Learning and Homeostasis: Drug Addiction and the McCollough Effect

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The contribution of conditioned responses (CRs) to homeostasis may be seen by examining seemingly disparate phenomena of color vision (aftereffects and chromatic adaptation) and drug addiction (withdrawal symptoms and tolerance). Color aftereffects may be elicited by nonchromatic stimuli previously paired with color (the McCollough effect, [ME]). Similarly, pharmacological aftereffects may be elicited by nonpharmacological stimuli previously paired with a drug (withdrawal symptoms). The authors summarize evidence indicating that both the ME and withdrawal symptoms are CRs. The chromatic CR is expressed as chromatic adaptation in the presence of color, and the ME in the absence of color. The pharmacological CR is expressed as pharmacological adaptation (tolerance) in the presence of the drug, and withdrawal symptoms in the absence of the drug. Both drug withdrawal symptoms and the ME are manifestations of the contribution of conditioning to normal homeostatic regulation. The authors discuss the implications of this conclusion for understanding regulatory processes and the evolution of behavioral mechanisms.

We present a further elaboration of the relationship between pharmacological and chromatic opponent processes. We suggest that some seemingly disparate phenomena of drug addiction and color aftereffects are manifestations of a common, regulatory mechanism. This mechanism is Pavlovian conditioning, and the contribution of conditioning to the maintenance of homeostasis may be appreciated both by drug and by vision researchers.

Drug Effects and Learning

The model we are proposing is based on the belief that learning is the primary underlying cause of the development of drug tolerance. (Ramsay & Woods, 1997, p. 170)

The effects of many drugs decrease over the course of exposure to the drug, the phenomenon being termed tolerance. Tolerance generally is attributable to opponent responses compensating for the drug effect: "pharmacodynamic or physiological tolerance results from the secondary induction by the drug of compensatory, homeostatic feedback mechanisms" (Haefely, 1986, p. 355–356). Evidence has accumulated for about 30 years that learning is central to tolerance (e.g., Cohen, Keats, Krivoy, & Ungar, 1965; Poulos & Cappell, 1991; Siegel, 1991): "There no longer is any question about the importance of associative factors in drug tolerance" (Poulos & Cappell 1991, p. 391). As discussed by Ramsay & Woods (1997), the contribution of learning to tolerance is best appreciated by examining the effects of a drug the very first time it is administered.

Acute Tolerance and Withdrawal

The measured effects of many drugs decrease during the course of a single exposure the first time the drug is administered. For example, epinephrine increases both heart rate and blood pressure. Over the course of a single, long infusion of epinephrine, during which the concentration of the drug at receptor sites is maintained at high levels, the cardiac effects

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nevertheless decrease (e.g., Bevan, 1983). Similarly, over the course of a single, long infusion of morphine the analgesic effect of the drug decreases (e.g., Tilson, Rech, & Stolman, 1973; Wei & Way, 1975). This adaptation to a drug, over the course of the initial administration, is termed acute tolerance.

The existence of acute tolerance is evidence that the pharmacological stimulation initiates adaptive responses that compensate for the primary drug effect (Haeckel, 1986; Ramsay & Woods, 1997). The observed effect of a drug is the net result of primary, drug-induced changes and these secondary, compensatory responses. As the compensatory responses are increasingly mobilized by the primary drug effect, the primary drug-induced changes become attenuated, and the observed drug effect decreases.

Further evidence for drug-compensatory responses may be seen when the drug effect is abruptly ended (e.g., the infusion is terminated, or an antagonist is administered). The compensatory response, now having less to compensate for, is apparent. Thus, upon termination of epinephrine infusion (and the hypertensive and tachycardic effects of the drug), a decrease in blood pressure and heart rate (compared to undrugged baseline levels) may be seen (e.g., Bevan, 1983). Similarly, upon termination of a morphine infusion (and the analgesic effect of the drug), an increased sensitivity to painful stimuli is noted (e.g., Tilson et al., 1973; Wei & Way, 1975). These drug aftereffects, seen following termination of an initial drug effect, are termed acute withdrawal symptoms.

Chronic Tolerance and Withdrawal

Typically, drugs are not administered as constant long infusions. Rather, administration is by means of a brief injection, and the effects are measured following the termination of the injection. When such measurements are made following each of a series of drug administrations, the drug effect frequently is noted to become progressively smaller over the course of these administrations. For example, the sixth injection of morphine induces less analgesia than the first injection (e.g., Siegel, 1977), and the sixth injection of epinephrine induces less tachycardia than the first (Subkoff & Zilov, 1937). Chronic tolerance refers to this decreasing effect seen following each successive administration of a drug. The term tolerance, as it is generally used, refers to such chronic tolerance.

Chronic tolerance, like acute tolerance, is mediated by compensatory responding. That is, at some time following a series of drug administrations, if the drug is no longer administered, chronic pharmacological aftereffects may be seen. These withdrawal symptoms, seen after chronic administration, may be termed chronic withdrawal symptoms, but generally are termed simply withdrawal symptoms.

Acute tolerance results from drug-compensatory processes reflexively elicited by a drug (e.g., Haeckel, 1986).1 Chronic tolerance (hereafter termed tolerance) results (at least in part) from drug-compensatory processes elicited by cues that, in the past, have been paired with the drug. The contribution of such learning to tolerance is incorporated in a Pavlovian conditioning interpretation of tolerance.

Pavlovian conditioning and tolerance. Pavlov (1927, pp. 35ff) suggested that the administration of a drug could be viewed as a conditioning trial; the drug effect served as the unconditioned stimulus (UCS), and the immediately antecedent environmental cues served as the conditioned stimulus (CS). Some years ago, it was suggested that “conditioned drug responses are commonly opposite in direction to the unconditioned effects of the drug” (Siegel, 1975, p. 499), and these “compensatory” conditioned responses (CRs) attenuated the drug effect and mediated tolerance. The pharmacological CR, then, was conceived as being opposite in direction to the pharmacological unconditioned response (UCR)—at least in instances in which tolerance occurred—a position contrary to Pavlov’s view that the CR was similar to the UCR.

The conditioning analysis of drug administration subsequently has undergone several important modifications, primarily as a result of critical analyses of pharmacological conditioning by several authors (Dworkin, 1993; Elkeboom & Stewart, 1982; Poulos & Cappell, 1991; Ramsay & Woods, 1997; Wikler, 1973). It is now apparent that the initial application of the Pavlovian conditioning paradigm to drug administration was somewhat superficial. The UCR to a pharmacological stimulus, in common with reflex responses to other stimuli, consists of responses generated by the central nervous system (CNS). The drug effect that initiates these CNS-mediated responses is the UCS (not the UCR). For many effects of drugs, the UCR consists of responses that compensate for drug-induced perturbations. These unconditionally elicited compensatory responses are responsible for acute tolerance (Ramsay & Woods, 1997). After some pairings of the prodrug CS and the pharmacological UCS, the drug-compensatory responses are elicited as conditioned responses (CRs). As noted by Dworkin (1993), the analysis now closely follows Pavlov’s (1927) conceptualization of conditioning:

So far as is known, the classical conditioning process itself is without any intrinsic capacity to sense the direction of homeostatic error and generate appropriate compensation... If conditioned responses are compensatory, they are conditioned compensatory responses and not conditioned conditioned responses... Conditioned drug responses, when adequately isolated, dissected, and understood, exemplify in an uncomplicated way the phenomenon first described by Pavlov: The conditioned reflex resembles the unconditioned reflex, and as it develops, it augments the effect of the unconditioned reflex. (Dworkin, 1993, p. 38)

Perhaps the first example of the contribution of conditioning to drug tolerance was presented by Subkoff and Zilov (1937) over 60 years ago. They injected dogs with epinephrine (adrenaline) on a number of occasions (one injection every few days), and noted that the tachycardic effect of the drug decreased over the course of repeated injections (i.e., tolerance developed). On

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1 Although acute tolerance typically is attributed to drug-compensatory responses unconditionally elicited by the drug, there is a potential role for instrumental learning in acute tolerance (Dworkin, 1993; Ramsay & Woods, 1997). During the early part of an initial drug infusion, organisms may acquire a behavioral strategy that is negatively reinforced by a reduction in the drug-induced disturbance. For example, when administered a drug that induces hypothermia, organisms may learn to make postural adjustments that conserve body heat (Ramsay & Woods, 1997).
a final test session, they placed the dog in the injection stand and administered an inert substance (Ringer’s solution). On this test, a decrease in heart rate was observed:

It follows that the mere reproduction of the experimental conditions in which the animal is accustomed to receive adrenaline is alone sufficient to set in motion the mechanism, by means of which the animal counteracts the high vascular pressure produced by adrenaline. (Subkow & Zikov, 1937, p. 295)

Subsequent research has demonstrated conditioned compensatory responses with respect to many effects of a variety of drugs (e.g., see Siegel, 1991), including commonly abused drugs, such as opiates (Grisel, Wiertelak, Watkins, & Maier, 1994; Hinson & Siegel, 1983; Krank, Hinson, & Siegel, 1981; Mucha, Volkovskis, & Kalant, 1981; Raffa & Porreca, 1986), alcohol (see review by Siegel, 1987), and caffeine (Andrews, Blumenthal, & Flaten, 1998; Roxin, Reff, Mark, & Schull, 1984). When the drug is administered in the context of the usual drug-administration cues, these CRs attenuate the drug effect and contribute to tolerance.2

There is a considerable amount of evidence supporting the contribution of Pavlovian conditioning to tolerance (e.g., Poulos & Cappell, 1991; Ramsay & Woods, 1997; Siegel, 1991). The original phenomenon that inspired development of the conditioning model was described in a number of experiments conducted by Clifford Mitchell and colleagues between 1969 and 1973 (e.g., Kayan, Ferguson, & Mitchell, 1973; Kayan, Woods, & Mitchell, 1969), and has been termed the Mitchell effect (Siegel, 1978, p. 345).

The Mitchell effect. In Mitchell’s experiments, morphine was administered on several occasions, with the same environmental cues associated with each drug administration. Over the course of repeated administrations, rats (and humans, see Ferguson & Mitchell, 1969) developed tolerance to the analgesic effect of the drug, but this tolerance was far more pronounced in the presence of cues previously paired with morphine than in the presence of alternative cues.

Many subsequent experiments have confirmed and extended the findings of Mitchell and colleagues. The Mitchell effect, now generally termed the situational-specificity of tolerance (e.g., Siegel, 1976), has been demonstrated with respect to many effects of a variety of drugs (Siegel, 1989, 1991). Situational-specificity is seen with respect to tolerance to alcohol (e.g., Lé, Poulos, & Cappell, 1979), nicotine (e.g., Epstein, Caggilula, & Stiller, 1989), opiates (reviewed by Siegel, 1991), naloxone (Goodison & Siegel, 1995b), benzodiazepines (reviewed by Siegel, 1986), pentobarbital (e.g., Cappell, Roach, & Poulos, 1981), phencyclidine (Smith, 1991), immunoenhancing drugs (Dyck, Driedger, Nemeth, Osachuk, & Greenberg, 1987), cholecystokinin (Goodison & Siegel, 1995a), carisoprodol (Flaten, Simonsen, Waterloo, & Olsen, 1997), and haloperidol (Poulos & Hinson, 1982). It is seen in many species, from snails (Kavaliers & Hirst, 1986) to humans (e.g., Dafters & Anderson, 1982; Flaten et al., 1997). The most dramatic demonstrations of tolerance situational-specificity concern tolerance to the lethal effects of drugs. Following a series of drug administrations, each in the context of the same cues, tolerance develops to the 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 (Siegel, 1984, 1989; Siegel, Hinson, Krank, & McCully, 1982), morphine (Siegel & Ellsworth, 1986), pentobarbital (Vila, 1989), and alcohol (Melchior, 1990; Melchior & Tabbers, 1982, but see Neumann & Ellis, 1986; Tabbersky & Amit, 1993). The Mitchell effect is expected on the basis of the conditioning analysis. That is, drug-associated cues elicit the conditioned compensatory responses that attenuate the drug effect; thus, tolerance is greater when tolerance is assessed in the presence of drug-associated cues than when it is assessed elsewhere.3

Pavlovian conditioning and withdrawal symptoms. Drug tolerance and chronic withdrawal symptoms (hereafter termed withdrawal symptoms) are highly correlated (e.g., see Koob, Stinus, Le Moal, & Bloom, 1989; Peper, Grimmbergen, Kraal, & Engelhart, 1987). Moreover, to a great extent withdrawal symptoms are compensatory responses: “As a general pharmacological principle, it can be asserted that withdrawal effects are usually opposite to acute drug effects” (Poulos & Cappell, 1991, p. 402). According to the conditioning analysis, the relationship between tolerance and withdrawal, and the fact that most withdrawal symptoms are drug-compensatory responses, are attributable to the fact they are both manifestations of the same conditioned compensatory drug response.

When the drug is administered in the context of the usual drug-administration cues, conditioned compensatory responses attenuate the drug effect and contribute to tolerance. However, if there is no drug effect (i.e., the usual cues for drug administration are present, but the usual drug is not administered), these CRs achieve full expression because they are not modulated by a drug effect. Such pharmacological CRs, displayed in such circumstances, are termed withdrawal symptoms:

Consider the situation in which the addict expects a drug, but does not receive it; that is, no drug is available, but the addict is in an environment where he or she has frequently used drugs in the past, or it is the time of day when the drug is typically administered, or any of a variety of drug-associated stimuli occur. Research with animals demonstrates that presentation of cues previously associated with drug administration, but not followed by the drug, results in the occurrence of drug-compensatory CRs . . . In the situation in which the drug addict expects but does not receive the drug, it would be expected that drug-compensatory CRs would also occur. These CRs normally counter the pharmacological disruption of functioning which occurs when the anticipated drug is administered. However, since the expected drug is not forthcoming, the CRs may achieve expression as overt physiological reactions, e.g., yawning, running nose, watery eyes, sweating . . . or form the basis for the subjective experience of withdrawal sickness and craving. (Hinson & Siegel, 1982, p. 499)

2 There are associative interpretations of tolerance that do not emphasize the contribution of conditioned compensatory responses. The most prominent of these is Baker and Tiffany’s (1985) habituation model. Several investigators have critically evaluated the various models and discussed the relationships among them (e.g., Cepeda-Benito & Tiffany, 1996; Poulos & Cappell, 1991; Siegel, 1989).

3 Evidence for tolerance situational-specificity, and the role of drug-compensatory conditioning in such specificity, may have been known to opiate users in the 19th century (Siegel, 1983).
DRUG ADDICTION AND THE MCCOLLOUGH EFFECT

There is much experimental (both human and nonhuman animal) and epidemiological evidence that so-called withdrawal symptoms, seen long after the last exposure to a drug, are especially pronounced in the presence of drug related cues (e.g., Defner-Rappold, Azorlosa, & Baker, 1996; Kelsey, Aranow, & Matthews, 1990; Ternes, 1977); that is, "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, 1991, p. 412). The powerful effect of drug related cues is also apparent in many clinical reports (see Siegel, 1988). For example, several clinicians have reported that opiate withdrawal symptoms are displayed when, during behavior therapy sessions (even with long-detoxified former addicts), drugs are discussed (O'Brien, 1976; Wikler, 1977). Others have observed that pictures or videotapes of drug-associated stimuli elicit withdrawal symptoms (Sidereoff & Jarvis, 1980; Teasdale, 1973). Finally, when former addicts are released from a prolonged period in a drug-free environment (after a period of imprisonment or impatient treatment), they frequently report that they experience opiate withdrawal symptoms when approaching drug-associated cues (e.g., when the subway approaches the old neighborhood; O'Brien, 1976, see also Wikler 1977).

The dynamic features of tolerance and withdrawal, and the contribution of conditioned responding to the expression of these pharmacological phenomena, may be seen in other systems. One system that is accessible and extensively studied is color vision.

Color Effects and Learning

At the very least, it is clear that describing the McCollough and related effects in the terminology of classical conditioning leads to viable predictions across a wide variety of experimental conditions. (Brand, Holding, & Jones, 1987, p. 316)

Continued presentation of a color (say, green) over a period of some minutes causes the color to become desaturated (e.g., Vimal, Polkorny, & Smith, 1987; Walker, 1986). The phenomenon is attributable to color-opponent responses. The color-opponent response may be seen the same way as a drug-opponent response is seen, that is, sudden termination of the eliciting stimulus. Upon termination of the green stimulus there is a red aftereffect. Such acute chromatic adaptation to a color, mediated by a chromatic compensatory response, is parallel to acute pharmacological tolerance and acute withdrawal symptoms.

Following repeated, brief, presentations of a color, a phenomenon parallel to chronic drug tolerance is seen. That is, the color becomes progressively desaturated. For example, following several hundred presentations of an illuminated green square (each 2 s in duration), the green is judged to be less saturated than it was initially (Allan, Siegel, & Linders, 1992). Moreover, 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). That is, just as tolerance to a drug is especially pronounced in the presence of cues that have been associated with the drug in the past (the Mitchell effect), adaptation to a color is especially pronounced in the presence of cues that have been paired with color in the past.

This chromatic Mitchell effect, like the pharmacological Mitchell effect, is mediated by compensatory processes. That is, the chromatic aftereffect is elicited by cues paired with color. The phenomenon is termed a contingent color aftereffect and was discovered by Celeste McCollough in 1965.

The McCollough Effect

McCollough (1965) demonstrated that exposure to colored vertical and horizontal grids results in a complementary color aftereffect contingent upon grid orientation. The orientation-contingent color aftereffect is now known as the McCollough effect (ME). The ME is easily demonstrated. For example, after an induction period consisting of presentations of a grid made of green and black horizontal bars alternating with another grid made of red and black vertical bars, participants report negative color aftereffects contingent upon grid orientation; they report that achromatic horizontal grids appear pink, and achromatic vertical grids appear green.

Since McCollough's (1965) initial demonstration, there have been reports of hundreds of experiments concerning the ME (Humphrey, 1998), and McCollough's original observations have been extended. For example, it is not necessary to present two complementary colors, each paired with a different pattern, during ME induction. Only a single colored pattern need be presented; thus, if a participant is exposed only to a green horizontal grid for 15 min, an achromatic horizontal grid is seen as reddish (e.g., Allan & Siegel, 1997b). Moreover, there have been many reports that a variety of features, other than orientation, will contingently elicit a color aftereffect following pairing with color (e.g., Allan & Siegel, 1997b; Siegel & Allan, 1992; Siegel, Allan, & Eissenberg, 1992). Generally, the term ME has been used to describe any contingent color aftereffect (not just those elicited by orientation).

The ME is a fascinating phenomenon for several reasons. It is very robust, and is seen not only in adult humans, but also in young children (e.g., Meyer, Coleman, Dwyer, & Lehman, 1982), monkeys (Macquaire, Meyer, & Baizer, 1980), and pigeons (Roberts, 1984). Most remarkably, the ME is very persistent. McCollough (1965) reported that the ME (unlike an acute color aftereffect) is seen "an hour or more" (p. 1115) after induction. Results of subsequent research indicated even more dramatically the long-lasting nature of the ME. After only 15 min of ME induction, the aftereffect persists for days, weeks, and perhaps even months (Jones & Holding, 1975). Thus, the color-opponent response may be seen, in response to a color-paired feature, long after the last experience with the color.

Pavlovian Conditioning and the ME

The ME and the Mitchell effect are more than alliteratively similar; they both are demonstrations of contingent adaptation (to colors and drugs, respectively). Also, there is considerable...
evidence that the ME like the Mitchell effect, is due to Pavlovian conditioning (Allan & Siegel, 1997a, 1997b; Murch, 1976; Siegel & Allan, 1992). According to the conditioning interpretation of the ME, the feature paired with the color (e.g., bar orientation, in McCollough’s 1965 original demonstration) is the CS, and the color-opponent response elicited by the color is the unconditioned response (UCR). After some pairings, the CS alone elicits the color aftereffect. Thus, following induction, presentation of the feature (e.g., a horizontal, achromatic grid) elicits the color aftereffect as a CR. According to this associative interpretation, the ME is a CR.

If the usual chromatic grid (rather than an achromatic grid) is presented after induction, the ME is not apparent as it blends with the colored grid. In these circumstances, the chromatic CR elicited by the grid serves to attenuate the saturation of the color; that is, the color is desaturated in the presence of a CS previously paired with the color. According to this analysis, contingent adaptation to color results because the effect of the assessed color is attenuated by the chromatic CR that is the ME.

Chromatic and Pharmacological Associations

The McCollough effect can be considered a paradigmatic case of compensatory conditioning, albeit within the visual system. (Schull, 1979, p. 78)

The associative interpretation of drug tolerance and withdrawal is supported by the results of many experiments indicating that nonpharmacological manipulations of drug-paired cues have conditioning-like effects (e.g., Siegel, 1991). Similarly, the associative interpretation of contingent chromatic adaptation and the ME is supported by the results of experiments indicating that manipulations of color-paired cues have conditioning-like effects (e.g., Siegel & Allan, 1992). Thus, the acquisition of both the pharmacological and chromatic phenomena are retarded by CS preexposure (so-called latent inhibition; see Skowbo, 1988; Tiffany & Baker, 1981) and by manipulations that decrease the contingency between the putative CS and UCS (Panselov & German, 1982; Siegel et al., 1992). Both drug tolerance (e.g., Siegel, Hinson, & Kránk, 1981) and the ME (e.g., Murch, 1976) display evidence of inhibitory learning as a result of negative CS-UCS contingencies. Both phenomena display extinction (e.g., Siegel, 1977; Skowbo, 1988), stimulus generalization (e.g., Caggia, Epstein, Antelman, & Saylor, 1991; Eisensberg, Allan, Siegel, & Petrov, 1995), and retardation by partial reinforcement (e.g., Kránk, Hinson, & Siegel, 1984; Siegel & Allan, 1987). Both display a variety of compound conditioning effects, such as overshadowing (e.g., Siegel & Allan, 1985; Walter & Riccio, 1983) and blocking (Brand et al., 1987; Dafters, Hetherington, & McCartney, 1983). As discussed elsewhere, it would be difficult to explain drug tolerance and withdrawal symptoms (e.g., Siegel, 1991), or chromatic adaptation and contingent aftereffects (e.g., Siegel & Allan, 1992), without acknowledging the crucial role of Pavlovian conditioning.

Conditioned Responses as “Withdrawal Symptoms”

The illusion is an example of the so-called McCollough effect, a phenomenon well-known to psychologists. . . . Physicians should be aware of the phenomenon so as not to mistake it for a hysterical symptom or a manifestation of a neurological disease. (Greenwald, Greenwald, & Blake, 1983, p. 315)

As noted, drug-opponent responses, contingently elicited by drug-associated cues long after the last administration of the drug, typically are termed withdrawal symptoms. Color-opponent responses, seen in response to color-associated cues long after the last presentation of a chromatic stimulus, typically are termed McCollough effects. It makes as much sense to label the contingently elicited drug aftereffect a drug withdrawal symptom as it does to label the contingently elicited color aftereffect a color withdrawal symptom. They both are CRs that would attenuate the effect of UCS if the usual UCS were presented.

The consequences of chromatic conditioned responding (in the absence of color) are less striking than the consequences of pharmacological conditioned responding (in the absence of the drug). Drug-paired cues may elicit somatically uncomfortable responses. These pharmacological CRs may include neurochemical alterations that lead to the subjective state of craving (Markou et al., 1993). The existence of these pharmacological CRs sometimes is cause for medical and legal concern. Color-paired cues just elicit illusory colors. Nevertheless, contingent color aftereffects (in common with pharmacological CRs) have been cause for distress, and labeled as medical symptoms.

The medical literature contains reports of individuals, working with monochrome (green) computer displays, complaining of erythropsia—vision tinged with red (see summary by Allan, Siegel, Collins, & MacQueen, 1989). This symptom, seen after extensive use of the green display, had been labeled complementary chromatopsia (Kahn, Fitz, Psaltsis, & Ide, 1984). Complementary chromatopsia is sufficiently uncomfortable to cause some computer operators to seek medical advice (Greenwald et al., 1983; Kahn et al., 1984). Following the description of complementary chromatopsia in the medical literature, several investigators demonstrated that letters of the alphabet were one of the many patterns that, following pairing with color, contingently elicited aftereffects (Allan et al., 1989; Humphrey, Skowbo, Symons, Herbett, & Grant, 1994). Complementary chromatopsia was readily interpretable as an aftereffect contingently elicited by stimuli that were similar to the green monitor display, and not a symptom of hysteria or visual system pathology (e.g., Greenwald et al., 1983; Lockhead, 1983; Walraven, 1985).

We would like to go further. We suggest that drug withdrawal symptoms, in common with the ME, are indeed not manifesta-

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1 Just as not all pharmacological researchers readily embraced the conditioning analysis of drug tolerance (e.g., Hayes & Mayer, 1978), not all vision researchers readily accept the conditioning analysis of the ME (e.g., Dodwell & Humphrey, 1990). Elsewhere, it has been suggested that there is overwhelming evidence that the ME is a CR (e.g., Allan & Siegel, 1986, 1993, 1997a, 1997b; Eisensberg et al., 1995; Siegel & Allan, 1992, 1996; Siegel et al., 1992). Although we, and others (e.g., Brand, Holding, & Jones, 1987; Murch, 1976; Skoane, Ost, Ehrséidje, & Henderson, 1989; Schull, 1979; Westbrook & Harrison, 1984), have found the Pavlovian conditioning interpretation of the ME compelling, some investigators have not (e.g., Bedford, 1995; Dodwell & Humphrey, 1990; Durbin & Profitt, 1996).
tions of a disorder. Rather they are manifestations of normal, homeostatic regulation.

Learning and Homeostasis

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

A unifying concept in physiology is homeostasis — regulatory processes that oppose the effect of physiological disturbances: "any paper published today, at least in physiology, which is worth the paper it is printed in, should further clarify a homeostatic mechanism" (Langley, 1973, p. 293). The term homeostasis was neologized by Walter Cannon almost 70 years ago (Cannon, 1929) and subsequently elaborated in his well-known book, The Wisdom of the Body (Cannon, 1932). The scientific study of learning started at about the same time, and many of the pioneering learning researchers believed that they were studying regulatory physiology. As noted by Pavlov (1927),

it is pretty evident that under natural conditions the normal animal must respond not only to stimuli which themselves bring immediate benefit or harm, but also to other physical or chemical agencies — waves of sound, light, and the like — which in themselves only signal the approach of these stimuli. (p. 14).

The study of responding to signals of stimuli "which themselves bring immediate benefit or harm" is now known as Pavlovian conditioning.

Cannon’s (1929, 1932) concepts were readily assimilated by early conditioning researchers:

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 adaptive mechanisms which nature has provided in conditioning. (Culler, 1938, p. 134)

Sixty years ago, when teleological analyses of learning were not yet disdained, Elmer Culler (1938) was able to assert that the function of the CR was "to make preparatory adjustments for an oncoming stimulus. . . The CR, in brief, is nature's way of getting ready for an important stimulus" (p. 136). Pharmacological conditioned compensatory responses are evidence that one "gets ready" for a drug, and the ME is evidence that one "gets ready" for a color. That is, in the case of both pharmacological and chromatic stimuli, the effect of the unconditioned stimulation initially is attenuated by unconditioned responding. These UCRs become augmented by CRs that grow in strength over the course of repeated unconditioned stimulation.

As discussed by Dworkin (1993), the system is self-limiting. Over the course of repeated drug administrations, the drug effect decreases only until tolerance is complete (the drug no longer has an effect). Similarly, over the course of repeated chromatic presentations, the color becomes increasingly desaturated until it appears colorless. In both cases, as the UCS becomes increasingly attenuated over the course of repeated trials (as it is increasingly attenuated by the CR) it supports less and less associative strength: "by minimizing the effect of the initiating disturbance the conditioned reflex arrests its own growth" (Dworkin, 1993, p. 129).

Evolution of Behavioral Mechanisms

The extensive mechanisms of classical conditioning did not evolve for the edification of psychologists, but to enhance the survival of the species. (Overduin, Dworkin, & Jansen, 1997, p. 228)

Why do drug-associated cues elicit so-called withdrawal symptoms? Is it a case of "a seeming unwisdom of the body" (Dole, 1977, p. xi)? Why do achromatic patterns appear colored if they have a history of being paired with color? "Presumably, they [MEs] do not exist simply to provide amusing perceptual demonstrations!" (Gregory, 1987, p. 108). Withdrawal symptoms and MEs exist for the same reason as other CRs exist. Both are manifestations of the tendency to associate paired events. Various theorists have proposed a variety of reasons why it makes good sense to associate temporally contiguous events (Alcock, 1996; Hollis, 1982, 1997), but one reason is adaptation to potentially dangerous challenges. As discussed here, the effects of drugs are attenuated if they are administered in situations previously paired with drug effects. As discussed by others, immunological challenges (Djuric, Markovic, Lazarac, & Jankovic, 1989), metabolic alterations (Moore-Fade, 1986), and episodes of hypothermia (Kissiager & Riccio, 1995; Riccio, MacArty, & Kissinger, 1991) are all also attenuated if these perturbations occur in situations in which they have occurred in the past. Humans and other animals have developed a single general mechanism — learning — that is relevant to maintaining homeostasis in many different systems. However, noting that a trait enhances homeostatic regulation does not address the issue of why this trait has evolved: "The ultimate criterion of adaptive functional organization is not health or happiness or homeostasis, but contribution to fitness" (Daly, 1997, p. 1). Rather, it must be argued that conditioned compensatory responses increase the likelihood that organisms will survive and reproduce.

Pharmacological conditioning provides a clear example of the contribution of such CRs to inclusive fitness: "In perhaps no other case has the adaptive value of the CR been demonstrated so dramatically" (Hollis, 1997, p. 960). We have suggested that the ME is yet another manifestation of this same process, yet the adaptive value of the chromatic CR clearly is less dramatic. Although a person may die if he or she does not respond with drug-compensatory responses to drug-paired cues (Siegel, 1984; Siegel & Ellsworth, 1986; Siegel et al., 1982; Vila, 1989), a person would not suffer a similar consequence if he or she did not respond with chromatic-compensatory responses to color-paired cues.

It is very tempting to offer some "just-so" story to justify a behavioral trait as the result of natural selection (Gould & Lewontin, 1979). Indeed, it is conceivable that adaptation to unchanging components of the environment, including color, increases the likelihood of detecting changing components that are important for survival, such as features indicating prey or predators. Contingent adaptation to color would ensure that the adapted response is not inappropriately exhibited when the environment is altered. This is an example of "naive adaptationism"
(Gould & Lewontin, 1979). Other investigators have offered different functional interpretations of the ME (Bedford, 1995; Dodwell & Humphrey, 1990), and these alternatives have been critically discussed elsewhere (Allan & Siegel, 1993, 1997a).

We suggest that such speculation about the adaptive significance of the ME misses the point. Conditioned responses function to produce reflexive behaviors in advance of the stimulus that unconditionally elicits the reflex. An organism’s reproductive potential is increased as a result of the fact that it responds conditionally, as well as unconditionally. It is unlikely that there has been natural selection specifically for the ME, any more than there has been natural selection for conditioned knee-jerk reactions elicited by a CS paired with patellar-tendon stimulation (Twinnmyer, 1902/1974), conditioned defecation elicited by CS paired with an enema (Bachrach & Morin, 1932), or conditioned pharmacological responses elicited by a CS paired with a drug administration. Rather, selection has favored the organism that has the general ability to anticipate events. This ability may be seen both in situations in which it is clearly adaptive (e.g., drug conditioning), and situations in which it may well serve no useful purpose (e.g., the ME).

In the language of evolutionary theorists, we are suggesting that CRs represent a “domain-general,” rather than a “domain-specific,” adaptation (Barkow, Cosmides, & Tooby, 1992; Bock & Cardew, 1997). Several theorists have discussed the evolution of such general abilities, applicable to many challenges:

natural selection should lead to the emergence not only of perceptual, behavioral, and cognitive mechanisms that are adapted to the specific circumstances faced by particular species, genders, and domains, but also of mechanisms that are adapted to the general circumstances faced by all so-called higher organisms. (Shepard, 1992, p. 526)

The proclivity of humans and other animals to make conditioned compensatory responses is one example of such a mechanism “adapted to the general circumstances.” Because of these conditioned responses, organisms may survive a high dose of a drug that would otherwise be lethal. One may study the role of learning in such situations, in which the opponent process organization is necessary for survival. One may also study it in an accessible system, like color vision, that exhibits the same dynamics but which does not have such spectacular dependent variables.

References


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