Learning and the wisdom of the body

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According to Spence, the learning researcher's task is to explain the relationship between experimental variables and behavior changes occurring with practice. Spence eschewed biological speculation. In contrast, for a biologist, "explanation" consists of ascertaining how the observed behavior increases reproductive success. Fundamental to achieving reproductive success is survival to sexual maturity, and such survival depends on homeostatic mechanisms attenuating the effects of physiological disturbances that threaten existence. Drugs are one way of disrupting homeostatic functioning, and studies of drug effects indicate that homeostatic mechanisms are engaged not just by pharmacological perturbations, but also by stimuli that signal such perturbations. Similarly, we attenuate the effects of a variety of nonpharmacological stimuli by such anticipatory homeostatic adjustments. The learning researcher is a homeostasis researcher.

Learning is one of the physiological mechanisms that give the body its wisdom. (Dworkin, 1993, p. 185)

Why study learning? Pavlov (1927) thought that the topic elucidated central nervous system physiology (the subtitle of *Conditioned Reflexes* is *An Investigation of the Physiological Activity of the Cerebral Cortex*). As a student of Darwin, Pavlov also saw his research as providing "evidence of the power of natural selection" (Gray, 1980, pp. 32–33). Similarly, many of the early animal learning researchers were concerned about the biological significance of learning. It was clear to them that organisms are more likely to survive and reproduce if they learn to adjust to signals for biologically important events (see Hollis, 1997).

The rationale for studying learning, at least in North America, had changed a few decades later. By the 1950s, biological concepts were not a major feature of animal learning research in general, and Kenneth Spence's approach to the area in particular. For Spence, the research agenda for the learning researcher was clear: "(1) the specification of the experimental variables, environmental and organic, that determine the observed behavioral changes that occur with practice, and (2) the formulation of the functional interrelations (laws) holding between these sets of variables" (Spence, 1951, p. 690). Biological speculation was a diversion from the task: "Spence expressed a fear that such speculations would produce confusion and avoided any physiological interpretations of his theories" (Kendler & J. T. Spence, 1971, p. 33). Recently, many findings from the animal learning and ethology literatures have led to a resurgence of interest in explaining learning as a biological trait that has evolved to increase reproductive success (Domjan, 2005; Hollis, 1997; Matthews, Domjan, Ramsey, & Crews, 2007).

The most basic requirement for achieving reproductive success is survival to sexual maturity. Such survival requires that the organism deal with the moment-to-moment challenges to its existence posed by a hostile environment. To survive, we need stability in many systems: concentration of various chemicals in our blood, internal temperature, blood pressure, etc. If any of a multitude of physiological variables varies outside of a narrow range for any length of time, we get sick and then we die.

Claude Bernard is generally given credit for initiating the study of the ways in which we meet such challenges to survival. We manage to deal with an inhospitable environment because we have developed reflexive responses that counter the effects of the environmental challenges.

Far from being indifferent to the external world, the higher animal is on the contrary in a close and wise relation to it, so its equilibrium results from a continuous and delicate compensation established as if by the most sensitive of balances. (Bernard, 1878/1974, p. 85)

The processes by which these compensations achieve balance are termed "homeostasis" (from Greek words meaning "to remain the same"). The word was neologized by Walter Cannon (W. B. Cannon, 1929), and subsequently elaborated in his well-known book, *The Wisdom of the Body* (W. B. Cannon, 1932). As succinctly summarized by W. B. Cannon (1932): "If a state remains steady, it does so because any tendency toward change is automatically met by increased effectiveness of the factor or factors which resist the change" (p. 281).

W. B. Cannon (1932) discussed homeostatic mechanisms involved in maintenance of internal constancy when an organism is challenged by thermic or metabolic stimuli. Drugs provide another sort of challenge to homeostatic regulation. Indeed, the study of drug addiction is, to a great extent, the

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study of homeostatic mechanisms engaged by pharmacological stimuli. In the last 25 years, there has been a considerable amount of research concerning the role of learning in drug addiction. The purposes of the present article are to show that these pharmacological conditioning findings are of general applicability in understanding the contribution of learning to homeostasis, and, more importantly, to make the case that the study of learning is important because it explicates a major mechanism of homeostatic regulation, and therefore the survival of the organism.

Pavlovian Conditioning, Drug Addiction, and Homeostasis

It is an accepted corollary of evolutionary principles that any response is the means whereby a living organism restabilizes processes which have been temporarily unbalanced by the stimulus evoking that response. This concept of a self-regulating mechanism has been amply documented by Cannon. . . . admirable as these autonomic stabilizers are, they do not approach in range and flexibility the adjustive mechanisms which nature has provided in conditioning. (Culler, 1938, p. 134)

Events occurring during drug administration correspond to a Pavlovian conditioning trial. Cues accompanying the primary drug effect function as conditional stimuli (CSs). The direct effect of the drug constitutes the unconditional stimulus (US). Prior to any learning, this pharmacological stimulation elicits responses that compensate for the drug-induced disturbances (unconditional responses, URs). After some pairings of the predrug CS and pharmacological US, drug-compensatory responses are elicited as conditional responses. Such conditional compensatory responses (CCRs) have been demonstrated with respect to many effects of a variety of drugs, including commonly abused drugs such as opiates, ethanol, and caffeine (see Siegel & Ramos, 2002). These CCRs mediate the development of tolerance by counteracting the drug effect. For example, in rats tolerant to the hypothermic effect of alcohol, administration of an inert substance in the presence of alcohol-associated cues results in *hyperthermia* (Siegel, Baptista, Kim, McDonald, & Weise-Kelly, 2000). This hyperthermia is a CCR that attenuates the thermic effect of alcohol administered in the presence of alcohol-paired stimuli.

According to the conditioning analysis, drug tolerance and withdrawal symptoms are both manifestations of the same CCRs. When the drug is administered in the context of the usual drug-administration cues, CCRs attenuate the drug effect and contribute to tolerance. However, if the usual drug is not administered in the presence of the usual cues, these CCRs achieve full expression because they are not modulated by a drug effect. Such CCRs, displayed in such circumstances, are termed *withdrawal symptoms*.

It is the anticipation of the drug, rather than the drug itself, that is responsible for these symptoms. . . . some drug "withdrawal symptoms" are, more accurately, drug "preparation symptoms." (Siegel & Ramos, 2002, p. 171)

These CCRs elicited by drug-associated cues include the readily observable drug-compensatory responses and less readily observable neurochemical responses that are interpreted as craving.

The implications of the drug conditioning findings for understanding practical problems related to drug addiction and treatment have been reviewed elsewhere (Siegel & Ramos, 2002). The purpose of this article is to argue that these findings indicate that the learning researcher is a homeostasis researcher, and the learning researcher should consider not only the formulation of the laws holding between experimental variables (as stipulated by Spence), but also the functional significance of these laws.

Evidence for the Conditioning Analysis of Tolerance

There no longer is any question about the importance of associative factors in drug tolerance. (Poulos & Cappell, 1991, p. 391)

Before discussing the relationship between pharmacological conditioning research and the wider topic of the role of learning in homeostasis, the drug conditioning literature will briefly be reviewed (for more comprehensive reviews, see Ramos, Siegel, & Bueno, 2002; Ramsay & Woods, 1997; Siegel, 2005; Siegel & Ramos, 2002).

Parallels between conditioning and tolerance.

Consistent with the conditioning analysis, a variety of manipulations that attenuate the expression of conditional responding also attenuate the acquisition of tolerance. Thus, in common with other CRs, the expression of drug tolerance is disrupted by presenting a novel external stimulus ("external inhibition"), or by altering the putative CS (changing the context of drug administration in an unpredictable manner). The acquisition of tolerance is retarded by partial reinforcement, CS-preexposure, and inhibitory learning. Like other CRs, drug tolerance displays stimulus generalization, and a flattening of the generalization gradient as a result of extending the interval between acquisition and assessment. Tolerance also displays extinction, spontaneous recovery, sensory preconditioning, occasion setting, and a variety of compound conditioning effects, such as overshadowing and blocking. Also, posttrial events that affect memory consolidation similarly affect the rate of tolerance acquisition; thus electroconvulsive shock or frontal cortical stimulation decreases the rate of acquisition of morphine tolerance, and glucose facilitates the rate of acquisition of morphine tolerance.

Situational specificity of tolerance. The original phenomenon implicating CCRs in tolerance has been termed the "situational specificity of tolerance" (Siegel, 1976). Situational specificity of tolerance is readily demonstrated. An organism is administered a drug in a particular environment on a number of occasions, sufficient for tolerance to be apparent (i.e., the magnitude of the drug-elicited response is less than it was originally). If the drug is administered again, but in the absence of the usual cues that had previously been present at the time of drug administration, tolerance is attenuated. Situational specificity of tolerance is very general. It has been seen

with respect to tolerance to a variety of effects of various drugs, and in many species, from snails to humans (see Siegel et al., 2000). Situational specificity is expected on the basis of the conditioning analysis of tolerance; that is, drug-associated cues elicit the conditional homeostatic responses that attenuate the drug effect. Thus, tolerance is greater when assessed in the presence of drug-associated cues than when assessed elsewhere.

Situational specificity of tolerance has been demonstrated in experiments that have cues explicitly paired with a drug effect, or that have used *opportunistic designs* that rely on the subjects' extra-experimental conditioning histories. An example of an opportunistic design is that of Remington, Roberts, and Glautier (1997), who reported that the same amount of alcohol induced less impairment when college students consumed the alcohol in an alcohol-associated beverage (beer-flavored beverage) rather than a liquid that had not previously been associated with alcohol (a blue, peppermint-flavored beverage). Similarly, tolerance to the cardiac effect of caffeine is more pronounced if the caffeine is administered in the context of the usual caffeine-administration cues (i.e., consumed in coffee) than if the same blood level of caffeine is obtained with an administration procedure that does not incorporate these gustatory cues (i.e., intravenous administration; Siegel, Kim, & Sokolowska, 2003).

The most dramatic demonstrations of the situational specificity of tolerance concern tolerance to the lethal effects of drugs. Following a series of drug administrations involving escalating doses, each in the context of the same cues, tolerance develops to the potentially lethal effect of that drug, as long as it is administered in the usual context. Altering the context of drug administration increases the lethality of several drugs, including heroin, pentobarbital, and alcohol. Although experimental work indicating the importance of drug-associated cues to tolerance to drug lethality has been done with rats and mice, there are clinical reports indicating that an alteration in predrug cues may be responsible for some instances of opiate overdoses experienced by drug addicts and by patients who receive drugs for pain relief (Gerevich, Bácskai, Farkas, & Danics, 2005; Gerevich, Bácskai, & Kurimay, 2004; Gutiérrez-Cebollada, de la Torre, Ortuño, Garcés, & Camí, 1994; Siegel, 2001).

Findings demonstrating situational specificity of tolerance indicate that a drug that is unexpected (because it is presented in the context of cues that had not previously signaled the drug) has a larger effect than a drug that is expected (i.e., presented in the context of cues that had signaled the drug). In fact, it is a general finding that expected events—even nonpharmacological events—have a smaller effect than unexpected events.

Situational Specificity of Adaptation to Nonpharmacological Stimuli

On this occasion, Mr. Blake knows beforehand that he is going to take the laudanum—which is equivalent, physiologically speaking, to his having (unconsciously to himself) a certain capacity in him to resist the effects. (Collins, 1868/1994, p. 465)

If a person is keyed to meet an external influence, he *invariably* exhibits resistance to it. . . . When the impression is absolutely unexpected the reflex movement is effected exclusively through the nervous center connecting the sensory and motor nerves. But if the stimulation is expected a new mechanism interferes with the phenomenon seeking to suppress and inhibit the reflex movement. (Sechenov, 1863/1965, pp. 12–13)

We have suggested that (the fictional) Mr. Blake's "certain capacity. . . . to resist the effects" of laudanum, attributed by Wilkie Collins (in his novel *The Moonstone*) to the fact that Mr. Blake was expecting the drug, is a conditional homeostatic response elicited by drug-associated cues (Siegel, 1983). Similarly, the "new mechanism" hypothesized by Sechenov to occur when "stimulation is expected" is the conditional homeostatic response elicited by cues paired with the nonpharmacological stimulation. There are many examples of such anticipatory homeostatic responses mediating adaptation in a variety of systems.

Situational specificity of adaptation to stress-induced analgesia. Although situational specificity of tolerance has been demonstrated with respect to a variety of effects of many drugs, most demonstrations involve tolerance to the analgesic effect of morphine. Stressful stimuli also elicit analgesia. Blustein and colleagues have demonstrated that there is situational specificity of adaptation to the analgesic effect of repeated electric shocks, and the analgesic effect of repeated episodes of cold-water swimming (Blustein, Ciccolone, & Bersh, 1997, and Blustein, Hornig, & Bostwick-Poli, 1995, respectively).

Situational specificity of adaptation to diuretic stimulation. An early demonstration of situational specificity of adaptation concerned diuretic stimulation (Eagle, 1933). In a distinctive environment, water-deprived dogs consumed 500 ml of a milk–water mixture daily. The dogs were prepared with bilateral fistulae of ureters, and urine formation was assessed. Although there was considerable variability in urine formation, the trend clearly displayed adaptation to the limited fluid access schedule. That is, urine formation decreased over the course of repeated sessions. Following such adaptation, the dog was again offered the fluid, but in a very different environment, and a marked increase in urine formation was noted. When the dog was returned to the usual experimental room, the adapted response (characterized by minimal diuresis) was again evidenced.

Situational specificity of adaptation to chromatic stimulation. Hurvich and Jameson (1974), in discussing parallels between the organization of the color vision system and the organization of many other systems, suggested that color vision may be a useful model to evaluate homeostatic regulation generally. Responses to chromatic stimuli (in common with responses to many other forms of stimulation) display adaptation; that is, continued presentation of a color (say, green) over a period of some minutes causes the color to appear desaturated (e.g., Vimal, Pokorny, & Smith, 1987; Walker, 1986). Similarly, following repeated brief presentations of a color, the color becomes progressively desaturated. For example, following several hundred

presentations of an illuminated green square (each 2 sec in duration), the green is judged to be less saturated than it was initially (Allan, Siegel, & Linders, 1992). This desaturation is far more pronounced if the color is assessed in the presence of cues previously paired with color than in the presence of alternative cues. The phenomenon has been termed "contingent adaptation to color" (Allan et al., 1992). For example, following presentations of a green square containing horizontal black lines (a horizontal grid), green is perceived as desaturated only in the presence of the horizontal grid, and not in the absence of a grid, or in the presence of an alternative grid orientation (Allan et al., 1992). The similarities between context specificity of chromatic adaptation and context specificity of pharmacological adaptation (i.e., drug tolerance) have been discussed elsewhere (Siegel & Allan, 1998).

Just as tolerance to a drug is mediated by a pharmacological CCR, adaptation to a color is mediated by a chromatic CCR: the perception of a complementary color aftereffect. Thus, cues associated with a green color (grid orientation, or a variety of other visual patterns) elicit a perception of magenta when they are presented as achromatic test stimuli. This "contingent color aftereffect" may be seen long after the last pattern-color pairing. Contingent color aftereffects were first reported by Celeste McCollough (McCollough, 1965) and have come to be known as the *McCollough effect*. Although there are various interpretations of the McCollough effect, we have made the case that it is a chromatic CCR that mediates contingent adaptation to a color, much as CCRs elicited by drug-associated cues mediate drug tolerance (Siegel & Allan, 1992, 1998).

Situational specificity of adaptation to hypothermic stimulation. Adaptation to hypothermic stimulation is evidenced by smaller and smaller reductions in body temperature over the course of repeated applications of hypothermic stimulation (induced, for example, by brief immersions in cold water). The results of several experiments by Riccio and colleagues indicate situational specificity of such adaptation to cold (Kissinger & Riccio, 1995; Riccio, MacArdy, & Kissinger, 1991).

In our research concerning the role of learning in thermic adaptation, we used olfactory stimuli to signal hypothermia. Prior to the start of conditioning, all rats were surgically implanted with radiotelemetric temperature transmitters, permitting continuous remote monitoring of temperature (see McDonald & Siegel, 2004). During the adaptation phase of the experiment, rats were immersed in 4° C water for 1 min once every other day for 10 days. During each immersion session, rats were placed in a perforated Plexiglas restraint for 26 min. The design of the restraint permitted presentation of an olfactory stimulus (either lemon or peppermint) throughout the restraint period. Following 5 min of restraint (and odor exposure), the restrained rats were placed in a container containing the cold water (the restraint was tilted so that the rat's head was not submerged). Following 1 min of cold water immersion, the rats were removed from the water. They remained in the restraint for an additional 20 min after the immersion period. On those alternate days that rats

were not subjected to the cold water immersion, they were treated as they were on immersion days, except that the container did not contain any water, and the odor presented (either lemon or peppermint) was the odor *not* presented on immersion days. Thus, during the adaptation phase, all rats received five exposures to one odor paired with cold water immersion, and five exposures to the alternative odor without any immersion. It was expected that rats would display adaptation to the hypothermic effects of the cold water immersion.

Following adaptation, all rats received a test session. They were treated as they were on adaptation immersion sessions, except that the odor present was the one paired with nonimmersion. Thus, on the test session, rats previously immersed in the presence of the lemon odor were immersed in the presence of the peppermint odor, and vice versa. Situational specificity of hypothermia adaptation would be manifest as a renewal of the adapted hypothermic response. Finally, following the test session, all rats received a readaptation session in which they were again immersed in the presence of the odor that had signaled immersion during the adaptation phase.

The difference between the each of the 20 postimmersion minutes and the last preimmersion minute was computed for each rat for each session. Figure 1 summarizes adaptation to hypothermia seen during the adaptation phase of the experiment. The figure depicts the mean (± 1 SEM) immersion-induced temperature decrease seen on the first (Day 1), middle (Day 3), and final (Day 5) adaptation sessions. Hypothermic adaptation was apparent in this phase of the experiment; that is, the immersion-induced hypothermia decreased over the course of repeated immersions.

The results of the test and readaptation sessions are summarized in Figure 2. For purposes of comparison with the final adaptation session level of responding, Figure 2 also again displays the final (Day 5) adaptation session. As can be seen in Figure 2, on the test session, rats immersed in the presence of the odor that had not previously signaled immersion were more hypothermic than they were on either the prior session (final adaptation session) or the subsequent session (readaptation session). On both the final adaptation session and the readaptation session, rats were tested in the presence of the usual immersion-paired odor. These results confirm and extend the results of Riccio and colleagues (Kissinger & Riccio, 1995; Riccio, MacArdy, & Kissinger, 1991), and clearly indicate that adaptation to cold-water hypothermia is situationally specific.

Results of an experiment by Kissinger and Riccio (1995, Experiment 4) provide further evidence that learning contributes to hypothermic tolerance. These investigators briefly immersed rats in cold water once per day for four days. For rats assigned to a Different group, the cues signaling each immersion varied on each of the four days. For rats assigned to the Same group, the same cues signaled each immersion on each of the four days. As would be expected if hypothermic adaptation were mediated by an association between cues signaling the cold exposure and the effects of the exposure, adaptation was far more pronounced in Same-group rats than it was in Different-group rats. These results not only indicate that learning

Figure 1. Mean (± 1 SEM) immersion-induced temperature decrease seen on the first (Day 1), middle (Day 3), and final (Day 5) hypothermia adaptation sessions.

Figure 2. Mean (± 1 SEM) immersion-induced temperature decrease seen on the final adaptation session and posttest readaptation session (rats immersed in presence of usual immersion-paired odor on both occasions), and test session (rats immersed in the presence of the odor that had not previously signaled immersion).

contributes to hypothermic adaptation, but also are further evidence of the similarity between such adaptation and drug tolerance. Prior to Kissinger and Riccio's report, Epstein, Caggiula, Perkins, McKenzie, and Smith (1991) similarly demonstrated that tolerance to the tachycardiac

effect of nicotine in humans is attenuated if the cues signaling each of five cigarette-inhalation sessions are different rather than the same.

On the basis of an associative account of adaptation to repeated cold-water immersion, it would be expected that

cues signaling immersion elicit a CCR—hyperthermia—that compensates for the impending hypothermic stimulation (just as cues signaling a drug effect elicit a CCR that attenuates the impending pharmacological stimulation). Kissinger and Riccio (1995) described preliminary observations consistent with such an anticipatory hyperthermic CR. In fact, some years earlier, MacArthur (1979) described an anticipatory hypothermic response in a naturalistic study of adaptation to cold water immersion in the muskrat. Muskrats routinely forage beneath the ice in winter. Although they display substantial hypothermia if they are forced into cold water, they display only a small hypothermic response during natural periods of foraging in icy waters. Using temperature telemetry procedures, MacArthur demonstrated that muskrats display an elevation in body temperature preceding an underwater foraging excursion. The results indicate that “muskrats may ‘prepare physiologically’ for foraging activity in winter by elevating T_b [body temperature] prior to departing from the dwelling lodge and entering water at near-freezing temperatures” (MacArthur, 1979, p. 33)—that is, they demonstrate a hyperthermic CCR in preparation for cold-water immersion.

Situational specificity of unconditional response diminution (conditional diminution of the unconditional response). As summarized above, situational specificity of drug tolerance is but one example of situational specificity of adaptation to a variety of different stimuli: stress, diuretic, chromatic, and hypothermic. There also is evidence of such cue-induced attenuation of unconditional responding in more traditional Pavlovian conditioning preparations; that is, following some number of CS-US pairings, the UR often is smaller when the US is signaled by the usual CS, but not when the US is presented in an unsignaled manner. Such conditional diminution of the UR has been demonstrated in many conditioning preparations: salivary conditioning in dogs, electrodermal conditioning in humans, and eyelid conditioning in both humans and rabbits (see reviews by Goddard, 1991; Honey, 2000; Kimmel, 1966; Marcos & Redondo, 2002). For example, in an experiment involving electrodermal conditioning, Baxter (1966) demonstrated that the UR decreased over the course of training in participants receiving paired CS-US presentations, but not in participants receiving the CS and US presentations in an unpaired manner. Such findings are similar to those involving drug tolerance—tolerance to the analgesic effect of morphine is seen in rats receiving a distinctive cue and the opiate in a paired manner, but not in those receiving the cue and opiate in an unpaired manner (Siegel, Hinson, & Krank, 1978).

Interoceptive Cues

There can be no doubt that not only an analysis of the external world is important to the organism—but it is also necessary that an upward signaling and an analysis takes place of what occurs within itself. In a word, apart from the above-mentioned external analyzers, there must exist internal ones. (Pavlov, 1949, p. 169)

Most Pavlovian conditioning research involves the use of exteroceptive CSs—tones, lights, and such. Similarly, most studies of conditioning effects on tolerance and withdrawal have manipulated exteroceptive cues. Exteroceptive cues are external and public; they are apparent to both the organism experiencing the drug effect and the experimenter studying the drug effect. Distinctive visual, auditory, or olfactory cues present at the time of drug administration are all examples of exteroceptive cues. In contrast, some cues for a drug are internal and private—they are apparent only to the drug-taker. There is evidence that such *interoceptive* cues become associated with a drug effect and elicit homeostatic CRs that contribute to tolerance. Moreover, research implicating interoceptive cues in drug tolerance further illustrates similarities in adaptation to pharmacological and nonpharmacological stimuli. The role of interoceptive cues in drug tolerance has been reviewed (Kim, Siegel, & Patenall, 1999; Siegel et al., 2000; Weise-Kelly & Siegel, 2001), and thus will be summarized only briefly before I discuss the role of such cues in adaptation to nonpharmacological stimuli.

Interoceptive Cues and Drug Tolerance

Tolerance was observed when the subjects injected the opiate, but not when the same dose was received by unsignaled intravenous infusion. (Ehrman, Ternes, O'Brien, & McLellan, 1992, p. 218)

It is possible that an integral part of the stimulus complex acting as the CS in studies involving opponent CRs is the drug itself. To the extent that when any drug is administered, a reliable predictor of the presence of any specific dose will be [the] lower “functional” dose of the drug, as the drug gradually increases in body tissue after administration, it follows that drug onset may be a critical part of the CS complex controlling the compensatory CR. (Goudie, 1990, p. 679)

We have reported the effects of two categories of interoceptive cues on drug tolerance and withdrawal. One is the internal-proprioceptive cue incidental to drug self-administration. The second is the pharmacological cuing that occurs whenever a drug is administered.

Self-administration cues. Typically, humans self-administer the drugs that they use. Such self-administration is a characteristic of both illicit (e.g., cocaine, heroin) and licit (e.g., nicotine, ethanol) drug use. Although some psychopharmacology researchers investigate effects of drugs that are self-administered (especially the rewarding effects), most researchers administer the drug to subjects. Thus, much of what we know about the effects of drugs, such as the development of drug tolerance, is based on results of studies in which the experimenter—not the subject—administered the drug.

If drug delivery is contingent on a response, interoceptive response-initiating (or response-produced) cues are paired with the drug effect. Thus, on the basis of a conditioning analysis of tolerance, we might expect tolerance to be more pronounced when a drug is self-administered

than when it is passively received. There is considerable evidence that this is the case.

Mello and Mendelson (1970) provided perhaps the first demonstration of the importance of the self-administration contingency in a drug effect. Alcoholic men were allowed to ingest alcohol in each of two conditions: when they wished (spontaneous condition), or only during experimenter-determined intervals (programmed condition). Tolerance was greater in the same individuals following the spontaneous condition than following the programmed condition. Similarly, Ehrman et al. (1992) evaluated the effects of hydromorphone in humans under two conditions: when they intravenously self-administered the drug, and when the drug was infused by the experimenter. Tolerance was seen only in the self-administering subjects.

Studies of the effect of the self-administration contingency with nonhuman animals generally use a yoked control design. With this design, each time a subject assigned to a self-administration (SA) group makes a particular response (e.g., presses a lever in an operant chamber), the same amount of drug is administered to that subject and to another, yoked (Y), subject. Thus, both SA and Y subjects receive the same dose of the drug equally often and at the same intervals. Several investigators have reported that, after some drug experience, the effects of the drug are greater in Y than in SA rats; that is, tolerance is less pronounced in Y animals (see Weise-Kelly & Siegel, 2001).

Pharmacological cues (homotopic learning). In most Pavlovian conditioning research, the CS and US are two very different stimuli, presented in different modalities (e.g., light and shock). However, it is also possible to demonstrate conditioning when the CS is from the same modality as the US. Dworkin (1993) distinguished between these two types of conditioning situations. He applied the term *heteroreflexes* ("heterotopic conditioned reflexes") to the traditional, two-stimulus conditioning preparation, and distinguished heteroreflexes from *homoreflexes* ("homotopic conditioned reflexes"). In the case of homoreflexes, the CS and US are presented in the same modality and differ only in intensity. Such homotopic learning has been demonstrated with drugs; that is, a small dose of a drug can be an effective cue for a larger dose of that same drug—termed "intradrug conditioning" (Siegel et al., 2000). Several investigators have suggested that intradrag conditioning findings have important implications for understanding the contribution of interoceptive learning to tolerance. Whenever a drug is administered, there is an opportunity for homotopic learning because of the normal time-effect curve of the drug. That is, each drug administration potentially pairs drug onset cues with the later, larger drug effect (e.g., Goudie, 1990; Greeley, Lê, Poulos, & Cappell, 1984; King, Bouton, & Musty, 1987; Mackintosh, 1987; Tiffany, Petrie, Baker, & Dahl, 1983). Such learning that may take place within each administration has been termed "intraadministration conditioning." Early studies evaluating the potential for drug-onset cues to elicit CCRs that mediate tolerance evaluated intradrag conditioning as a way to imitate the pairings that are hypothesized to occur within each administration.

Intradrag conditioning. Greeley et al. (1984) provided the first demonstration of intradrag conditioning. In their experiment, rats in a Paired group consistently received a low dose of ethanol 60 min prior to a high dose of ethanol. Another group of rats (Unpaired) received the low and high doses on an unpaired basis. When tested for the tolerance to the hypothermic effect of the high dose following the low dose, Paired rats, but not Unpaired rats, displayed tolerance. Moreover, if the high dose of ethanol was not preceded by the low dose, Paired rats failed to display their usual tolerance. This tolerance, dependent on an ethanol-ethanol pairing, was apparently mediated by a thermic CCR; Paired rats, but not Unpaired rats, evidenced hyperthermia (opposite to the hypothermic effect of the drug) in response to the low dose of ethanol. There also is evidence that a small dose of morphine may serve as a cue for a larger dose of the opiate, and control the display of morphine tolerance (Cepeda-Benito & Short, 1997; Sokolowska, Siegel, & Kim, 2002) and withdrawal (McDonald & Siegel, 2004).

Intraadministration conditioning. Intradrag conditioning requires the pairing of a small dose of a drug with a larger dose of that same drug. More recently, procedures have been described to evaluate intraadministration associations that putatively are simulated by this procedure. To directly evaluate such intraadministration associations, a drug is repeatedly administered via intravenous infusion (each infusion lasting, for example, for 60 sec). The effects of the drug-onset cue can be evaluated by presenting only the initial part of the infusion (e.g., a 6-sec infusion). Using this procedure, we have provided evidence that intraadministration associations make an important contribution to drug tolerance (Kim & Siegel, 2001; Kim et al., 1999; Sokolowska et al., 2002).

Interoceptive Cues and Adaptation to Nonpharmacological Stimuli

While interoceptive conditioning is by its nature more limited than is exteroceptive conditioning with respect to total kinds and variety of stimulations, the interoceptive kinds of stimulations are, on the other hand, by their very nature much more recurrent, periodic, and organism-bound, making interoceptive conditioning an almost built-in function that is constantly generated and regenerated in the very process of living and acting. (Razran, 1961, p. 97)

Findings summarized above indicate that two types of interoceptive stimuli, self-administration cues and homotopic cues, can act like exteroceptive CSs and elicit CRs that mediate drug tolerance. Such stimuli also elicit CRs that mediate adaptation to nonpharmacological stimuli.

Self-administration cues. Just as a self-delivered drug has a smaller effect than a passively received drug, a variety of self-delivered nonpharmacological events elicit smaller responses than those events elicit if they are passively received.

Perceptual stimuli. We have discussed similarities in associative analyses of drug tolerance and associative analyses of certain perceptual phenomena (Siegel & Allan, 1998). Findings indicating that the magnitude of a

response to a self-administered drug is less than the magnitude of a response to a passively received drug also have a counterpart in the perception literature. The vestibular ocular reflex provides an example of the contribution of self-delivery on perceptual functioning (see review by Dworkin, 1993, pp. 1–2). If an experimenter presents a subject with objects moving in the subject's visual field at more than 1–2 Hz, the objects become blurred. However, if the subject's behavior causes objects to move (e.g., by head movements), no blurring is detected—a sharp image is seen, despite the fact that objects may move as rapidly as 5–6 Hz. Thus, there is more “tolerance” to visual disruption caused by moving objects if the subject, rather than the experimenter, causes the movement.

Motion-induced sickness. Just as we adapt to the effects of a self-administered drug more quickly than we do to the effects of a passively received drug, we adapt to the effects of self-administered motion more quickly than we do to the effects of passively experienced motion; that is, motion sickness is less likely to occur in an individual controlling the motion than in the individual passively exposed to the same vestibular and visual stimulation. Indeed, it is a matter of common observation that “the driver is rarely sick even though subject to sickness when he is a passenger” (Howard & Templeton, 1966, p. 136).

The observation has been amply confirmed in the laboratory. For example, Rolnick and Lubow (1991) collected data from pairs of subjects exposed to the same “nauseogenic” stimulation for 6 min on a rotatable platform. One participant, the “controlling subject,” operated a joystick that controlled the direction and velocity of motion. A second, “noncontrolling” subject was exposed to the same rotational stimulation at the same time, but had no control over the motion. The 2 simultaneously run subjects wore helmets connected by a rigid rod, ensuring that head motion was equivalent. Illness and well-being were measured with rating scales. Compared to noncontrolling subjects, controlling subjects “were less likely to terminate rotation prior to the completion of its course, showed reduced symptoms of motion sickness, and less decrement in their well being” (Rolnick & Lubow, 1991, p. 875). Additionally, 59% of the controlling subjects agreed to participate in future similar experiments, compared with only 18% of the noncontrolling subjects. More recently, similar conclusions concerning motion controllability and motion sickness have been obtained in experiments that use virtual reality displays to simulate actual motion (see Stanney & Hash, 1998).

Aversive stimuli. There is evidence that electric shocks are less aversive when humans deliver the shocks to themselves than when the experimenter delivers the shocks. Vernon (1969) reported that male university students assigned to a “self-shock” group tolerated higher levels of shock intensity before they “could not endure a stimulus of higher intensity” (p. 813) than did students assigned to an “other shock” group (who were shocked by the experimenter): “It is clearly apparent that, other factors being equal, self-inflicted pain is less aversive than pain inflicted by others” (p. 813).

Perhaps the most extreme example of the differential effectiveness of self-administered and passively received

aversive stimuli is found in clinical cases of self-injurious behavior. Some patients engage in self-punitive behaviors that result in tissue damage to themselves; yet, paradoxically, these same patients find exogenously administered painful stimuli to be aversive. Indeed, this paradox can be exploited—the frequency of self-punitive behaviors can be reduced by punishing the self-injurious behaviors with therapist-administered aversive stimuli (e.g., Linscheid, Pejeau, Cohen, Footo-Lenz, 1994). The paradox was elaborated over 40 years ago by Stengel (1965). He studied “low grade defectives with a propensity to self-damage and self-mutilation” (p. 797), and noted that “in injuring themselves they showed no outward indication of feeling pain, rather some indication of pleasure” (p. 797). Nevertheless, the responses of these patients to externally administered pain was not unusual; that is, they found it aversive:

The discrepancy between the reactions to self-inflicted and extraneous noxious stimuli shown by low-grade subnormals is a puzzling observation and worthy of the interest of students of perception. It indicates that self-inflicted pain is experienced differently from pain the source of which is outside the body. (p. 797)

However, as further noted by Stengel (1965), one need not look at special populations for an illustration of the very different effect of self-administered and passively received stimulation. A “very striking example” (p. 797) of the difference is seen with a more familiar situation: tickling. A self-administered tickle elicits a smaller response than a passively received tickle.

Tickle stimuli. Subsequent to Stengel's (1965) observations, a rather esoteric literature concerning the contribution of self-administration to tickling responsivity has developed. In the first sentence of perhaps the first paper describing a systematic analysis of the problem, Weiskrantz, Elliot, and Darlington (1971) asked, “Why is it that most people cannot tickle themselves?” (p. 598). Although they did not answer the question, Weiskrantz et al. invented a rather ingenious tickle machine to conclusively demonstrate that people do, indeed, find experimenter-elicited tickles much more ticklish than subject-elicited tickles. This conclusion, although a matter of common experience, has also been replicated in additional laboratory research (e.g., Claxton, 1975; Hoshikawa, 1991). More recently, there appears to be renewed appreciation in the profundity of the observation that we cannot effectively tickle ourselves (e.g., Blakemore, Wolpert, & Frith, 2000; Wolpert & Flanagan, 2001).

Homoreflexes and adaptation to nonpharmacological stimuli. As summarized above, there is ample evidence that small drug effects become associated with later, larger drug effects, and elicit CCRs that attenuate the larger drug effect. Many normally occurring physiological events contain the potential for homoreflexes, and such associations may serve an important regulatory function. Dworkin hypothesized that homoreflexes may serve as “*in situ* mechanisms for adjusting the gain of regulatory reflexes” (Dworkin, 1993, p. 79). Thus, when homeostatic

disruptions occur (e.g., moment-to-moment changes in blood pressure), early deviations may be detected and function as interoceptive homotopic CSs (because, in the past, they have been paired with later, larger deviations). That is, they elicit CCRs that attenuate the effect of the perturbation. A number of elegant experiments by Dworkin and colleagues (Dworkin & Dworkin, 1999; Tang & Dworkin, 2007a, 2007b) have demonstrated how Pavlovian conditioning of this sort contributes to homeostatic regulation of blood pressure. In his book *Learning and Physiological Regulation*, Dworkin (1993) has discussed the potential for such homotopic learning to contribute to homeostatic regulation in many systems.

Ivan P. Pavlov, Walter B. Cannon, and Contemporary Regulatory Physiology

Cannon and Pavlov were close friends, and when Pavlov came to America, he stayed with the Cannons in a house on Divinity Avenue. . . . (Skinner, 1966, p. 74)

Pavlov lamented the fact that his work did not sufficiently influence physiological thought. In 1935, at one of his regular "Wednesday Meetings," he commented: "Strange as it may seem, many physiologists, authors of text-books, do not cite any data concerning our experiments with conditioned reflexes" (Pavlov, 1957, p. 620). Surprisingly, this was true of the books written by Walter Cannon, despite the fact that Pavlov and Cannon were friends and colleagues. That is, although we now know that learning contributes to homeostatic regulation, this notion was apparently not appreciated by the pioneering researchers in the relevant fields,

Pavlov (born 1849, died 1936) and Cannon (born 1871, died 1945) had great respect for each other's research and frequently corresponded with each other. They met several times: in 1923, when Pavlov made his first visit to North America; in 1929, when Pavlov attended the International Physiological Congress in Boston; and in 1935, in Lenin-grad, at another meeting of the International Physiological Congress (B. Cannon, 1994). Unfortunately, the Cannon–Pavlov correspondence has been lost (B. Cannon, 1994), and we are left with an enigma—these men apparently had little intellectual effect on each other. Pavlov did not incorporate homeostatic concepts in his conditioning work, and Cannon did not incorporate concepts of conditioning in homeostatic regulation. That is, for Cannon, homeostatic responses were reflexively generated in response to a perturbation, and these responses attenuated the perturbation—a negative feedback analysis of physiological regulation:

Cannon's career cast a towering and generally positive influence over twentieth-century physiology, but his concept of regulation began with Bernard and never went beyond the physics and engineering of the mid-nineteenth century; consequently, he failed entirely to appreciate the far reaching implications for homeostasis of the extraordinary experiments and brilliant insights of his personal friend Ivan Pavlov. (Dworkin, 1993, p. 185)

It was many years after the deaths of these men that the necessity to incorporate associative principles into Cannon's conceptualization of homeostasis was recognized.

Starting about 50 years after *The Wisdom of the Body* was published, some physiologists realized that Cannon's analysis of homeostatic regulation was incomplete. In an attempt to incorporate findings concerning circadian effects on the regulation of potassium balance, Moore-Ede (1986) concluded "a mature understanding of homeostasis should encompass both 'reactive' responses to changes in physiological variables that have already occurred and the 'predictive' responses initiated in anticipation of predictably timed challenges" (Moore-Ede, 1986, p. R737). In attempting to understand several homeostatic systems—for example, the adjustment of blood circulation to exercise, water intake, and thermoregulation—Somjen (1992) suggested that "the central nervous system (CNS) anticipates present and future need on the basis of past experience" (p. 184). These (and other) physiologists have recognized that the negative feedback models of homeostasis that characterized Cannon's view of the process are inadequate, and some sort of anticipatory or feedforward mechanism is crucial. However, just as learning researchers have not generally promoted their findings as relevant to understanding the wisdom of the body, regulatory physiologists have not generally incorporated the wealth of available learning research in their understanding of this feedforward process. Somjen (1992) concluded, "Truly, the body appears to be wiser than even Walter Cannon had thought" (p. 184). Although some psychologists have realized that this additional "wisdom" is provided by basic learning processes (e.g., Dworkin, 1993; Matthews et al., 2007; Poulos & Cappell, 1991; Siegel & Allan, 1998; Woods & Ramsay, 2007), the contribution of Pavlovian conditioning to homeostatic regulation is not widely acknowledged.

Why Study Learning?

If the average American psychologist had been asked to identify the core discipline of his subject in the early fifties, he would have pointed to animal learning theory. Over the last two decades, however, the status of the subject has been on a steady decline. . . . (Dickinson, 1981, p. 3)

The past 100 years of Pavlovian conditioning have told researchers much about how the conditioned response develops (Pearce & Bouton, 2001) but little about why it develops. (Matthews et al., 2007, p. 758)

In the era of Kenneth Spence—and in no small part because of Spence's influence—learning was *the* central topic in experimental psychology. Spence's agenda for the discipline has achieved many successes. Elaboration of "laws of learning" has been important not only for learning researchers, but also for those with various other interests in experimental psychology (Siegel & Allan, 1996). Although it no longer is the case that the search for such laws is the principal activity of most psychology laboratories, there is clear and growing evidence that we

must understand the laws of learning if we are to understand the crucial contribution of learning to homeostatic regulation.

As succinctly stated by Horrobin (1970), "for the animal organism the central problem of existence is that of maintaining the stability of its structure and function in the face of constant internal and external assaults" (p. 1). The learning researcher, then, is studying the central problem of existence.

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