Conditioning of Successive Adaptive Responses To The Initial Effects of Drugs*

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Abstract—Data in the literature indicate that conditioned responses (CRs) generated by repeated pairing of conditional stimulus (CS) with administration of a neurotropic drug may resemble its unconditional effects or they may be opposite in direction; furthermore, the CRs may change as such pairings are continued. In explanation, it is hypothesized that as in conditioning of physiological reflexes, a CS repeatedly paired with administration of a neurotropic drug eventually comes to activate central "processing" events that are evoked by the "stimulus" properties of the drug, *i.e.*, the effects of the drug at receptor sites inside or outside the pia mater which lie in the afferent arms of "reflex" neural circuits; or, the CS comes to activate central processing events that are evoked by centripetal feedback responses to the effects of the drug at receptor sites in the processing or efferent arms of reflex neural circuits. Depending on the receptor site action of the drug, the conditioned autonomic and/or neuromuscular responses that are observed may be in the same direction as, or opposite in direction to the unconditioned effects of the drug. With continued pairings of CS and drug, the unconditioned processing events evoked by the stimulus properties of the drug, and hence the CRs also, change in consequence of compensatory (sometimes "overshooting") biochemical alterations proximal to the receptor site of action of the drug, induced by negative or positive neuronal feedback mechanisms. These concepts are utilized in a theory of opiate addiction and relapse.

I OWE THE PRIVILEGE of participating in this Symposium to Dr. Perez-Cruet who invited me to "speculate in public" on a concept that has intrigued me for some 25 years (Wikler, 1948). Lest it sound stranger than I think it is, allow me to develop the concept from some elementary principles, even at the risk of boring you with repetition of the obvious. (1.) The nervous system can be conceived as an integrated organization of neural circuits consisting of an afferent arm (the neurons of which may be outside or inside the pia mater), a central processing arm, and an efferent arm which ultimately innervates somatic and autonomic effectors. (2.) Through eons of evolutionary development, changes in the external or internal environment have come to function as unconditioned stimuli (USs) which activate or de-activate the afferent arms of such cir-

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cuits, thereby evoking central processing activities and peripheral effector responses (URs) which we judge to be "adaptive". Bulbospinal reflexes are the simplest examples of such adaptive responses to stimuli, but at least for present purposes, the term reflexes is extended to include all inborn responses to stimuli as defined above, wherever their sites of neuronal activation or de-activation may be (*e.g.*, chemoreceptors, osmoreceptors, thermoreceptors, etc. inside the central nervous system, as well as chemoreceptors, baroreceptors, other interoceptors and exteroceptors outside it). (3.) When a "neutral" stimulus is paired repeatedly with a US, what become conditioned are central processing activities identical with, or similar to those evoked by the US. Eventually, this procedure results in evocation of a conditioned response (CR) by the previously neutral, but now conditional stimulus (CS). Such CRs are also usually judged to be adaptive, but through the process of schizokinesis and autokinesis (Gantt, 1953), they may become "maladaptive." (4.) The biologically foreign chemical substances we call "psychotropic drugs" may act on the afferent, the processing, or the efferent arms of neural circuits under consideration, or on two or all three of them, but by analogy with conditioning of reflexes, it is postulated that *only those drug effects are conditionable which are consequences of the unconditioned "stimulus properties" of those drugs, i.e.*, their ability to activate or de-activate neurons in the afferent arm, thereby evoking processing activities and efferent responses that are identical with or similar to those evoked by "natural" stimuli. In the cases of drugs that act, not on the afferent, but on the processing or efferent arm, or at effector sites, CRs may be developed, given the proper temporal continguities, through consequences of such initial drug effects as result in unconditioned "feedback" activation or de-activation of afferent arms of the same or of diffrent circuits. However, such CRs are not identical with or similar to the initial drug effect; rather, one would expect them to be opposite in sign—"conditioned adaptations" to the initial "drug effect." (5). In the presence of a "foreign" chemical (*i.e.*, drug) at neuronal receptor sites, unconditioned bio-feedback mechanisms, normally evoked by consequences of "natural" stimulation, are called into play, counteracting the effects of that drug at those receptor sites, and it is postulated that on repeated administration of a given drug, such "counteradaptations" may become intensified and even overshoot. Furthermore, depending on the drug and the capacity of the organism to develop them, new unconditioned counteradaptations may be mobilized which, may likewise overshoot. Such counteradaptations are generally thought to underlie the phenomena of tolerance with physical dependence (Wikler, 1972). (6). It is postulated still further that, in consequence of such progressive

counteradaptations, the processing activities evoked by the unconditioned stimulus properties of certain drugs, and the CRs that develop with continued pairing of a CS with administration of such drugs, change over a period of time. Thus, when a CS is paired with such a drug repeatedly but at long intervals between drug administrations, the CR that is generated may resemble the initial UR evoked by the stimulus properties of that drug, but if the intervals between drug administrations are short, the CS may evoke a counteradaptive CR, generally opposite in sign to the initial UR (unconditioned adaptive response) and the initial CR (conditioned adaptive response).

Searching the literature in the 1940's for evidence that might support this concept, I found a report by Kun and Horvath (1947) entitled, *The Influence of Oral Saccharin on Blood Sugar.* These investigators found that oral administration of .05 gm of saccharin dissolved in 80 ml of water, given either in a single dose or in four divided doses at 10 min intervals, produced in human subjects (total N=15) a drop of 12-16 per cent (from control values) in blood sugar levels, maximal at 30 minutes and persisting through 40 minutes after the single dose, but persisting through 75 minutes after the divided doses. At these times, the differences from blood sugar levels after drinking water were significant at P values ranging from < 0.02 to < 0.001 (by the Fisher t test), and the investigators suggested that "this phenomenon is due to the sweet taste, which may act as a reflex mechanism to induce insulin secretion." I would prefer to interpret the phenomenon as an example of a second order conditioned adaptive response, inasmuch as saccharin, *per se,* is not known to have any pharmacological actions, and therefore its hypoglycemic effects must have been exerted by the similarity of its taste to that of sugars which, through a lifetime of conditioning, had come to evoke insulin secretion, a reflex adaptive response to postprandial hyperglycemia.

However, some of the more recent findings in the area of blood sugar regulation do not seem to fit the conditioned adaptive response concept. Thus, in rats, Balagura (1968) reported conditioning of glucagon-induced hyperglycemia to the injection procedure, and Woods *et al.* (1968) found that insulin-induced hypoglycemia could be conditioned to a complex CS. Also, Woods, *et al.* (1970) reported evidence that such conditioned hypoglycemia is due to conditioning of insulin secretion, and Woods *et al.* (1972) were able to reproduce both of these conditioned responses after repeated injections of tolbutamide, instead of insulin. It may be remarked, however, that the physiological mechanisms by which these hormones alter blood sugar levels are still incompletely understood. Thus, very recently, Woods (1972) reported that conditioned hypoglycemia,

produced by repeated pairings of a complex CS with insulin injections, could be prevented by bilateral (cervical) vagotomy performed two weeks prior to the conditioning sessions, or by subcutaneous injection of atropine methyl bromide (5 mg/kg) 20 minutes before the testing trial (Guanethidine, 15 mg/kg, given intraperitoneally two hours before testing, did not prevent the appearance of conditioned hypoglycemia). Woods (1972) suggests that conditioned hypoglycemia (to injections of insulin) is mediated by the vagus nerves, which cause secretion of insulin from beta pancreatic cells either through direct synaptic connections, or indirectly through release of a hormone, most likely secretin, from the gut, which in turn causes insulin secretion. Fitting either of these concepts is the fact that vagotomy abolishes the normal gastric response to hypoglycemia (Anand, 1967), thus providing a possible neural (synaptic) circuit for the conditioned response. Teleologically, however, a conditioned hypoglycemic response, generated by a hypoglycemic US, is not an adaptive one. But where, in nature, does a neutral stimulus come to be paired with insulin injections? Viewing the regulation of blood glucose levels from a "naturalistic" standpoint, one would expect that the intricate neuro-endocrinal mechanisms, involving the pancreas, the liver and the adrenal gland (both medulla and cortex), as well as the anterior pituitary gland, should be under at least partial control by higher central nervous system activity, and that such control should be "adaptive." In keeping with this expectancy, is the observation that ". . . hyperglycemia produced in an isolated dog's head, connected to the body only through the nerve supply, results in hypoglycemia of the body . . ." (Anand, 1967). One would further expect then, that natural concurrence of a neutral stimulus with eating, especially of carbohydrates, would eventually result in the generation of an "anticipatory" hypoglycemic response to that CS (Kun and Horvath, 1947). In the laboratory, we may isolate one or another of the components of the complex regulatory process and condition it maladaptively (*cf.* results of Balagura and of Woods *et al.*). However, in keeping with the principle of "biological adaptation," it would be interesting to see if, after *prolonged* pairing of a neutral stimulus with administration of insulin or tolbutamide, initial conditioned hypoglycemia gives way subsequently to conditioned hyperglycemia, through conditioning of *successive* adaptive responses to the "initial" effects of these agents; and conversely, conditioned hypoglycemia in the case of glucagon.

The literature search also revealed that, as would be expected from the concept, the "direct" effects of peripherally acting drugs could not be conditioned. Thus, Gantt *et al.* (1937) could not condition adrenalin hyperglycemia in dogs or rabbits; in the latter

species, they remarked that (p. 405), ". . . an increase of the glycemia after the saline injection was observed in only seven experiments (26%); there was often a decrease after the saline . . ." Unfortunately, how often a decrease after saline injection was observed cannot be inferred from the tabular data. Likewise, Kleitman (1927) could not condition pilocarpine salivation in dogs. The method he used was to inject 0.5 mg/kg of pilocarpine (initially i.v., then s.c.) every other day, and measure rates of pre-injection salivation. Not surprisingly, he found that "during the 15 minutes that the animals spent in the stand prior to receiving pilocarpine, not one drop of saliva was secreted in the entire period of this study" (p. 687). It would have been interesting to know if dogs receiving saline injections only on the same schedule and under the same conditions secreted at least a few drops of saliva during the pre-injection periods. On the other hand, Finch (1938a), using a similar but technically more refined method, did detect very small but incremental secretions of saliva during comparable periods before injection of pilocarpine, but no saline-injection controls appear to have been used.

It occurred to me then (Wikler, 1948) that, rather than looking for conditioned less-than-normal salivary secretion after repeated injections of pilocarpine, it would be easier to look for conditioned more-than-normal salivation after repeated injections of atropine. Accordingly, a subcutaneous injection of atropine was given each morning to four dogs and four cats in their individual home cages. The doses ranged from 0.5–10.0 mg/kg for the dogs, and 0.5–5.0 mg/kg for the cats. No attempt at quantification of the salivary response was made, but the degree of salivation was estimated roughly in terms ranging from "mouth dry," to "moist," to "sopping wet," to "profuse and ropy." Observations for evidence of conditioned salivation were made just prior to injection of atropine (or, later, saline) each morning, *i.e.*, approximately 24 hours after the last previous injection. Conditioned increase in salivation was observed in every animal as early as the fifth day, but the intensity and stability of the phenomenon varied greatly. Generally, the earliest sign of conditioned salivation was seen immediately after the subcutaneous injection of atropine. As daily injections of atropine continued, the animals were observed to salivate just before the scheduled injection; in two of the dogs, this occurred at sight of the needle and syringe, and in one of the cats, immediately after transfer to the table on which the cats were placed for their injections. After a variable period of daily atropine injections, salivation to saline injections was noted in all of the animals, but this response extinguished eventually when saline injections were permanently substituted for atropine. One "control" cat was given saline injections

only for 73 days; no salivation was observed except on the 28th and 42nd days (after the saline injection).

While these experiments were in progress, I learned that Mulinos and Lieb had described conditioned salivary responses in chronically atropinized dogs and cats in 1929, and that Finch (1938b) had confirmed his results. Mulinos and Lieb (1929) attributed this phenomenon to conditioning of a "stimulant" effect of atropine on the medulla oblongata, while Finch (1938b) offered no explanation. Aside from the lack of evidence for any "stimulant" effect of atropine, Mulinos and Lieb's explanation seems untenable, inasmuch as Korol *et al.* (1966a) demonstrated conditioned salivation to atropine methyl nitrate (which exerts far greater anticholinergic effects peripherally than centrally), as well as to atropine sulfate. They also investigated the physiological mechanisms involved in the genesis of this phenomenon. They observed that, after repeated intravenous injections of atropine or methylatropine (in dogs), conditioned mydriasis developed *pari passu* with the development of conditioned salivation. Similar development of conditioned mydriasis and conditioned salivation on repeated administration of the complex anticholinergic compound, Ditran, was also reported by Lang *et al.* (1966b). Noting that pre-treatment with the alpha-adrenergic blocker, phenoxybenzamine, selectively inhibited the mydriatic response, while the beta-adrenergic blocker, propranolol, preferentially inhibited the salivary response, Korol *et al.* (1966a) concluded that ". . . the salivary and mydriatic responses resulted from conditional physiological adaptation mediated through a central sympathetic reflex with efferent alpha and beta adrenergic pathways."

Consistent with this conclusion is the finding that in the dog, the catecholamine receptors in the submaxillary gland are exclusively of the beta-adrenergic type (Emmelin and Holberg, 1967) although in the rat, they are of both the alpha- and the beta-adrenergic types (Emmelin *et al.*, 1965). However, it should be noted that, in the dog, the conditioned salivary response to atropine is also blocked by atropine or Ditran, (Lang *et al.*, 1966b). Further complicating interpretation of the functional significance of conditioned salivation to atropine are the well known facts that chronic atropinization results in "pharmacological denervation supersensitization" of the salivary gland to both acetylcholine and to catecholamines (Emmelin *et al.*, 1951, 1952; Emmelin, 1961) and that "paralytic secretion" (unconditioned) can be induced by a variety of procedures (asphyxia, parenteral injection of cocaine or morphine) that induce a centrally initiated downward discharge to the adrenal medulla, with consequent elevation of circulating catecholamine levels (Emmelin *et al.*, 1951; Emmelin, 1952). The question at issue is whether the

conditioned salivary response during chronic atropinization represents an unconditioned potentiation (by salivary gland "supersensitization") of a specific conditioned, central adaptation to peripheral blockade of salivary secretion, or merely a non-specific conditioned, central adaptive response to noxious stimulation. Perhaps this question could be answered by supersensitizing the salivary glands of dogs by daily *uncued* injections of atropine through permanently indwelling intravenous catheters, bringing the dogs into experimental chambers at random times of the day for subcutaneous injections of some drug that produces noxious but neither anticholinergic nor cholinergic nor antiadrenergic nor adrenergic effects, and then testing them periodically 24 hours after the last previous dose of atropine in the experimental chambers before and after subcutaneous injection of normal saline. If conditioned salivation fails to develop, then the non-specific hypothesis can be rejected in favor of the specific one. Then one would have to contend further with the problem of the role that central supersensitization to acetylcholine (Friedman and Jaffe, 1969; Friedman *et al.*, 1969) may play in the development of a specific conditioned salivary response to atropine. Perhaps this could be evaluated by comparing the rates and degrees of development of conditioned salivary responses to atropine and to methylatropine.

In the cases of drugs acting on biogenic amine receptors in the salivary glands, the adaptive conditioning hypothesis would predict that the conditioned response should be *opposite* in direction to the direct consequences of the initial effects of such drugs on those receptors. However, in the cases of many drugs, the observed unconditioned physiological consequences are, in part, compensatory or adaptive responses to such initial receptor effects. In such instances, the hypothesis would predict that the conditioned responses should be in the *same* direction as the unconditioned responses. Thus, using dogs with exteriorized carotid arteries in skin loops, Lang *et al.* (1967) repeatedly sounded a buzzer (CS) for a fixed period of time before and during intravenous injection of 5 per cent glyceryl trinitrate or 1 per cent phentolamine hydrochloride (US). Eventually, the CS alone evoked responses smilar in direction to those of the US, namely tachycardia, certain characteristic changes in the electrocardiogram, and fall in blood pressure. Lang *et al.* (*loc. cit.*) note that both glyceryl trinitrate and phentolamine lower blood pressure through direct vasodilatory actions, and that the cardiac changes produced by these drugs appear to be central reflex mechanisms compensating for the fall in blood pressure. They also suggest that ". . . the conditioned fall in blood pressure is also a compensatory feed-back mechanism in anticipation of a rise in blood pressure due to conditional tachycardia caused by inhibition

of vagal tone. The dilation and hypotension may be due, therefore, to excessive inhibition of sympathetic constrictor tone occurring as an adaptive over-compensation."

On first consideration, it would seem that the famous experiments of Podkopaev with apomorphine and by Krylov with morphine (Pavlov, 1927) yielded results that are incompatible with the conditioned adaptive hypothesis as it applies to drugs. Thus, repeated pairing of an auditory CS with apomorphine eventually produced, in dogs, moistening of the lips, salivary secretion and "some disposition to vomit" upon presentation of the CS alone. Likewise, repeated subcutaneous injections of morphine produced, in dogs, signs of ". . . nausea, with profuse secretion of saliva, followed by vomiting and then profound sleep" when the dogs merely witnessed the preparations for the injection, or received an injection of some "harmless fluid." Conditioned salivation to morphine was also observed by Collins and Tatum (1925) and by Kleitman and Crisler (1927). However, since the classical investigations of Wang and Borison (1950) and Wang and Glaviano (1954), we know that apomorphine and morphine induce emesis, not by a direct action on the medullary vomiting center, but by indirect (reflex) activation of this center through actions on the medullary chemoreceptor trigger zone. The anatomical-physiological basis of morphine-salivation, as such, appears not to have been investigated, but its close temporal association with morphine-emesis suggests the likelihood that this phenomenon, too, is a reflex response to an interoceptive action of morphine. Hence, conditioned vomiting and salivation to morphine can be regarded as examples of conditioning of adaptive responses to the direct effects of these drugs. As for conditioned morphine-sedation or sleep (Krylov, in Pavlov, 1927; Levitt, 1964), it may be pointed out that among the depressant actions of morphine are those on the ascending reticular activating system (ARAS) (Sawyer *et al.*, 1955; Silvestrini and Longo, 1956; Gangloff and Monnier, 1957). In theories relating the ARAS to sleep-walking mechanisms, little is said about how depression of this nonspecific sensory tract results in the neuromuscular-autonomic changes that define sleeping, or conversely, how excitation of the ARAS produces the signs of waking. Obviously, the ARAS is only the afferent arm of a circuit that must include central processing and efferent arms that control the activities of the cranial nerve and spinal somatic motor and autonomic nuclei. Hence, unconditioned morphine-sleep may be regarded as a reflex response to decreased non-specific sensory input, and in accordance with the conditioned adaptive hypothesis, one would expect that morphine-sleep should be conditionable. For analogous reasons, the hypothesis would predict that amphetamine-arousal (with increased activity) should be condition-

able, inasmuch as it has been shown that amphetamine exerts an excitatory action on the ARAS (Elkes *et al.*, 1954). Evidence for the conditionability of the activity-enhancing and activity-depressing effects of various drugs has been reviewed very recently by Pickens and Dougherty (1971).

It has been stressed that at least certain of the signs of the unconditioned effects of centrally acting drugs are reflex or adaptive responses to their initial actions. However, in the cases of many drugs, the organism is capable developing new, successive adaptations to such initial actions when the drug in question is administered repeatedly, especially at short intervals. Such counteradaptations are intimately involved in the development of tolerance, with or without physical dependence. One such counteradaptation, originally demonstrated for certain barbiturates, is hepatic microsomal enzyme induction (Conney, 1967) which produces some degree of tolerance without physical dependence. Very recently, Roffman and Lal (1972) reported that mice subjected repeatedly to a CS (airflow) paired with acute hypoxia which, unconditionally, produced hypothermia and prolongation of hexobarbital narcosis, eventually responded to the CS alone with opposite phenomena (hyperthermia, shortening of hexobarbital narcosis and enhancement of *in vivo* hexobarbital metabolism). There was no evidence of conditioned induction of hepatic drug-metabolizing enzymes, but inasmuch as propranolol blocked the conditioned enhancement of hexobarbital metabolism, these investigators hypothesized that the response was mediated by activation of an unbound beta-adrenergic receptor; on the other hand, conditioned hyperthermia appeared to be mediated by release of adrenal epinephrine, since this response was blocked by phenoxybenzamine, and conditioned hyperthermia did not develop in adrenal-demedullated mice. Roffman and Lal *(loc. cit.)* interpret their results in terms of "operant" conditioning of compensatory temperature-elevating and drug-metabolizing mechanisms. However, inasmuch as in their studies presentation of the US (or, in operant terms, the "reinforcer") was not contingent on "emission" of the to-be-conditioned behaviors (hyperthermia, shortening of hexobarbital narcosis and increased hexobarbital metabolism), their procedures actually conformed to the classical conditioning paradigm. In my opinion, the neural mechanisms of classical and operant conditioning are the same, the phenomenological differences being due to the differences in what is reinforced: a reflexly-elicited UR in the case of classical conditioning, and an emitted UR in the case of operant conditioning, the *reinforcing event* in *both* cases being the delayed activation of rewarding or punishing limbic structures that follows presentation of the US and the UR which the US elicits. If this surmise is correct, then two behaviors are con-

ditioned in operant conditioning: the emitted behaviour in which the experimenter is interested, and the UR elicited by the reinforcer (US) in which he is usually not interested. Exceptionally, Shapiro (1960) recorded parotid salivary secretion as well as lever presses during acquisition of food-reinforced responding in dogs, and found that not only the emitted lever presses, but also the respondent salivary secretion became conditioned. Stein (1964) has offered an interesting suggestion about how such postulated delayed activation of limbic structures may be the critical reinforcing event (p. 94): "Pairing an operant response with reward may be viewed as an instance of Pavlovian conditioning. Response-related stimuli (environmental as well as internal) are the conditioned stimulus and the reward is the unconditioned stimulus. By virtue of the pairing, the medial fore-brain bundle *go* mechanism is conditioned to response-related stimuli. Thus, on future occasions, any tendency to engage in the previously rewarded behaviour initiates facilitatory feedback by an activation of the *go* mechanism, and thereby increases the probability that the response will run off to completion. In the case of punishment, periventricular activity is conditioned to stimuli associated with the punished operant. This decreases the probability that the operant will be emitted in the future because feedback from the *stop* mechanism will tend to inhibit the behaviour." As Stein points out, this mechanistic model could explain the "teleological" concept of "expectation of reinforcement" in terms of a conditioned reflex. Be this as it may, Roffman and Lal's findings can be recast in terms of classical conditioning as follows: US, hypothermia and prolongation of hexobarbital narcosis due to direct, unconditioned effects of hypoxia (at 21°—23° C.); UR, unconditioned reflex or adaptive temperature-elevating and drug-metabolizing mechanisms (latent, masked during hypoxia); CS, airflow, a neutral stimulus; CR, same as the reflex or adaptive UR, namely hyperthermia, shortening of hexobarbital narcosis and enhancement of hexobarbital metabolism. Therefore, whether interpreted classically or operantly, Roffman and Lal's findings are in accord with the conditioned adaptive and counteradaptive hypothesis.

Microsomal enzyme induction (hepatic) also plays a role in the development of "metabolic" tolerance to ethanol (Lieber and DeCarli, 1968), and in the cases of morphine and other opiates, decreased hepatic N-demethylation may also contribute to the development of tolerance (Axelrod, 1956). However, the development of tissue tolerance is the main factor in counteradaptation to the continued presence of morphine or other opiates in the central nervous system, and probably plays a major role in the development of chronic tolerance to barbiturates and ethanol as well. Such tissue tolerance, which is intimately associated with physical dependence,

has been explained in terms of "pharmacological disuse supersensitization," "recruitment of pharmacologically 'redundant' neural circuits," "induction of new receptors," and "enzyme expansion" (Wikler, 1972). These theories overlap to a considerable extent and common to all is the concept of counteradaptation to direct effects of the drugs in question. Implicit in the conditioned counteradaptive hypothesis is the concept that, given the appropriate CS-US temporal contiguities, the CRs that develop *change* during chronic administration of a drug, against the direct effects of which the central nervous system is capable of developing new counteradaptations. Thus, in the case of morphine, one would expect that initially, the CRs would be similar to the reflex URs discussed earlier in this paper. Later, however, the CRs would be similar to the tissue counteradaptations underlying chronic tolerance and physical dependence—*i.e.*, the CR's would be similar to morphine-abstinence phenomena. Furthermore, inasmuch as autonomic CRs are notoriously resistant to extinction, the persistence of such CRs after withdrawal of morphine and subsidence of the ensuing unconditioned abstinence syndrome could be a powerful factor (conditioned drive) in facilitating relapse. This hypothesis was first proposed in 1948 in the form shown in Table 1 (Wikler, 1948). Subsequently, the formulation was modified to include the rather obvious component of operant conditioning of drug-seeking behavior (Table 2, Wikler, 1961). In its present form (Table 3, Wikler, 1972), the dynamics of drug dependence are presented in terms of reinforcing processes, sources of reinforcement, reinforcing events, and behavior. In this formulation, the critical issues pertaining to the roles of classical and operant conditioning are stated under the headings, *Sources of Reinforcement* and *Reinforcing Events* (Table 3). Although several of these issues remain to be investigated, a considerable body of clinical and experimental evidence that is at least consonant with the theoretical model has been reviewed in some detail very recently (Wikler, 1972).

It will be noted that in this model, it is postulated that when a CS is paired with direct pharmacological reinforcement, the CR that develops is opposite in direction to the agonistic effects of the drug (Table 3, III. Secondary Pharmacological. A. Direct. Column, *Sources*). On first consideration, this assumption is difficult to reconcile with the findings of Roffman *et al.* (1972). These investigators injected morphine in rats four times daily, gradually increasing the dose until the rats received a total daily dose of 200 mg/kg. Each injection was preceded by the sounding of a bell for one minute. On abrupt withdrawal of morphine, the rats exhibited hypothermia, one of the characteristic signs of early morphine-abstinence in this species. However, when the CS (now consisting of sounding the bell

TABLE 1.* Conditional Response Concept of interrelation of "Physical" and "Psychic" Dependence in Morphine Addiction

Agent	Uncondtional Stimulus (U.S.)	Unconditional Response (U.R.) (Mainly subcortical)	Subjective Concomitant (U.R.)	Agent	Conditional Stimulus (C.S.)	Conditional Response (C.R.) (Mainly cortical)	Subjective Concomitant (C.R.)
Food	Taste and smell of food	Salivation	Hunger	Bell	Meaning of sound	Salivation	Hunger with craving for specific food used in experiments
Electric shock	Pain	Defence Reactions	Fear or Rage	Bell	Meaning of sound	Defence Reactions	Fear or rage directed toward electric shock
Atropine (Drug acting peripherally)	Dryness of the mouth	Salivation	Thirst(?)	Injection	Meaning of injections	Salivation	Thirst with aversion to atropine
Apomorphine or Morphine (In dogs) (Drugs acting centrally)	(By-passed)	Vomiting	Nausea	Injection	Meaning of injections	Vomiting	Nausea with aversion to apomorphine or morphine
Morphine (In dogs)	Direct central emetic effects	Salivation	Nausea	Injection	Meaning of injections	Salivation	Nausea with aversion to morphine
Morphine in non-tolerant subject	(By-passed)	Direct central effects of morphine	Sedation	Injection	Meaning of injections	Direct effects of morphine	Sedation, etc. with liking for, or dislike of morphine
Morphine in tolerant subjects	Direct central effects of morphine	Abstinence Changes	Anxiety	Injection	Meaning of injections	Abstinence Changes	Anxiety with craving for morphine

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TABLE 2.* Dynamics of Drug Abuse (Instrumental Conditioning Paradigm)

Phases	I Episodic intoxication ("Euphoria")	II Pharmacogenic dependence ("Addiction")	III Relapse after cure ("Habituation") Early	 Late
Discriminative Stimuli	More frequently: "Bad associates" Less frequently: Medical contingencies	"Bad Associates"	Medical and Law-enforcement contingencies	"Bad Associates" Sensorial effects of drugs
Reinforcement Processes Schedules	Occasional	Continuous or aperiodic	Extinction by "satiation" (not non-reinforcement)	Variable
Sources Primary	Anxieties (Homeostatic, sexual) Curiosity Boredom Anhedonia	Mainly homeostatic and sexual anxieties induced by cellular "counter-adaptations" to repeated doses of "addicting" drugs	Same as in II but decreasing after peak	Conditioned sources of reinforcement, generated mainly in phases II and III (Early)
Secondary	"Anomie" Hostility	Status in "addict-society"	Hostility Guilt	
Auxiliary	"Effort" factor	"Effort" factor (intensified)	Generalization of anxiety	
Behavioral phenomena	"Experimenting" with drugs	Progressive increase in dosage ("tolerance") "Hustling" for drugs	Abstinence syndrome	Conditioned abstinence phenomena (fragmentary)
Drug effects	Objectively unwarranted "sense of unusual well-being" "Indifference" "Elation"	Gratification of "craving"	Relief of Abstinence—distress	As in I plus "drive" (Conditioned "Hustling"?)

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TABLE 3.* Reinforcing Processes in Opioid Dependence

Reinforcing Processes	Sources of Reinforcement	Reinforcing Events	Behavior
I. Social Street corner society; slum "big shots;" cultist rituals and beliefs.	Need to belong; boredom; anomie; hostility to "establishment."	Acceptance by deviant subculture.	Drug-taking in accordance with rituals; affirmation of cultist beliefs.
II. Primary Pharmacological			
A. Direct (non-drug engendered = "psychic dependence")	1. Intrinsic (cerebral drug-sensitive "reward" systems?) 2. Developmental ("personality"): "anxiety" in *particular* situations.	1. Relatively non-specific drug effects (release or blockade of NE, DA, ACh, etc. in brain) 2. *Specific* pattern of agonistic actions of opioid drugs.	1. Subjective: "high;" "thrills" (i.v. only). Objective: elated behavior. 2. Subjective: "content;" "coasting." Objective: "nodding;" "leveling" of performance.
B. Indirect (drug-engendered = "physical dependence").	Early abstinence changes (manifest or detectable by subject's cerebral sensors); restlessness, etc.	Suppression of early abstinence by next dose of opioid. NOTE: Tolerance has developed to "directly" reinforcing effects of opioids.	Subjective: "craving" and satisfaction of "craving." Objective: "hustling" for opioids; increasing dose and frequency of opioid-taking (*appetitive* reinforcement)
III. Secondary Pharmalogical (conditioning of reinforcing processes to "exteroceptive" and "interoceptive" stimuli). A. Direct B. Indirect	Classically conditioned CNS changes (counter-adaptive to agonistic effects of opioids) A. Conditioned inhibition of CNS "reward" systems. B. Conditioned abstinence changes.	Agnostic effects of opioids as in II. A & B, but after II. A *and* B, suppression of conditioned abstinence is more reinforcing.	Subjective: A. "low;" "disgusted." B. "sick;" "got the flu;" "need a fix." Objective: A. depressive behavior. B. signs of opioid abstinence (conditioned); renewed "hustling;" RELAPSE

Note: "reinforcement" is the consequence of interaction between sources of reinforcement and reinforcing events.

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for one minute followed by injection of saline) was presented, the abstinence-hypothermia was reversed, and the onset of abstinence-hypothermia could be delayed for 1, 2 or 3 days by presenting the CS every 12 hours for the periods indicated. However, it should be noted that, although in the nontolerant rat parenterally administered morphine produces a *fall* in rectal temperature (Lotti *et al.*, 1965a), tolerance to this hypothermic effect develops during chronic administration of morphine, and then each injection of morphine produces a *rise* in temperature (Martin *et al.*, 1963). Although Lotti *et al.* (1965b, 1966) view such morphine-hyperthermia as an effect of morphine to which tolerance does not develop, their data do not rule out the alternative interpretation that the hyperthermic response is a counteradaptive tissue (hypothalamic) reaction to the direct hypothermic effect of morphine. Since in Roffman *et al.'s* (1972) experiments, the CS preceded each morphine injection in rats made tolerant to the drug, the reversal of abstinence-hypothermia (itself possibly an indirect consequence of other, complex physiological and metabolic disturbances) by the CS could be explained as a result of elicitation by the CS of a counteradaptive (hyperthermic) CR.

From this point of view, the sharp distinction that is usually made between "psychic dependence" (direct pharmacological reinforcement) and "physical dependence," (indirect pharmacological reinforcement) becomes untenable. By definition, both are consequences of interactions between certain agonistic drug actions and organismic sources of reinforcement, in the first case non-drug engendered, and in the second case, drug-engendered (Wikler, 1971). However, it may be questioned whether, after the first few doses of any of the drugs of abuse, including those said not to produce physical dependence (amphetamines, cocaine, cannabis products), the organismic sources of reinforcement remain non-drug engendered. We know that many of these drugs release, block reuptake of, or otherwise alter the effects of neurohumoral transmitters on their receptor sites. We also know that the central nervous system is equipped with elaborate neural positive and negative feedback circuits which serve to counteract such direct drug effects. Perhaps such neural feedback circuits tend to overshoot, and thereby create new, drug engendered sources of reinforcement without manifest withdrawal signs of a familiar sort (*e.g.*, opiate, barbiturate or ethanol abstinence phenomena), so that after a few self-administered doses of cocaine, for example, the human or animal drug-user continues in this practice, not because of the "high" produced by the first dose but because of the "low" ("counteradaptive") response that followed. Perhaps also, given the appropriate CS-US temporal contiguities, it is the counteradaptive response that becomes con-

ditioned, so that long after cocaine-withdrawal, presentation of the CS elicits the conditioned feedback overshoot (experienced as a low) which, functioning as a conditioned drive, impels the operantly-trained subject to resume self-injection of that drug—precisely as in the case of conditioned morphine-abstinence, though the specific neural events involved may be different. Of course, this is pure speculation, and as I am not a brain biochemist, I must leave it to others to judge whether or not these speculations are worth investigating. As a final "perhaps," I might say that more complete understanding of the biochemical processes involved in psychic as well as in physical dependence, and of their conditionability, is more than likely to provide us with new, pharmacological modes of intervention for therapeutic purposes.

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