both reversible and unaffected by order, since significant effects were limited to the treatment factor [$F(1, 14) = 8.68$, $P < 0.01$].

Another type of change was also apparent, which consisted of a slow overall reduction of ESR frequencies, on which the physostigmine facilitation became superimposed. In fact, a trend analysis on PRE and POST data showed a significant increase of the DIs [trials $F(1, 14) = 10.31$, $P < 0.01$].

Discussion

The data reported above can be summarized as follows (see Table 3):

(1) A maximal or near-maximal disinhibition of ESRs was observed with scopolamine and with amphetamine. One of the graphs (Fig. 4), reporting averaged response frequencies instead of difference scores, shows that ESRs became as frequent or almost as frequent as CARs after treatment with these agents, and that response changes were maintained in successive treatment sessions.

(2) In spite of similar ESR enhancements, the amphetamine and the scopolamine profiles showed only a partial overlap, since (a) CAR rates were little affected by amphetamine in well-performing animals, obviously due to a ceiling effect, while a slight, but significant, response reduction was observed after some of the scopolamine treatments; and (b) relative to ESR enhancements, ITR enhancements were much more marked after amphetamine than after scopolamine.

(3) LSD-25 and chlordiazepoxide caused moderate enhancements of ESR

TABLE 3
Summary of the Results Obtained in Locomotor Avoidance Tasks^a

Drugs	Avoidance			Extinction		
	Active (CARs)		Passive	Signaled (ESRs)		Unsignaled (ITRs)
	High baselines	Low baselines & acquisition	Low baselines	High baselines	Low baselines	Low baselines
Scopolamine	0- ^b	+++	+++ ^c		+++	+
Amphetamine	0+	+++	++ ^d		+++	+++
LSD-25 ^e	0+	++	0 ^d		+	0+
Chlordiazepoxide	0-	- ^f	- ^f		+	0+
Physostigmine ^g	0-	0-	0- ^h	--		0-
Chlorpromazine	---	---	0-	---		0-

^aHigh and low baselines indicate response frequencies, and not good or bad performance. Results on passive avoidance, and several of the data on active avoidance, are from Bovet and Gatti, 1963; Bignami *et al.*, 1965; Bovet *et al.*, 1965; Bignami, 1967; Carro-Ciampi and Bignami, 1968; Rosić and Bignami, 1970a, 1970b; Bignami and Rosić, 1971.

^bSee Carro-Ciampi and Bignami, 1968, and Bignami and Rosić, 1971, for conditions which can accentuate the depressant action on locomotor avoidance.

^cIn the L⁺NL⁻ task; for smaller effects in other tasks see Review section; Rosić and Bignami, 1970a; Bignami and Rosić, 1971.

^dData limited to the L⁺NL⁻ task.

^eLimited to low to moderate doses endowed with a mild "stimulant" action (up to 0.1 mg/kg).

^fNo data available; see, however, the facilitation observed in several active avoidance situations, the anticonflict effect, and the disinhibition of passive avoidance reported in various tasks (Review section; Bignami, 1976b; Gray, 1976).

^gLimited to lower doses (up to 0.075 mg/kg), since the overall depressant action of higher doses overshadows the facilitation of differential responding.

^hA more marked deviation from control rate, allowing some facilitation of differential responding during the acquisition of active-passive avoidance discrimination, was observed by Rosić and Bignami, 1970b.

frequencies, which could be clearly distinguished from those induced by scopolamine and amphetamine since response levels during CI-CS compounds remained much below CAR levels.

(4) Chlorpromazine induced a dose-dependent depression of all responses, with the size of this effect depending mainly on pretreatment baselines (i.e., floor effects were obviously responsible for the small changes of ITR rates in general, and of ESR rates in well-performing animals).

(5) The repeated administration of small doses of physostigmine to

animals with little or no differential responding depressed ESRs more than CARs, the net effect being a slight facilitation of discrimination performance.

Several of the changes summarized above provide direct confirmation of some tentative conclusions presented in the Review section, therefore, they will not be discussed in detail. This applies to (i) the maintenance of scopolamine and amphetamine changes over a series of consecutive treatment sessions, confirming that the desensitization observed in the corresponding active-passive avoidance task depended on relearning in the presence of adverse consequences of hyperresponding, rather than on a "genuine" pharmacological tolerance; (ii) the nonspecificity of the response depression caused by chlorpromazine, indicating in particular that the absence of an enhancement of low baseline responses with active-passive avoidance contingencies was not due to high response cost, and therefore supporting an explanation based on psychomotor depression, rather than those based on fear changes, or loss of stimulus control, or associative deficits; and (iii) the facilitation of differential responding by small doses of physostigmine, indicating that the effects of this drug on discrimination are similar in spite of different response-reinforcement relations in no go trials, and can therefore be ascribed mainly to a response change.

On the other hand, several problems raised by some of the findings with scopolamine, amphetamine, LSD-25, and chlordiazepoxide (compare Tables 1, 2, and 3) require to be analyzed in view of an assessment of the heuristic value of alternative explanations. In fact, the scopolamine profile seems to combine the features of both a sensory and a motor change. Amphetamine effects are highly suggestive of a motor bias, but the data discussed in the Review section make it clear that this is due to the particular combination of response and reinforcement factors prevailing in locomotor avoidance discriminations. The LSD-25 profile, although strongly indicative of a drive enhancement or disinhibition, creates perplexities because of the limited size of response enhancements in conditioned inhibition paradigms which should maximize the consequences of such a drive bias. Finally, the partial disinhibitory effects of chlordiazepoxide in active avoidance-extinction tasks create difficulties of interpretation. Due to the marked antipunishment action of the drug in various situations, these changes cannot be ascribed to a drive enhancement or disinhibition, while the low disinhibition asymptotes speak against a widespread response change.

Scopolamine Effects: Inferences on Sensory-Motor Interfaces

The data confirmed previous findings with active-passive avoidance tasks, showing that scopolamine enhancements of low baseline responses to no go signals can take place either without, or with minimal, changes of active avoidance responses. This confirms that not only associative and motivational models, but also sensory changes *per se* ("impaired discrimination," "impaired

stimulus sensitivity"), cannot explain the consequences of central muscarinic blockade. In principle, a response disinhibition model could account not only for an enhancement of previously suppressed responses, but also for a variable interference with high baseline responses (as one of the consequences of response competition). However, the differences between ITR enhancements induced by scopolamine and those induced by amphetamine also pointed out that sensory factors influenced the consequences of the former, more than those of the latter treatment, thereby making it highly unlikely that the scopolamine syndrome can be explained by a genuine motor bias.

In the experiments with active avoidance-extinction tasks the interaction between scopolamine treatment and cue factors was limited to marked differences between response enhancements, respectively, in the presence and in the absence of CI-CS compounds (ESRs versus ITRs), without significant differences between the easier (N^+LN^-) and the more difficult task (L^+NL^-). Vice versa, previous experiments with the corresponding active-passive avoidance tasks had shown a much greater disinhibition in the L^+NL^- than in the N^+LN^- paradigm. In other words, the reduction of response cost allowed a maintenance of marked stimulus nonequivalences in the acquisition phase (Frontali and Bignami, 1974), and also confirmed the general role of cue factors in the scopolamine syndrome (ESR versus ITR enhancements), but eliminated the correlation between task difficulty and size of drug-induced disinhibition.

The different influence of cue arrangement on scopolamine-induced changes, as a function of response-reinforcement relations in no go trials (passive avoidance versus extinction) deserves to be analyzed in some detail, since several alternative explanations appear possible with the present state of knowledge. In the first place, it must be emphasized that the differences in discrimination learning due to opposite stimulus arrangements (L^+NL^- versus N^+LN^-) were superimposed on marked differences due to the contingency in no go trials (much slower development of differential responding in the case of active avoidance-extinction tasks than in the case of active-passive avoidance tasks; Frontali and Bignami, 1974). As a consequence, it appears possible that the absence of treatment $\times$ cue interactions with a conditioned inhibition paradigm was due to limitations inherent in the measurements taken. For example, a lowering of response cost might have been sufficient to increase the drug disinhibition in the N^+LN^- task from a "low" to a "high" level, while a comparable room to demonstrate an equivalent increase in the drug effect was not available in the L^+NL^- task, which showed a high sensitivity even with a passive avoidance contingency.

Vice versa, further tests using more sensitive measurements (e.g., rate measurements during no go signals of longer duration, instead of a yes-no response criterion during brief signals) might indicate that the absence of treatment $\times$ cue interactions in active avoidance-extinction tasks is not an

artifact. In this instance, one should provisionally conclude that (i) non-pharmacological acquisition experiments served mainly to emphasize cue factors which exert a general influence on emission and withholding of locomotor responses in an active avoidance context, to a considerable extent independently of response-reinforcement relations in no go trials, while (ii) scopolamine experiments allowed to show that different mechanisms may underlie locomotor response withholding with different combinations of cues and response-reinforcement relations.

If the high order interaction between antimuscarinic treatment, cues, and response-reinforcement relations is confirmed, further work should be directed to understanding whether the differences due to the contingencies in no go trials are qualitative or quantitative ones. By making reference to the discussion in the Review section, one can define a qualitative difference as one due to a reliance on separate mechanisms for response withholding (e.g., response extinction as a consequence of fear inhibition in the case of differentiation or conditioned inhibition paradigms versus "active" response withholding as a consequence of fear activation in the case of active-passive avoidance paradigms), and to a separation of signaling systems in the two instances (extension of Konorski's hypothesis from positively to negatively motivated tasks). One can also define a quantitative difference as one due to the reception of "strong" punishment for hyperresponding in active-passive avoidance tasks and of "mild" punishment for hyperresponding in active avoidance-extinction tasks (Dąbrowska's explanation of the analogies between avoidance discriminations with symmetrical reinforcement and avoidance discriminations with nonreinforced signals originally eliciting the active avoidance response). Such difference in punishment intensity might well be the cause of shifts in the reliance on one or the other type of sensory-motor interface. It can be emphasized at this point that a wide variety of behavioral tests can be adapted to assess whether particular stimuli have acquired response-suppressing properties mainly via the acquisition of fear-inhibiting properties, or mainly via the aversive properties of their nontermination by the organism's responses, or via both processes, depending on the stage of discrimination learning. Therefore, it appears likely that a closer analysis of the features of response suppression as a joint function of cues and response-reinforcement relations can pave the way towards the understanding of the sensory-motor changes induced by central cholinergic blockade.

The alternative assumptions made above indicate that, whatever the explanation of the differences in treatment effects which have been discussed so far, great caution should be exerted in extrapolating across situations. In fact, it is widely acknowledged that the acquisition and maintenance of various types of active avoidance responses are not amenable to unifactorial models with general validity. For example, the role of pseudoconditioning phenomena, of classically conditioned response changes, and of reinforcement

processes depending on particular response-reinforcement relations can vary not only as a function of cues and responses, but also as a function of apparently less important factors, e.g., the uni- or bidirectionality of a particular locomotor task. As a consequence, one should not be surprised if the properties of reinforced and nonreinforced stimuli, as well as the interactions between treatments, cues, and other test factors, were found to be different in various situations, e.g., one- and two-way avoidance tasks.

Before concluding the discussion on scopolamine one must add that the peculiar features of the antimuscarinic syndrome can contribute to explain the psychodysleptic properties of these drugs in humans, which can be marked by a considerable aversiveness. On the one side, studies with a Garcia paradigm conducted in animals have shown that quaternary antimuscarinics acting mainly, although not exclusively, outside the CNS can be as active as, or even more active than, tertiary compounds with strong central actions (e.g., Berger, 1972; review by Vogel, 1976). On the other side, the available information is insufficient to assess at the present moment whether or not the peculiar changes induced by central muscarinic blockade contribute to the variable aversiveness of the drug experience in humans. The past history of the subject and the context in which the drug experience takes place might well be found to play a considerable role, since the motor-act differentiation deficit often favors outputs that either are irrelevant in the situations in which they are emitted, or have adverse consequences at the reinforcement level.

Amphetamine Effects: Inferences on Reinforcement-Response Interfaces

The marked ESR and ITR enhancements observed in amphetamine-treated animals are in agreement with the tentative conclusions which were drawn in the Review section. In fact, these data point out that when preparedness factors—those descending from locomotor response requirements in a negative reinforcement context—and reinforcement factors—those descending from the active avoidance contingency in part of the schedule—are combined to exert additive effects, then the drug tends to induce a hyper-responding which is, in the average, much less dependent on cue factors than that obtained with scopolamine. On the other hand, ITR enhancements after amphetamine, although constantly more marked than those induced by scopolamine, were not uniform across tasks (L^+NL^- versus N^+LN^-) and/or replications. A closer analysis of individual data indicated that these differences in averaged ITR enhancements (after doses sufficient to induce a maximal, or near-maximal, ESR elevation) were due mainly to a high interindividual variability in the ITR changes induced by amphetamine, relative both to ESR changes after the same drug and to either type of response change after scopolamine. In fact, in some animals there was a considerable overlap of ITR enhancements caused by amphetamine and by scopolamine at doses equiactive on ESRs, while other animals showed much

larger ITR elevations after the former, than after the latter agent (the converse was not observed).

The data so far available, while supporting the expected differences between the scopolamine and the amphetamine syndrome, do not allow definite conclusions about the role of cue factors in the latter syndrome. The tentative inferences in the Review section had been that cue factors might influence amphetamine changes mainly by affecting the balance between the direct stimulation of highly prepared response outputs in a particular drive state and the stimulation of reinforcement mechanisms activated by particular response-reinforcement relations. Therefore, the problem in further research is to identify testing conditions that do not affect amphetamine changes of ESRs, but can induce uniformly higher or uniformly lower response changes in the absence of signals. For example, one could attempt to reduce the reliance on exteroceptive response feedbacks in active avoidance trials by using signals not terminated by responses both in go and in no go trials. The finding of constantly higher ITR levels after amphetamine with these contingencies might suggest that the variability of response enhancements when the active avoidance CS (but not CS in the presence of CI) is terminated by a response is due to interindividual differences in the relative reinforcing values of exteroceptive and interoceptive feedbacks during avoidance acquisition. A countercheck on this type of explanation can be provided by eliminating the ceiling phenomenon descending from constantly high generalization levels in conditioned inhibition paradigms. In fact, the use of graded differences between active avoidance and extinction signals could eventually show whether or not amphetamine hyperresponding in the absence of cues is a function of ESR responding in acquisition, again providing information on drug effects as a function of the feedbacks available for avoidance reinforcement.

A failure to account for the variability of amphetamine hyperresponding in the absence of cues by the approach outlined above might make it necessary to take several steps back, i.e., to reanalyze the role of several factors that can lead to either discrete, or to generalized response enhancements in simple tasks. The experiments in this area (see several examples in the Review section) have so far dealt with differences due to changes in more than one test factor at a time. On the other hand, recent work on bidirectional locomotor tasks has shown that within a given situation one can separate pseudoconditioned response changes (Izquierdo, 1974a, 1974b, 1975, 1976) or classically conditioned response changes (Izquierdo, 1976; Katzev and Mills, 1974) from changes depending on the active avoidance contingency (and therefore, presumably, on a reinforcement mechanism). While amphetamine effects on pseudoconditioned and on avoidance responses have been shown to be in the same direction, it remains to be established whether or not hyperresponding to signals and hyperresponding outside signals remain in

constant relation to one another with the pseudoconditioning, the classical, and the avoidance paradigm.¹⁷

Before concluding the discussion on amphetamine it should be mentioned that the interactions between treatment, response, and reinforcement factors which have been emphasized in the Review section and in the present discussion deserve close consideration when analyzing the effects of this and of similar compounds in humans. In fact, studies of the reinforcing properties of the drug experience have pointed out both rewarding and punishing consequences of amphetamine treatments, with the former shown mainly by self-administration experiments (reviews by Schuster and Thompson, 1969; Schuster and Johanson, 1974), and the latter appearing both in conditioned aversion experiments and in preference tests (Cappell and LeBlanc, 1971, 1973; Carey, 1973; Martin and Ellinwood, 1973, 1974; review by Vogel, 1976; see also the data by Breda *et al.*, 1969, for a possible role of drug aversiveness in learning studies with post-trial injection). This contradiction might depend at least in part on the fact that the amphetamine syndrome includes both an effect on reinforcement systems and a response bias, which depending on situational factors can interact to determine whether the ability to meet reinforcement requirements is enhanced or reduced.

LSD-25 Effects: Drive Changes versus Multifactorial Explanations

As pointed out in the Review Section, the data obtained with LSD-25 in go-no go avoidance tasks are apparently not difficult to interpret, since other things being equal they show significant response enhancements during no go signals with an extinction contingency, but not with a passive avoidance contingency. This profile of effects on discriminations with negative reinforcement, while excluding associative changes as well as sensory or motor impairments considered *per se*, points in the direction of a drive enhancement or disinhibition. However, it is only fair to add that asymptotic response enhancements obtained with LSD-25 in conditioned inhibition paradigms (i.e., in situations marked by prolonged periods of nondifferential responding to CS and CI-CS) were far from dramatic. This may be taken as indirect evidence that fear inhibition by a safety signal (CI) did not have an exclusive role in response suppression, but coexisted with a punishment mechanism activated by nontermination of CS by an avoidance response in the presence of CI (see previous discussion of the inferences by Dąbrowska, 1975).

The drug effect was about the same in the N^+LN^- and the L^+NL^-

¹⁷One of the experiments showing amphetamine enhancements of a punished response in monkeys (see Review section) used a fixed interval schedule with alternating periods of presence and absence of the stimuli paired to shock delivery. In general, low control baselines of S^Δ responding were little modified by amphetamine. In one animal, however, S^Δ baselines were somewhat higher, and amphetamine enhancements were quite marked (Orloff and Stretch, 1975).

tasks, in spite of the marked differences between the two discriminations which have been discussed in previous sections. Furthermore, the incomplete disinhibition obtained rules out the possibility that the absence of treatment $\times$ cue interactions be due to measurement artifacts (e.g., the ceiling phenomena mentioned in the discussion on scopolamine). As a consequence, the drug-induced changes should be provisionally ascribed to an action on drive-modulating mechanisms, rather than to an action on one or the other of several possible interfaces between different types of sensory analyzers and drive centers. With the present state of knowledge, this tentative inference cannot lead to indiscriminate extrapolations, but rather, it should be used as a working hypothesis to design further experiments. In fact, the possibility of an effect on interfaces between sensory and drive mechanisms, rather than on mechanisms responsible for drive inhibition in general, cannot be discarded simply on the basis of discrimination experiments using a particular response, negative reinforcement, and two symmetrically opposite CS and CI arrangements. In this regard, one must mention a preliminary report that places a considerable emphasis on changes in stimulus sensitivity after LSD-25 treatments (Brown and Cooper, 1975), which were measured by an analysis similar to that yielding evidence for sensory changes after antimuscarinics (Warburton, 1972, 1976) and for response changes after amphetamine (Robbins and Iversen, 1973; Warburton, 1976).

Some recent work, although not contradicting a motivational explanation of the changes observed in go-no go and other discrimination tasks (see Review section), also points out that simple (unifactorial) models of LSD-25 effects might constitute a gross oversimplification. This applies in particular to some findings by Izquierdo (1975, 1976), showing that at least part of the avoidance facilitation previously observed by several experimenters can be ascribed to an enhancement of pseudoconditioned and classically conditioned responses. Besides pointing out a partial overlap of the LSD-25 and of the amphetamine profiles (compare, e.g., Vázquez and Izquierdo, 1970; Izquierdo, 1974a, 1975, 1976), some of these experiments also showed substantial differences between the dose-response function for orienting and pseudoconditioned responses (with much larger effects at 0.3, than at 0.075 mg/kg), and that for avoidance responses (facilitated by 0.075 mg/kg and apparently unmodified by 0.3 mg/kg) (Izquierdo, 1975). Furthermore, the adrenergic blocker dibenamine did not affect, or else potentiated, the LSD-25 stimulation of orienting and pseudoconditioned responses. Vice versa, the same agent antagonized the stimulant effect of the smaller dose on avoidance, and led to a marked antiavoidance action of the 0.3 mg/kg dose.

The data mentioned above obviously suggest that separate LSD-25 induced changes are responsible, respectively, for a "hyperreactivity" bias and for an "amphetamine-like" bias, which depending on the dose can work either in the same direction, or in opposite directions. The former change is also

supported by studies showing an enhancement of startle responses by the drug (Miliaressis and St. Laurent, 1974; Davis and Sheard, 1974). The present discussion cannot be extended to the complex biochemical changes induced by LSD-25, nor to systematic comparisons between its behavioral effects and those of agents that interfere with central 5HT system functions. It should be pointed out, however, that the latter drugs induce a hyperreactivity syndrome which differs both from the amphetamine stimulation and from the antimuscarinic disinhibition, while the partial overlap between their effects and those of LSD-25 seems to confirm that the hallucinogen profile depends both on antiserotonergic and on sympathomimetic properties.

The above considerations can lead to two provisional conclusions, showing the considerable interest of further work with LSD-25. The first, is that one-factor models, such as the one based on drive disinhibition or the one proposed by Swonger and Rech (1972; see Review section), might well constitute "neuropsychological artifacts" created by the coexistence of two separate effects, especially at low doses causing response enhancements which appear to be easily controlled by an increase in response cost. The second conclusion is that a provisional acceptance of both one- and two-factor models as working hypotheses can have remarkable heuristic value. In fact, the former should lead mainly to an extension of the work on both classical and instrumental discriminations, with different stimuli, responses, and reinforcers, considering (i) the evidence on antagonistic relations between consummatory and preparatory outputs, which can help separating genuine drive-disinhibition phenomena (attenuation of nonreinforcement consequences in a context of previous or concurrent reinforcement) from shifts in the balance between the activities of different drive systems (Konorski, 1967; Soltyśik and Gasanova, 1969; Soltyśik, 1975); (ii) the evidence on differences between nonreinforced stimuli with exclusive drive-inhibiting properties and those with mixed excitatory and inhibitory properties (Konorski, 1967), which can help separating a genuine drive disinhibition from a drive enhancement mimicking it; and (iii) the evidence on differences between stimuli with specific inhibitory properties on a particular drive system and those with less specific inhibitory properties acquired in "latent inhibition" paradigms (Rescorla, 1971), which can help separating drive disinhibition from changes in stimulus sensitivity of an "attentional" kind.

On the other hand, two- or more-factor models require in the first place an extension of drug interaction studies, along the lines suggested by the work of Swonger and Rech (1972) and of Izquierdo (1975). In fact, once the relative role of noradrenergic-dopaminergic components on one side, and of antiserotonergic components on the other side, has been clarified by investigations on various response changes induced by LSD-25, drug interaction studies might be extended to selected situations of a more complex type. This could eventually lead to a closer understanding of the mechanisms underlying

the peculiar disinhibition phenomena induced by LSD-25, which appear to have a remarkable interest in view of the unique psychodysleptic properties of the drug. In fact, it is conceivable that a reappearance of drive changes upon exposure to stimuli which had lost significance by extinction can lead either to positive, or to negative experiences, depending on the interactions between the past history of a given subject and the particular context in which the treatment is received.

Chlordiazepoxide Effects: The Need for Alternative Models

The data on chlordiazepoxide reported in the section on Results show a moderate ESR disinhibition in both active avoidance-extinction tasks. A slight CAR depression was also observed in the N^+LN^- task, which might help accounting for the fact that responses to CI-CS seemed to be somewhat less affected with the N^+LN^- than with the L^+NL^- stimulus arrangement. Moderate reductions of high baseline avoidance responses of various kinds have often been reported in benzodiazepine studies using pretrained animals (see the papers and monographs quoted in the Review section). Although the CAR depression was a limited one in the go-no go experiments reported above, it appears difficult to understand why it was observed only in the task using the more salient stimulus as the active avoidance CS. Of some relevance in this regard seem to be the data showing a benzodiazepine interference with pseudoconditioned responding to noise stimuli in shuttlebox tests (Izquierdo, 1974b). Therefore, the data on CAR frequencies in go-no go discriminations could be used to confirm that active avoidance learning relies more on highly prepared responses to particular stimuli in a particular drive state ("pseudoconditioning") and less on reinforcement mechanisms, with acoustic cues as compared with visual cues. This, of course, represents a highly tentative inference which is made here simply to underline the potential usefulness of further drug experiments on pseudoconditioning and avoidance learning with different combinations of cues and responses.

The finding of an ESR enhancement by chlordiazepoxide in active avoidance-extinction tasks confirms the widespread disinhibiting effects obtained with benzodiazepines in situations with either positive or negative reinforcement. By making reference to the data mentioned in the Review section, one can therefore subdivide behavioral changes induced by benzodiazepines into well-defined categories, i.e., (i) response enhancements which are explained most economically by a drug interference with suppression by response-contingent punishment (e.g., in conflict tasks and in particular types of avoidance tasks); (ii) various changes in the consequences of reward reduction, which can be explained either by an antipunishment model (according to a fear = frustration hypothesis; Gray, 1976), or by a direct effect on the mechanisms controlling the relations between consummatory and nonconsummatory activation and inhibition; and (iii) response changes directly

opposite to those that one would expect on the basis of an antiemotional or antipunishment model (e.g., in classical and instrumental differentiations with negative reinforcement; in some experiments measuring fear extinction).

A closer analysis based on some of the tentative inferences by Dąbrowska (1975), concerning possible analogies between some active avoidance-extinction tasks (those in which a nonreinforced signal is originally responded to) and the corresponding active-passive avoidance tasks, suggests that benzodiazepine-induced changes belonging to the last one of the groups outlined above might have to be further subdivided into two subgroups. In fact, if emotional changes triggered by nontermination of a nonreinforced fear-eliciting signal by an avoidance response, rather than fear inhibition, are responsible for suppression, then the benzodiazepine disinhibition in several situations would remain compatible with an antipunishment model (e.g., in active avoidance-extinction tasks).¹⁸ Vice versa, other results suggesting a retardation of fear extinction (Kumar, 1971; Kamano, 1972; Ziskind *et al.*, 1974), or showing a disinhibition of responses to nonreinforced signals in classical differentiations (Hidalgo *et al.*, 1968; Yamaguchi and Iwahara, 1974) are entirely incompatible with a model based on attenuation of punishment suppression. Therefore, further tests to assess the generality of these changes and to control with greater accuracy for confounding factors such as state dependence, appear to be essential in order to understand the mechanism of action of the compounds.

The rest of the present discussion should examine the possibility that the results of additional work along the lines suggested above will speak against the general validity of the antipunishment model, and therefore, that other explanations will have to be put to a test not only with regard to drug effects on negatively motivated behaviors, but also with regard to other types of changes (e.g., the attenuation of some consequences of nonreward). At this point, however, one must realize that alternative working models have never received sufficient attention, therefore, the only safe inferences are negative ones. For example, the use of a general disinhibition model without further qualifications (Hasegawa *et al.*, 1973; Yamaguchi and Iwahara, 1974) is to be rejected, since there are striking examples of responses which are readily disinhibited by some treatments, but not by benzodiazepines, and vice versa (e.g., the operants suppressed by a classical food CS reappear after amphetamine but not after benzodiazepines, while the converse applies in the case of punishment suppression; Miczek, 1973b). Furthermore, even if one could

¹⁸Of course, this may apply to the moderate disinhibition observed in the experiments reported above, particularly if evidence will be provided that (i) both a punishment and a fear extinction mechanism play a role in successive phases of active avoidance-extinction learning, and (ii) that the moderate chlordiazepoxide disinhibition can be ascribed to an interference with the punishment component, while the LSD-25 effect is due to an interference with the fear inhibition component.

show that the benzodiazepine attenuation of nonreward consequences is best explained by effects on the mechanisms that govern the relative strength of consummatory and nonconsummatory responses (Konorski, 1967; Soltysik and Gasanova, 1969; Soltysik, 1975), rather than by an interference with the emotional consequences of nonreward (Gray, 1976), still one would be at a loss when attempting to explain some of the changes in negatively motivated behaviors (e.g., the avoidance enhancements in some two-way and lever-press tasks). In this context, it can be underlined that even provisional working models with undeniable heuristic value have never been used to generate testable predictions. For example, a closer understanding of benzodiazepine effects on alimentary behaviors should rely not only on conventional measurements of appetitive (instrumental, operant) and consummatory responses, but also on the use of paradigms that allow to separate the activation of various outputs in the appetitive-consummatory continuum (Ellison and Konorski, 1965; Konorski, 1967; Kierylowicz, Soltysik, and Divac, 1968; Miyata and Soltysik, 1968, 1971); and this, independently of whether or not one is favorable to an antipunishment explanation of benzodiazepine influences on nonreward consequences.

Some of the neurophysiological features of the benzodiazepine syndrome lead to still other tentative models of behavioral changes which, however, must remain highly speculative ones for the moment. The compounds exert profound effects on neural mechanisms responsible for motor control at several levels, as shown both by the anticonvulsant action, and by the muscular relaxant properties. The latter suggest that one should assess whether or not at least part of the behavioral changes can descend from an interference either with the discriminability of proprioceptive response feedbacks, or with the ability to use such feedbacks for one or the other type of behavior control. In fact, the relative reliance on exteroceptive and proprioceptive cues in differential responding is amenable to experimental manipulations, and this not only by comparing classical and instrumental situations of various types, but also by using instrumental tasks that allow a reliance more on one, or on the other, of several sensory systems.

The general considerations in the previous paragraph are not to suggest that one should abandon working models based either on emotional consequences of nonreward, or on the relations between nonconsummatory and consummatory activation mechanisms, but rather to point out that experiments can be planned so as provide essential information on feedback utilization. As discussed in the Review section, the greater activity of benzodiazepines in conflict than in CER tests could be explained by the different involvement of response feedbacks in the two types of situations. Alternative explanations, however, are available (e.g., Huppert and Iversen, 1975), therefore other tests are necessary, using a broader range of behavioral

situations. For example, the alternation of reinforced and nonreinforced components (or more and less favorable reinforcement conditions) in several operant schedules can lead to different types of "inhibitory" consequences, depending on the experimental conditions. After some earlier evidence apparently pointing to the contrary, U-shaped (inhibitory) gradients around S^Δ have now been shown to occur even after discrimination training without "errors" (i.e., without responding upon first exposure to the nonreinforced signals) (Karpicke and Hearst, 1975), which extends to operant situations the findings on the "primary inhibitory stimulus" obtained in discrete-trial situations (see summary and discussion in Konorski, 1967). By definition, these gradients are established independently of the association of proprioceptive response feedbacks with nonreinforcement during S^Δ . Vice versa, peak shifts (i.e., a displacement in generalization tests of the highest response rate away from the former S^D , in a direction opposite to the former S^Δ ; Terrace, 1972) take place only when an S^Δ has been originally responded to. Therefore, this phenomenon is strictly related to the fact that the "true" S^Δ is a compound made up of the exteroceptive nonreinforcement signal and of the proprioceptive feedbacks of the response reinforced in S^D . Consequently, any data showing that inhibitory gradients centered around S^Δ and peak shifts are affected by drug treatment either similarly, or vice versa dissimilarly, would allow to understand whether or not benzodiazepine effects on "inhibitory" mechanisms are strongly tied to feedback discriminability and/or utilization in situations far removed from the CER and conflict tasks more often used.

Finally, it should be underlined that clinical data on benzodiazepines can only confirm the need for the above type of analysis in experimental animals. In fact, these data are compatible both with explanations based on antiemotional effects, or on antipunishment effects, and with explanations assigning a major role to a drug effect on feedback processing. In particular, it has been so far impossible to divorce direct effects of tranquilizers on "emotions" from effects mediated by an interference with "vicious circles" involving response feedbacks, e.g., the abnormal muscular tension initiated by anxiety, which leads to an aggravation of the anxiety state itself. Benzodiazepines clearly act as positive reinforcers in many human subjects, as shown by the increasing concern with overprescription, or even uncontrolled self-medication. On the other hand, experimental studies investigating the US functions of these drugs have pointed out a queer mixture of negatively reinforcing effects, of positively reinforcing effects, and of attenuation of conditioned aversions obtained by using agents such as lithium and amphetamine as the US (Cappell, LeBlanc, and Endrenyi, 1972, 1973; Cappell and LeBlanc, 1973). Therefore, a closer understanding of the mechanisms of action of benzodiazepines in animals appears to be essential both for a more

rational use in therapy, and for a control of abuse phenomena in an overmedicated society.

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