PLACEBO
Theory, Research, and Mechanisms

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A Conditioned Response Model of the Placebo Effect: Predictions from the Model

IAN WICKRAMASEKERA

THE PLACEBO EFFECT

A “placebo” may be defined as a presumably inert or neutral substance or procedure that elicits a therapeutic response (Beecher, 1959; Evans, 1974a, 1974b; Shapiro, 1971). Reviews of 26 double-blind studies covering 1991 patients found that approximately 35% of patients have severe clinical pain reduced by at least half of its original intensity by an inert substance or placebo drug. The placebo rate for experimentally induced laboratory pain, however, is considerably lower (Evans, 1974a). This discrepancy between the placebo rate in experimental and clinical pain strongly suggests that the psychological significance of the therapy situation is a major determinant of the magnitude of the placebo effect.

Placebo effects are not limited to chemical treatments, but may include surgical and psychological therapies. In a classic paper, “Surgery as a Placebo,” Beecher (1961) compared the results of enthusiastic and skeptical surgeons performing the once popular internal mammary artery ligation for angina pectoris. Two independent skeptical teams (Cobb, Thomas, Dillard, et al., 1959; Dimond, Kittle, & Crockett, 1958), using a single-blind procedure, performed a bilateral skin incision on all patients under local anesthesia, and in randomly selected patients the internal mammary artery was ligated. Dimond et al. (1958) found that 100% of the nonligated and 76% of the ligated patients reported decreased need for nitroglycerin and increased exercise tolerance. All nonligated patients showed improvement for more than 6 weeks, and followed patients remained improved 6 to 8 months later. Neither the ligated nor the nonligated group showed any improvement on electrocardiography. Cobb et al. (1959) team reported that 6 months after surgery five ligated and five nonligated patients reported more

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than 40% subjective improvement. Two nonligated patients showed dramatic improvement in exercise tolerance, and one nonligated patient even showed improved electrocardiographic results after exercise. These studies demonstrated that ligation of the internal mammary artery was no better than a skin incision, and that skin incision could generate a dramatic and sustained therapeutic effect.

Placebo effects are not limited to the relief of acute pain. Placebos may be useful in the therapy of coughs, headaches, asthma, multiple sclerosis, the common cold, diabetes, ulcers, arthritis, emesis, seasickness, cancer, parkinsonism, and other ailments (Beecher, 1955; Haas, Fink, & Hartfelder, 1959; Horningfield, 1964a, 1964b; Wolf, 1950). Nor are placebo effects limited to chemical and surgical treatments; in fact, a review of controlled studies of systematic desensitization (Kazdin & Wilcoxon, 1976) and a pioneering credible double-blind study of clinical biofeedback (Cohen, Graham, Fotopoulos, & Cook, 1977) have also found equally high rates of placebo response for these psychological treatments. For example, in the Cohen et al. (1977) study, subjects who received false feedback (the placebo treatment) improved clinically as much as those who received true feedback under double-blind conditions. In fact, an early study by Schmitzglabel and Traugott (1968) found that mechanical devices (like medical instruments) can also generate placebo effects, and I (Wickramasekera, 1977c) have elsewhere discussed the placebo effect of medical instruments in biofeedback.

The review above suggests that a therapeutic phenomenon like the placebo, which occurs across such a wide range of clinical treatment modalities (drugs, surgery, psychotherapies, biofeedback) and across such a wide range of physical and mental symptoms (pain, anxiety, edema, tachycardia, emesis, fever, vasoconstriction, phobias, depressions, etc.) to people who are physically or psychologically immobilized by symptoms or in a state of health deprivation, must be a true general ingredient in all clinical situations.

A review of the placebo literature leads to several conclusions: (1) A subset of patients show a significant therapeutic response to “inert” or “placebo” substances, procedures, and objects in any clinical study. (2) No reliable procedure exists to date to identify in advance this subset of patients. (3) The same subset may not reliably respond to placebos. (4) Any object or procedure offered with therapeutic intent can under the “right” conditions generate placebo effects. (5) The mechanism of the effect is unknown, and all the “right” conditions are unclear.

It has been found that a placebo can potentiate, attenuate, or negate the active ingredients in a drug (Shapiro, 1971). Placebos can have powerful effects on organic illness and malignancies, and can even mimic the effects of active drugs (Shapiro, 1971). Studies have found that dose–response and time–effect curves for an active drug and a placebo can be similar and that the side effects of an active drug and a placebo can be similar (Evans, 1974a).

A Conditioned Response Model

Clearly we are dealing with a real effect that has been regarded as a “nuisance,” for several reasons previously discussed (Wickramasekera, 1976b, 1977b, 1977c), and that has been summarized as follows: (1) Its action is not logically related to the known etiology of the disease or condition. (2) The mechanism of its action is unknown. (3) The effect is unreliable. (4) The effect may not be durable. (5) It is an effect that can occur in any therapeutic situation.

The effect has been called “nonspecific” because our ignorance of its parameters has limited our ability to manipulate the effect systematically. One purpose of the present chapter is to contribute toward the specification of what is now “nonspecific,” and toward a technology that will enable us to use some “nonspecified” effects in controlled, reliable, and specific ways. Eventually, perhaps, some placebo effects can be attenuated or negated in laboratory studies, and systematically manipulated to potentiate other specific effects in clinical studies. Such a psychological technology can increase the reliability of positive clinical outcome when active ingredients are used in routine clinical practice.

Many hypotheses have been advanced to explain the mechanism of the placebo response. Shapiro (1971) and T. X. Barber (1959) appear to favor a suggestion hypothesis, and Evans (1974a) appears to favor an anxiety reduction hypothesis. Frank (1973) and Stroebel and Glueck (1973) have stressed the role of expectancy in potentiating therapeutic response. In fact, Stroebel and Glueck (1973) have proposed a clinically useful way of approaching expectancy. For reasons of brevity, these analyses are not presented here; they are discussed elsewhere (Wickramasekera, 1976b, 1977b, 1977c). The present chapter offers a new model of the placebo

1. After this chapter was written and submitted for publication, one of the reviewers drew my attention to a relevant paper by Gleidman, Grant, and Teitelbaum (1957). I located and read this paper in July 1979. It was very exciting to note that Gleidman et al. advanced one of the central components of the present theory over 20 years ago. Their brief and excellent paper “summarizes some experiences in conditional reflex studies in dogs that relate placebo reactivity to established learning concepts” (Gleidman et al., 1957). The observations are cited in informal anecdotal style and deal with three groups of “unpublished” studies. The first group of studies “demonstrates that the effect of a person” can be conditioned. The second series stresses the importance of “central excitatory states” in conditioning. The third group of studies is “a miscellaneous one,” which pertains to the general state of the organism and the general setting with respect to placebo effects. Their thoughts with respect to the first point are almost identical to mine, and with respect to the second and third points, there is substantial implicit agreement. But there is no elaboration with respect to hypnosis, brain lateralization, and the possibility that the UCSs can be nonchemical behavioral events.

2. After this chapter was written and accepted for publication, the editor of Biofeedback and Self-Regulation, Dr. J. Stoyva, drew my attention (October 29, 1979) to a study by R. J. Herrnstein (1962). In this controlled study of the disruptive effects of scopolamine hydrobromide on lever pressing in the rat, physiological saline is shown to mimic the effects of scopolamine hydrobromide. Based on this study, Herrnstein infers that the placebo effect appears to be an instance of simple Pavlovian conditioning.
response, traces the predictions from this model, and presents the relevant subject, therapist, and procedural variables. This analysis points out that intrinsic to all unconditioned stimuli (UCSs) or reliably effective interventions or events (physiochemical, behavioral/psychological, or surgical) is the potential for Pavlovian conditioning (Pavlov, 1927) and therefore placebo learning.

This suggests that reliable mechanisms of pathophysiology that have clearly and sharply defined onsets and offsets can operate as UCSs. Chemicals and procedures that reliably and clearly turn on or off such pathophysiology can also operate as UCSs. Hence mechanisms of disease and healing may not be insulated from conditioning effects. The unconditioned response (UCR) is a function not only of the UCS, but also of an associated CS. The symptomatically immobilized and dependent patient in a state of health deprivation (not unlike food deprivation) is an ideal candidate for conditioning. Counterintuitively, it predicts that therapists who use active ingredients will get stronger placebo effects than those who use inert ingredients. The model also paradoxically predicts that progress in isolating active ingredients will inevitably lead to more and stronger placebo effects.

There is no systematic human evidence to support this model. But there is some strong controlled animal evidence (Ader, 1981; Drawbaugh & Lal, 1974; Goldberg & Schuster, 1967, 1970; Schuster & Thompson, 1969; Siegel, 1978; Wilker & Pesor, 1970) that supports the view that neutral stimuli can elicit complex biological and biochemical changes as postulated by the conditioned response (CR) model of the placebo.

ORIGINS OF THE CONDITIONED RESPONSE MODEL

Early in 1970 during clinical work (Wickramasekera, 1972a, 1973a) with patients with diagnosed chronic and continuous muscle contraction headaches of over 20 year's duration in electromyograph (EMG) feedback therapy, I made some puzzling observations. A subset of these patients reported relief of headache pain with startling rapidity. Often this occurred after no more than one or two sessions of EMG feedback therapy, and several sessions before they demonstrated any measurable ability to reduce the muscle tension levels in their head and neck. Since the etiology and mechanisms of muscle contraction headache are presumed to involve sustained contraction of muscles of the head and neck, changes in the verbal report of the intensity and frequency of headache pain should correlate with or follow, not precede, a drop in frontal EMG levels.

I wondered if this very short-latency therapeutic response was not a placebo response to the impressive and highly "credible" biofeedback instruments in anticipation of actual healing. It is well known that CRs mediated by the central nervous system (CNS) can have a shorter latency than a UCR, or, in this case, the actual reduction in muscle tension levels in the head and neck. I conceptualized the positive short-latency therapeutic response of this subset of patients as a type of fractional anticipatory goal response (Hull, 1952) or CR to the impressive electronic medical instruments used in this therapy (Wickramasekera, 1977c). This rapid therapeutic response (CR) to the sight of the biofeedback instruments (CS) was like conditioned salivation (CR), a fractional component of actual eating of food (UCR) that occurs in anticipation of food (UCS). The rapidity of this response reminded me of the well-known clinical observation that ingestion of aspirin often relieves the headache long before its pharmacological effect can occur. This placebo response group suggested that respondent or Pavlovian conditioning was one factor that could account for a portion of the positive therapeutic outcome in EMG feedback therapy for headache. At that time, the mechanism of therapeutic response in EMG feedback therapy for headaches was considered to be exclusively operant or Skinnerian conditioning of reduced frontal EMG.

THE CLINICAL SITUATION AND CONDITIONING PHENOMENA

This analysis predicts (1) that psychological responses (CRs) that were previously relegated to the realm of "nonspecific" factors can come to reliably attenuate or potentiate both health and illness; (2) that initially neutral stimuli (CSs) can come to either directly or indirectly influence the underlying physiochemical and cellular mechanisms (pathophysiology) of health and illness; and (3) that, theoretically, the influence of such variables on the symptom and mechanism of disease can be demonstrated in appropriately controlled double-blind studies in which the UCS (e.g., active chemical ingredient) is withheld.

Till as recently as the first two decades of this century, physicians had only a few active ingredients or UCSs (digitalis, opium) with which they could reliably control certain disease or disorder mechanisms. Yet for centuries physicians have inspired confidence in patients, and individual physicians have enjoyed high credibility and high social status. Physicians occupied positions of confidence long before they could reliably and effectively control pathophysiological mechanisms (UCRs) in any significant number of disorders. The CR model of the placebo can illuminate at least a part of this historical paradox. The perceived potency of a healer can stem not only from his or her ability to control pathophysiological mechanisms, but also from his or her ability to make an accurate and precise prediction of the time course, the specific changing symptoms, and the antecedents of disease. The ability to predict or prophesy requires only careful observation, recognition of the descriptive features of symptoms, access to medical records of prior observations, and a knowledge of the base rates of certain deviant biological events.
It is likely that patients frightened by the eruption of unfamiliar symptoms on their bodies and uncertain about their future were not prone to think analytically about their physicians’ behavior. Consequently, they confused the ability to predict biological symptoms accurately with the ability to control disease mechanisms, and attributed therapeutic potency to the physicians who reduced their fear and uncertainty by identifying and labeling their diseases and accurately predicting their symptomatic course. A physician’s predictive knowledge replaces disorganizing fear and uncertainty with a sense of familiarity, illusory control, and security. For centuries physicians have carefully observed, recorded, and labeled multiple common diseases and disorders. They were often also knowledgeable about the likely antecedents (e.g., hereditary or familial antecedents, dietary and environmental antecedents) of some of these disorders. A learned physician could easily recognize the specific symptoms a patient was currently experiencing, and could predict specific symptoms the patient would develop within 12 to 48 hours, as well as the sequence of symptomatic changes that would occur as the disease progressed. Such a physician also knew the death rate and sometimes the rate of spontaneous remission for the disease. This enabled the knowledgeable practitioner, after a brief physical examination, to make to the patient and his or her family uncannily accurate predictions about the patient’s current experiences and future experiences. As a specific disease (e.g., gonorrhea) progressed and the physician’s predictions about the symptoms were verified, the physician’s credibility escalated in the patient’s and the community’s perception. In addition, a knowledge of the likely antecedents of a disease or disorder (diet, hereditary factors, environmental exposure or trauma) could not only enable the physician to predict the future, but also to reveal to the patient the precursors of his or her illness from out of his or her past. In short, accurate prediction and postdiction have been and can be the basis of great perceived therapeutic potency and the basis of the illusion of control over the disease process. In the field of clinical practice, a physician is never asked to reinstate a cured disease (“do that again”) to demonstrate his or her control over the mechanisms of disease. Clinical practice never requires experimental replication of unpleasant illness.

This conditioning analysis of the historical health care situation demonstrates how perceived therapeutic potency can be acquired by simply being a good observer and having a detailed knowledge of the sequence of onset of specific symptoms of common diseases. The ability to recognize that one has confused prediction and description with control of pathophysiological mechanisms requires a level of analytic thought that is unlikely in a fearful and aroused patient.

These speculations lead to more general notion that all stimuli in the clinical therapeutic situation (the therapist and his or her behavior, the staff, the tools and procedures, the physical environment and furnishings, etc.) can be conveniently divided into two classes of events: (1) UCSs and (2) CSs or discriminative stimuli. This analysis assumes that all people who are sick as a result of disease, injury, or dysfunction are in a state of health deprivation that selectively sensitizes their attentional process to stimuli (UCSs and CSs) labeled “therapeutic” by their culture. The disruptive, uncomfortable, and perhaps life-threatening predicament of patients focuses their attention on stimuli that in vivo or vicarious social learning has shown to reduce the unpleasant drive stimuli associated with illness.

Unconditioned Stimuli

UCSs (physiological/chemical or behavioral/psychological) are a class of events that reliably elicit or increase the probability of therapeutic responses (UCRs) by altering the mechanisms of pathophysiology. An example of such stimuli would be behavioral responses (UCSs) that reduce the elevated frontal EMG levels that are presumed (Ostfeld, 1962; Wolff, 1963) to be etiological to muscle contraction headache pain. Theoretically, the definitive feature of UCSs in this analysis is their ability to reliably (within the limits of adaptation at the receptor or reflex level) alter the underlying response mechanism (sustained contraction of muscles of head and neck, or UCR) of disease, injury, or dysfunction, and eventually its observable physical and/or behavioral symptoms. Some UCRs (e.g., emesis, eyelid blink) can be triggered by multiple physical stimuli (UCSs). For example, both a puff of air and a loud noise may elicit an eyelid blink. Emesis may be elicited by both ipecac and mechanical methods like fingers in throat. But other UCRs may be elicited only by a narrow class of UCSs. For example, some acute infectious diseases are responsive only to a narrow class of antibiotics (UCSs), while most chronic diseases (e.g., cardiovascular disease, respiratory disease) are reliably responsive only to a combination of several interventions (UCSs), such as diet, medication, exercise, and lifestyle change (e.g., stopping smoking, alcohol reduction, etc.). The onset or offset of many chronic diseases appear to be determined by multiple UCSs. Some UCSs, or reliable elicitors or reinforcers of the mechanisms of disease or dysfunction, are easier to see and specify in medicine than in psychology—for example, the effect of appropriate doses of insulin (UCS) on the glucose metabolism response (UCR) of diabetics, or the effects of morphine (UCS) on the pain response (UCR) of the postsurgical patient, or the effects of penicillin (UCS) on pneumococcal pneumonia. Such UCSs (morphine, penicillin, insulin, etc.) are believed to operate directly or indirectly on the theoretical mechanism of the illness or its pathophysiology. In the original Pavlovian laboratory analogue, which is not obscured by presumed etiological mechanisms, the UCS, food in the mouth or the sight of food, will reliably elicit salivation (UCR), particularly if the animal is hungry (selectively sensitized to certain classes of stimuli by food deprivation). Similarly, the sight of a socially sanctioned healer (“doctor,” swami, or shaman) will reliably elicit “hope,” particularly if the person is health-deprived. “Health deprivation” is a general state of reduced physical
and psychological mobility and dependency induced in sick people by the eruption of unpleasant and unfamiliar physical symptoms (e.g., changes in skin color, edema, fever, pain on movement, boils and pus, respiratory distress, etc.). The state of health deprivation selectively sensitizes the patient to a class of stimuli (the healer, his or her substances, and his or her rituals) that have previously reduced unpleasant and unfamiliar symptoms. A state of health deprivation appears to be an important precondition for the learned component of disease or dysfunction.

**Conditioned Stimuli**

CSs are certain neutral stimuli that initially do not elicit a UCR (e.g., change in glucose metabolism, emesis), but that as a function of repeated association with an appropriate UCS (e.g., insulin, ipecac) can come to inhibit even temporarily the symptoms and/or underlying mechanism of the disease, either directly or indirectly. The neutral CS, as a function of contingency with the UCS, can now elicit a fractional anticipatory component of the UCR. Neutral stimuli (CSs) may also be associated with the onset of the underlying mechanisms or symptoms of disease or injury (UCSs). Such CSs may actually potentiate the disease or illness. CSs are ineffective with vertebrates if the UCR is elicited by a route other than the CNS (Hilgard & Marquis, 1940). CSs may alter some disease mechanisms indirectly by modifying, for example, neuroendocrine or other CNS mechanisms that can inhibit immunocompetence (Ader, 1981; Ader & Cohen, 1982; Bovbjerg, Ader, & Cohen, 1982) or that can theoretically disinhibit or potentiate immunocompetence. If, on the other hand, the UCR (depression, anxiety, pain, etc.) is elicited directly through CNS activity, then CSs may act directly on the presumed mechanism of the disorder (e.g., excessive sympathetic activation, depletion of norepinephrine, activation of endorphins, etc.) and rapidly cause a positive clinical outcome. For example, the ingestion of a tablet of aspirin is frequently reported to relieve headache pain long before the active ingredient (pharmacological effect) working peripherally can alter pain.

CSs may also operate as “safety signals” (Mowrer, 1960) to potentiate healing. Mowrer (1960) indicated that neutral stimuli associated with the offset of pain or fear can be termed “safety signals” because they are associated with the reduction of anxiety or equivalently with the arousal of “hope.” They indicate that the period of suffering is over. Neutral stimuli (CSs) in the health care situation can become conditioned by their association with either the onset of the mechanisms and symptoms of health or the offset of the symptoms and mechanisms of disease. Certain CSs or discriminative stimuli in the medical situation are repeatedly associated with the onset of potent UCSs (morphine, antibiotics, insulin). For example, CSs like syringes, stethoscopes, white coats, and certain behavioral procedures (cleaning the skin with alcohol swabs, physical examinations) are routinely paired with potent UCSs like morphine, insulin, and antibiotics.

Also, culture-specific cognitive verbal labels for places (“hospital,” “laboratory,” “emergency room,” “clinic”), procedures (“medical,” “scientific,” “graphing,” “measuring”) and persons (“medical,” “professor,” “doctor”) can also be associated with potent UCSs or active ingredients, and come to acquire conditioned properties. CSs reliably associated with the offset of aversive stimuli (electric shock, childbirth, ugly skin eruptions, headache, painful injury, etc.) can acquire conditioned positive reinforcing properties (Mowrer, 1960). In other words, these CSs come to operate like “safety signals” (Mowrer, 1960). These phenomena are well established in the laboratory (Kimble, 1961) and are discussed below.

**THE PLACEBO AS A CONDITIONED RESPONSE**

I propose that a variety of inert, neutral, or nonspecific substances, procedures, persons or places can come to function as CSs (Pavlov, 1927) or discriminative stimuli (Skinner, 1953) for the alleviation of anxiety, pain, dysfunction, trauma, and disease, if such CSs or discriminative stimuli have been repeatedly associated with the onset (see footnote 2) of powerful UCSs (e.g., like penicillin, nitroglycerine, insulin, morphine, etc.) that reliably relieve both the mechanisms and overt symptoms of illness (e.g., pneumococcal pneumonia, angina pectoris, diabetes, post-surgical pain).

Mowrer’s (1960) analysis of secondary reinforcement based on negative primary reinforcement points to other ways in which neutral stimuli can come to acquire both “nocebo” and placebo effects. Unfamiliar reactions (skin eruptions, pus discharges, etc.) and unpleasant symptoms (fever, pain, insomnia, etc.) are naturally occurring aversive reactions (UCRs) that are triggered by some underlying disease process, injury, or dysfunction (UCS). Neutral stimuli (CSs) associated with the onset and course of the disease reactions (UCRs) may become negative CSs. These CSs may elicit CRs that potentiate the UCRs or disease reactions, by either directly or indirectly inhibiting mechanisms of immunocompetence (Ader, 1981). Such CSs can be termed “nocebos” and the learned response to them a “nocebo response.”

In fact, it is sometimes observed that simply changing the patient’s physical environment (deleting those CSs or nocebos) will potentiate spontaneous remissions, when other variables (e.g., medication ingestion, degree of environmental structure, etc.) are held constant. This phenomenon is most often observed with the hospitalization of mental patients.

Neutral stimuli associated with the offset (due to spontaneous remission or delivery of an active drug) and diminution of unpleasant symptoms and/or painful disease processes (UCSs) may come to acquire positive conditioned properties for healing and anxiety reduction, and may operate as “safety signals” as discussed above. Instances of such neutral stimuli may be the arrival of the physician/therapist, the physical examination, the prescription of medication, and the rituals of medication ingestion.
Hence, CSs for pain reduction and healing can be produced in at least two ways: (1) by association with the onset of an active ingredient for healing (e.g., morphine, insulin, nitroglycerine, penicillin); (2) by association with the offset of the symptoms of an unfamiliar, unpleasant, and painful disease or injury. Finally, neutral stimuli associated with the onset of the symptoms (UCRs) of a painful and unfamiliar disease process may come to elicit conditioned anxiety and/or a fractional anticipatory disease response components, and may be called nocebos.

In view of the analysis above, the labels “inert” and “nonspecific” appear to be less heuristic today. Because this analysis suggests that a variety of neutral substances or procedures that are initially inert or do not reliably alter the underlying mechanisms of disease can, if repeatedly associated with appropriate UCSs, come either to attenuate or to potentiate the disease process and pathophysiology, based on conditioning mechanisms. This analysis predicts (1) that psychological responses (CRs) that were previously relegated to the realm of “nonspecific” factors can come to reliably attenuate or potentiate health and illness; (2) that initially neutral stimuli (CSs) can come to influence the underlying physiochemical and cellular mechanisms (pathophysiology) of health and illness, either directly or indirectly; and (3) that, theoretically, the influence of such variables on the symptom and mechanism of disease can be demonstrated in appropriately controlled double-blind studies in which the UCS (active chemical ingredient) is withheld.

The notion of active ingredients in a drug or procedure has generally been that which the relevant therapeutic theory singled out as specifically remedial for the condition. For example, penicillin is the active ingredient for pneumococcal pneumonia, according to therapeutic theory, because the disease is caused by pneumococcus, which is sensitive to penicillin. The notion of “specific activity” (Wickramasekera, 1977b, 1977c, 1980) in medicine has traditionally meant (1) that the therapeutic mechanism of action was exclusively a physiochemical one; (2) that the action of the active ingredient was logically related to the presumed etiology (pathophysiology) of the disease; (3) that the therapeutic effect was reliable; and (4) that the therapeutic effect was durable.

Clearly, the CR analysis given above of the placebo effect, and the new psychobiological models (Engel, 1977; Lipowski, 1977; Weiner, 1977) of disease and dysfunction, render the traditional notion of “specific activity” outmoded. On both theoretical and empirical grounds, it is clear that most modern chronic illness is multiply determined, and the present analysis points out that every disease process (UCR) may have a CR component and is therefore psychophysiological in nature. The Pavlovian concept of a UCS (physiochemical or psychological) as an independent variable may be more heuristic today than the notion of “specific activity.” As this analysis points out, illness and disease mechanisms are not insulated from conditioning effects. The UCR is a function not only of the UCS (specific ingredient), but also of any associated CS. This learning or conditioning effect is inevitable, given an intact complex CNS. The present analysis indicates that intrinsic to all effective interventions or events (chemical, surgical, psychological, or psychophysiological) is the potential for learning or Pavlovian conditioning. Learning that is initially electrical in nature and later physiochemical in character can lead to neuroendocrine and neuroimmunological changes that alter biological structures. Current models of disease (Engel, 1977; Weiner, 1977) suggest that changes in the dependent variable, or health (UCR), can be accounted for by several specifiable independent variables (UCSs) operating either directly or indirectly on the UCR, and that some of these independent variables (CSs) may be psychological in nature.

The literature of respondent conditioning clearly demonstrates that the response to a UCS (e.g., nitroglycerine) will inevitably involve two components. The first component will be a UCR (nonplacebo response) elicited by the active ingredient or UCS (e.g., nitroglycerine). The second component is a CR or learned fractional component of the UCR, elicited by neutral events surrounding the delivery of the drug. The latency and magnitude of these two response components may be different. The CR will have a shorter latency because it is centrally mediated. The CR will also be of smaller magnitude than the UCR. Hence, the UCS inevitably elicits two response components, a CR and a UCR. This analysis saliently points out that intrinsic to all effective interventions (physiochemical, surgical, or behavioral) is the potential for Pavlovian conditioning (Pavlov, 1927), and therefore for placebo learning. Counterintuitively, it predicts that therapists who use UCSs or active ingredients will get stronger placebo effects than those who use only CSs or neutral ingredients, because regular UCS-CS association strengthens the CR. This model also paradoxically predicts that progress in isolating UCSs or active physiochemical, surgical, or behavioral procedures will inevitably lead to more and stronger placebo effects. Thus, therapists who routinely use UCSs or active ingredients will eventually enjoy escalating placebo effects and may be perceived as “miracle workers,” when in fact only a part of their “miracles” can be directly traced to their use of UCSs or active pharmacological or surgical techniques. In this analysis, then, medical science emerges as a uniquely human historical endeavor to isolate UCSs or reliably effective ingredients (nitroglycerine, digitalis, etc.). Hence, the potential for respondent conditioning exists in all human situations (not just medical ones) in which UCSs are used or reliably effective events occur.

3. There are a few exceptional instances in which the CR and the UCR are in opposite directions (e.g., the UCR to atropine is a dry mouth, and the CR is salivation; the UCR to small doses of insulin is hypoglycemia, but the CR is hyperglycemia).
COMPONENTS OF THE CONDITIONED PLACEBO RESPONSE

The nature of the conditioned placebo response in healing is unknown today. It is probably a complex patterned psychophysiological response (Schwartz, 1976) that is a composite of (1) cognitive-verbal, (2) motor, and (3) physiochemical responses.

The Cognitive-Verbal Component

The cognitive-verbal component may be recognized subjectively as an emotion like "Hope" (Frank, 1973; Mowrer, 1960). But not all cognitive and emotional information processing is explicitly verbally mediated or conscious. There is new evidence from several converging experimental and empirical sources that a salient amount of cognitive and emotional information processing continues in the absence of conscious awareness (Davidson, 1980, in press; Nisbett & Wilson, 1977; Shevin & Dickman, 1980). In fact, in the case of overlearned behaviors that are critical to survival, or where channel space for conscious information processing is limited, unconsciousness and automaticity in response may be very adaptive features of behavior. Mowrer (1956) has proposed that neutral stimuli associated with the onset of pain (e.g., a common symptom of disease, dysfunction, or injury) will acquire drive (e.g., anxiety) properties, and that stimuli associated with the offset (cessation) of pain will acquire reinforcing properties ("hope") or will operate as "safety signals." CSs (cognitions, visual impressions, tactile-kinesthetic sensations) associated with the onset of the injury or unpleasant symptoms of disease (UCSs) will come to elicit conditioned anxiety. The visit to the "doctor," the prescription and ingestion of medication, and the like are neutral events ("safety signals") that have previously (in health care history) been associated with active pharmacological agents or UCSs and the offset or reduction of pain and discomfort. Hence, these "safety signals" (CSs) may have acquired anxiety- and/or uncertainty-reducing properties or even fractional anticipatory healing properties (the physiochemical correlates of which remain unspecified today). Neutral events like the visit to the doctor and the "prescription" can operate as conditioned "safety signals" that can inhibit the aversive conditioned anxiety (CR) from cognitions (CSs) and sensations (CSs) associated with the disease onset and maintenance. "Safety signals" like a white coat (CS) and a prescription (CS) can indicate that the period of pain, uncertainty, fear, and depression is over, and that the period of relief and healing is here. The safety signals can both inhibit anxiety and disinhibit the subjective emotion of hope.

The Motor Component

The motor component of the placebo response is probably strongly controlled by the patient's mood (emotions) and current environmental

A Conditioned Response Model

reinforcement contingencies. Current reinforcement contingencies may sometimes be able to override mood and alter motor behavior temporarily, prior to stable and positive changes in emotion. But generally, as the patient's mood starts to "feel better" and as the inhibition of motor activity by emotions like pain and depression recede, the patient may adapt his or her behavioral repertoire by resuming such normal activities as eating, copulating, and returning to work. These adaptive activities then fill the temporal and behavioral vacuums that were previously occupied by maladaptive uncertainty, fear, pain, and depressive cognitive-affective ruminations. These conditioned aversive cognitive-affective ruminations (occurring both consciously and unconsciously) probably potentiated the unconditioned components (UCRs) of the disease or injury. This analysis may be particularly relevant to chronic diseases and functional disorders (e.g., low back pain, diabetes, cardiovascular disorders, musculoskeletal disorders, cancer, etc.) where the long-term and intermittent reinforcement nature of the UCS (disease process, injury, or dysfunction) enhances the probability of conditioning effects. It is a well-established fact that intermittent reinforcement by the UCS will make a maladaptive cognitive, motor, or affective habit maximally resistant to extinction. The chronic intermittent activation of the disease mechanism by the UCS (physiochemical cause) may lead to increasingly pervasive aversive anticipatory cognitive and affective responses, markedly resistant to extinction, that inhibit the motor system even when the UCS is dormant or inactive in chronic diseases.

The Physiochemical Component

The physiochemical component of the placebo response probably involves at least two subcomponents: psychoneuroendocrine and psychoneuroimmunological components.

PSYCHONEUROENDOCRINE SYSTEM

It now appears that there are descending pain inhibitory pathways from the medial brain stem to the dorsal horn of the spinal cord (Cannon, Liebeskind, & Frank, 1978; Mayer, Wolfe, Akil, Carder, & Liebeskind, 1971). These pathways may involve both opiate and nonopiate mechanisms. The opiate mechanisms can be activated by endogenous morphine-like substances termed "endorphins," and apparently also by electrical stimulation of certain brain sites (e.g., periaqueductal gray matter, etc.). Whether certain types of state-specific cognitive-affective activity (e.g., hypnotic analgesia) can stimulate these brain sites is not known. It appears that the opiate mechanism can be activated within seconds of CNS stimulation; that the analgesic effects extend beyond the period of stimulation; and that the stimulation is particularly effective with clinical as opposed to experimental pain. It
appears that other rapidly activated nonopiate pain inhibitory systems (e.g., hypnotic analgesia) are not blocked by naloxone (J. Barber & Mayer, 1977; Goldstein & Hilgard, 1975; Mayer, Prince, Barber, & Rafii, 1976). A recent study (Levine, Gordon, & Fields, 1978) and two extensive literature reviews (Babcock & Fields, 1978; Verebey, Volavka, & Clouet, 1978) suggest that the activation of the endorphin system may be one of the primary chemical mechanisms of pain reduction in the placebo response. However, other cognitively initiated (hypnotic analgesia) but chemically mediated psychoneuroendocrine pain inhibitory systems may also exist (Sternbach, 1982).

There is good evidence that depression potentiates chronic clinical pain (Merskey & Hester, 1972; Taub & Collins, 1974), and it has been suggested that decreased functional activity in the endogenous opioid system may be linked to the pathophysiology of depression (Gold, Pottash, Sweeney, Martin, & Extein, 1982). Both pain sensitivity and deficits in pleasure (depression susceptibility) may be mediated through the catecholamines serotonin, norepinephrine, and dopamine, which are known to play a role in opiate action. Hence, one rapidly activated psychoneuroendocrine mechanism through which a placebo stimulus may reduce both depression and pain sensitivity is through the recruitment of the endorphin system.

**A Conditioned Response Model**

**DEVELOPMENTAL ASPECTS OF THE CONDITIONED PLACEBO RESPONSE**

**Historical Aspects**

Developmental, the child or immature organism, in a stage of dependency and deprivation, is the ideal candidate for conditioning or placebo learning. The reliable delivery of food, clothing, and shelter to dependent immature organisms is in the final analysis associated with the strength and intelligence of the adult parent. In the developmental history of the immature organism, the effective and reliable satisfaction of needs may be associated with certain neutral (CS) features of persons (height, weight, color), response styles (authoritarian, permissive), and places. The ability of an adult caretaker to intervene effectively and reliably to reduce discomfort, uncertainty, fear, and pain, or to produce specific changes (pain, fear) in the individual, the tribe, or the physical environment, is the original basis of the notion of active ingredients or UCSs. For example, a dominant adult male baboon who loses his teeth (UCS), or a political leader who loses his or her wits (UCS) due to senility, is likely to be pushed aside eventually by younger, stronger, and more intelligent members of the group, who can more reliably and effectively conceive (punish or reward) the older, weaker, and less intelligent group members. Both the dominant baboon and the leader will eventually encounter “placebo sag” (Wickramasekera, 1977b, 1977c) or “credibility extinction” as their active ingredients or UCSs (teeth, muscles, IQ) fade with senility. The potency of their “packaging” or neutral features (CSs) cannot be sustained without at least intermittent demonstrations of strength and intelligence (UCCs). From this analysis, general intelligence, a UCS, emerges as a potent and highly generalizable new (on the evolutionary scale) behavioral UCS. A complex active ingredient or UCS such as general intelligence can produce specific and reliable changes in both physiocochemical and psychological domains. General intelligence, then, coupled with pertinent information, can be a potent behavioral UCS, on a par with other active ingredients (e.g., physicochemical) and capable of producing respondent conditioning effects. “High credibility” in this analysis is a quality of any behaviors (stimulus events) that reliably produce credible and potent physical, biological, and/or psychological changes in the environment for one's own benefit or the benefit of others. Hence, baboons, leaders, and therapists who come to lean increasingly on their UCSs or packaging (neutral features) will inevitably encounter “placebo sag” as their active ingredients (muscles, teeth, IQ) or UCSs fade. They will be discovered to be “impostors” and historically identified as “quacks.” On the other hand, those who use primarily UCSs or active ingredients will get stronger placebo effects than quacks, will enjoy escalating credibility, and will be seen as miracle workers, when in fact only half of their miracles can be traced to their

**PSYCHONEUROIMMUNOLOGICAL SYSTEM**

There is now evidence that the immune system, the primary mechanism of healing, is not totally independent of the CNS and the psychosocial environment. At least three lines of evidence (hypothalamic lesions, adrenocorticotropic hormone [ACTH] and the adrenal cortical axis, and classical conditioning) suggest that the CNS events can potentially and reliably alter the immune system (Adler, 1981; Hirsch, 1982). More specifically, there is now evidence that anxiety and depression can inhibit the immune system (Rogers, Dubey, & Reich, 1979). There is also good experimental evidence that Pavlovian or respondent conditioning procedures can modestly but reliably reduce immunocompetence (Adler, 1981). Theoretically, respondent conditioning procedures may also be able to significantly potentiate immunocompetence, but this remains to be experimentally demonstrated. The clinical implications of this prediction are quite profound. Hence, through such CNS mechanisms as emotion and expectancy learning (Pavlovian conditioning), even the immune system may be influenced by placebo stimuli (CSs).

In summary, the placebo response is probably a composite of patterned, interacting verbal-subjective, motor, neuroendocrine, and neuroimmunological response systems that can attenuate or potentiate both the underlying mechanisms of pathophysiology and overt clinical symptoms.

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active ingredients or UCSs. The other half will be a function of the subjects' anticipatory responses (CRs) elicited by neutral features (CSs) of the "miracle workers." Science in this analysis emerges as a uniquely human quest to identify, isolate, and manipulate UCSs, so that our physical, biological, and psychosocial environments may be rendered more predictable, more reliably controllable, and more nearly explainable.

**Acquisition Phase**

A dependent organism is a prerequisite for effective conditioning. The physical and psychological immobilization of the organism by health deprivation (injury, infection, tissue, damage, high fever, disorientation, unpleasant and unusual symptoms, fear, and depression) creates both the prerequisite dependent patient role (Mechanic, 1972) and the opportunity for conditioning.

Fear, anxiety, and uncertainty can be inhibited and the attentional process brought to focus in expectant arousal, when parents or caretaker surrogates (doctors, priests, etc.) enter the health-deprived person's environment. The focusing of the attentional mechanism on the physician, and the inhibition of anxiety and fear by a psychophysiological attitude of expectant arousal (hope), are based on prior primitive and infantile social learning (opener, respondent, vicarious) in which parental entry and intervention are associated with the reliable offset of aversive events (danger and deprivation) and the onset of reinforcing events (food, protection from danger and pain, etc.). Parental figures have acquired the properties of "safety signals" (Mowrer, 1960) that inhibit fear and anxiety and disinhibit an attitude of expectant arousal (hope).

During the acquisition or credibility formation phase, the placebo stimulus and response to be conditioned probably involve: (1) awareness of the CS-UCS and the response-reinforcement contingency; (2) implicit or explicit verbal mediation of this contingency; and (3) conscious awareness of several culture-specific, socially learned credible "safety signals" (discriminative stimuli). These culture-specific credible safety signals (e.g., rattles, syringes, pills, potions, wands, stethoscopes, etc.) may or may not be verbally encoded as safety signals. The CSs or safety signals can inhibit worry, doubt, and skepticism. Worry can interfere with the operation of natural homeostatic healing mechanisms. For example, worry and doubt can cause sleep onset or psychophysiological insomnia, thereby inhibiting sleep onset and its healing neuroendocrine consequences. It is clear that the bulk of insomnia is psychophysiological and is caused by cognitive or physiological hyperactivity stimulated by anxiety and worry that is conscious or unconscious. There is also growing evidence that anxiety can inhibit the immune system (Rogers et al., 1979).

The inhibition of worry and doubt by conditioned safety signals (e.g., a placebo pill, an ointment) can make the patient more receptive to healing instruction suggestions given by a physician or therapist. Safety signals may potentiate the instructional signal by inhibiting "noise" or worry, and by improving reception of messages. For example, the migraine patient may be given suggestions to constrict cerebral arteries in the second (pain) phase of the disorder by relaxing and reducing sympathetic outflow. The patient with asthma may be given suggestions for bronchodilatation. A study by Luparello, Leist, Lourie, and Sweet (1970) in fact demonstrated that the pharmacological action of a bronchodilating drug (UCS) could be doubled on a measure of airway resistance if bronchodilating suggestions (CSs) were associated with the delivery of the drug (UCS). Hence, safety signals may also potentiate the action of active pharmacological agents (UCSs) by inhibiting "noise" or cognitions of uncertainty and doubt. Cognitions of uncertainty and doubt may operate as negative CSs that attenuate the effects of a UCS (active drug).

These discriminative stimuli or CSs may also influence the rate of acquisition of the placebo response by potentiating attentional and arousal mechanisms. These credible signals may be quite diverse: (1) The labeling of the therapist (e.g., "doctor," "swami," "professor," etc.) can influence his or her attention and arousal stimulus value in a given culture. (2) The credibility of the therapeutic setting (e.g., emergency room of a hospital, temple, university medical center, parking lot) can also influence the above-described mechanisms of learning. The university medical center, in North American culture, is the new temple of healing. (3) The credibility of the placebo per se (e.g., size, shape, color, taste) and the credibility of (the) administration ritual (e.g., oral vs. injection, a single dramatic or startling episode like surgery) can also influence attention and arousal conditions. (5) Finally and very saliently, the nature of the interpersonal relationship between the patient and the therapist (e.g., accurate empathy, confidence, warmth, authoritarianism) can influence the attention and arousal properties of these events. The attention and arousal value of these CSs can be directly related to the extent to which they have previously been reliably associated with specific and effective interventions on behalf of the patient when he or she was an immature and dependent organism.

In the acquisition of most new materials (e.g., math) or tasks (e.g., driving a car), it is likely that the specification of component responses facilitates conditioning. The sequential specification of the emission or elicitation of these component responses and the accurate verbal mediation of these component responses will reduce errors in the acquisition phase of learning. During this first phase, large individual differences in pertinent subject characteristics (e.g., autonomic nervous system lability, hypnotizability, general intelligence), a subject's history of reinforcement and punishment, and the culture-specific context of learning can influence placebo learning through the determination of attentional and arousal
mechanisms and the specification of what is a “credible” CS for a given subject.

Consolidation Phase

After the placebo response is well established through repeated association with potent UCSs or active ingredients, it probably (1) becomes increasingly abbreviated, (2) involves minimal or no awareness, (3) becomes rapid and automatic, (4) involves a bypass of the verbal or dominant hemisphere, and (5) preferentially involves the minor hemisphere. Hypnosis, like the consolidated placebo response, also appears to involve the nondominant hemisphere preferentially. Indeed, the conditioned placebo response may be potentiated or attenuated by some of the same variables that determine hypnotic responsivity; these variables are specified later. The importance of bypassing the dominant hemisphere is that the lack of verbal mediation, and the very rapid, automatic elicitation of the placebo response, make it relatively independent of the critical, skeptical, analytic mode of information processing that is typical of the dominant hemisphere. Hence, the short-latency placebo response occurs before doubt and skepticism (“noisy”) can inhibit or attenuate the response or “signal.” Stimulus events can directly elicit physiochemical or visceral changes without the interference of the critical, skeptical, filtering mode of information processing that is typical of the dominant hemisphere. This may be similar to the profound visceral and neuroendocrine changes that can occur in response to a CNS event (e.g., being charged by a lion in a dream) when there is an inhibition of critical, analytic brain functions during sleep.

Developmentally, the placebo response may begin as what Spence and Taylor (1951) and others (Cerekwicki, Grant, & Porter, 1968; Grant, 1972) have called a “V form” of classical conditioning, but it can develop into a “C form” of conditioning. The basis of this distinction is the degree of verbal mediation and volition involved in the CR. The mechanism of placebo responding is probably most effective when, in the “C” or second stage, it is increasingly automatic and involves a bypass of the dominant verbal hemisphere’s critical, analytic mode of information processing. In the “C” phase it is probably a short-latency, automatic response that can be labeled an “unconscious” response. Currently, the bulk of experimental evidence from several fields of empirical research (selective attention, cortical evoked potentials, subliminal perception) supports the position that the registration of perceptual stimulation can occur outside of conscious awareness (Dixon, 1971; Erdelyi, 1974; Kahneman, 1973; Nisbett & Wilson, 1977; Shevrin & Dickman, 1980) and may be consciously recognized only as a change in behavior or a subjective change in mood or feeling. There is also evidence unrelated to psychodynamic clinical speculation that many of the determinants of social behavior are not open to conscious inspection or specification (Nisbett & Wilson, 1977) and that a large part of cognitive and emotional activity occurs without conscious awareness (Davidson, 1980). It appears that overlearned and less conscious information processing is preferentially localized in the nondominant hemisphere (Luria & Simeritskaya, 1977) and that the frontal lobes are preferentially involved in emotional arousal (Davidson, in press).

PLACEBO RESPONDING

Health Deprivation, Anxiety, Dependency, and Placebo Responding

The eruption of strange physical symptoms on the patient’s body, pain, and discomfort all induce uncertainty and anxiety, from which the patient craves relief. This situation of physical immobilization (health deprivation) by symptoms like pain and fear reactivates earlier or regressive dependent attitudes, which increase the patient’s receptivity to direction from caretakers or credible healers. In other words, health deprivation makes the good placebo reactor particularly dependent and receptive to help from others. Effective conditioning requires a deprived, anxious, and dependent subject. Anxiety has been shown (Evans, 1974a; Thorn, 1962) to be reliably related to placebo responding. The acquiescence tendency or the tendency to agree (“yes-saying”) has been reliably but modestly and positively correlated with both placebo responding (Jospe, 1978) and hypnotizability (Hilgard, 1965). Hence, the results of several experimental and empirical studies reviewed by Jospe and Hilgard point to the role of anxiety, dependency, and the noncritical, nonskeptical mode (the nondominant-hemisphere or hypnotic mode) of information processing in placebo responding and hypnosis.

Placebo Responding and Hypnotizability

Shapiro (1971) has pointed out that laboratory tests of hypnotic susceptibility show an unreliable relationship to placebo responding. Several other analyses have also cast doubt on the existence of a reliable relationship between hypnotizability and the placebo response (Evans, 1969; Katz, Kao, Spiegel, & Katz, 1974; Moore & Berk, 1976; Thorn, 1962). It is possible that this unreliability is due to the activity of other moderating variables (e.g., low credibility, health deprivations, accurate empathy, authoritarianism, levels of attention and arousal, potency of instructional signals), which were not systematically manipulated in the studies relating hypnotic susceptibility and placebo responding. The observation of reliable and orderly relationships between complex events in the empirical world awaits attention to all the relevant variables.

The strongest evidence to date showing a lack of relationship between hypnotizability and placebo responding is a study by McGlashan, Evans, and Orne (1969). This study found the degree of hypnotizability to be
unrelated to the magnitude of the placebo response. However, there are several problems with making inferences and generalizing to a clinical situation from this laboratory study, and, therefore, any conclusion may be premature. First, the McGlashan et al. (1969) study was a study of experimental pain, and in several areas the parameters of experimental and clinical pain do not overlap (Melzack, 1973). Caution is necessary in generalizing from this otherwise excellent study to the phenomena of clinical pain. Second, in the McGlashan et al. study, there was a failure to use strong, extended, and specific instructions of dominant arm analgesia to mobilize the full potential of the highly hypnotizable subjects in the placebo analgesia session. The presentation of a rationale for a “drug” (placebo) can cognitively mobilize the hypnotic ability of the patient and can function as a hypnotic induction (Wickramasekera, 1976b). A study by Glass and Barber (1961) found that a placebo administered as a “hypnosis”-inducing drug was as effective as an actual trance induction in eliciting enhanced suggestibility. A more recent study of experimental pain by Knox and Gekoski (1981) has shown clearly that a subject’s level of hypnotizability is related to the placebo response. Evans (1967) reviewed two nonpatient and five patient studies of the relationship between suggestibility and placebo responding. In neither of the nonpatient studies, and in all but one of the patient (clinical) studies, there was a positive relationship between suggestibility and placebo responding.

I predict that with increased attention to those variables mentioned above as moderating the relationship between hypnotizability and placebo responding, more reliable and stronger relationships between suggestibility and placebo responding will emerge in clinical studies.

If the mechanism of the placebo response is conditioning, and if conditioning is enhanced by the degree of bypass of dominant-hemisphere functions (Saltz, 1973), then it is clear why good placebo responders, like good hypnotic subjects, inhibit the critical, analytic mode of information processing that is characteristic of the dominant verbal hemisphere. Good placebo responders tend to be individuals who are prone to see conceptual or other relationships between events that seem randomly distributed to others. They will inhibit the interfering signals of doubt and skepticism, which are consequences of the more analytic mode of information processing typical of the dominant (left) hemisphere. Like good hypnotic subjects, good placebo responders are likely to respond to the given stimulus properties of a drug potentiating it, out of their own rich subjective repertoires. Alternatively, they may negate or attenuate the effects of a UCS (drug) through negative attributions.

Shapiro (1971) describes placebo nonresponders as “rigid and stereotypic and not psychologically minded” (p. 445). There is a striking similarity between this description and that of a poorly hypnotizable subject. There is increasing evidence (Bakan, 1969; K. Graham & Pernicano, 1976; Gur & Gur, 1974; Lachman & Goode, 1976) that hypnotizability or suggestibility is predominantly a right-hemisphere (non-dominant or minor-hemisphere) function for right-handed people. Minor-hemisphere functions include holistic and imaginative mentation with diffused, relational, and simultaneous processing of information (Ornstein, 1973; Sperry, 1964); the tendency to “see” some relationship or “meaning” in data, however randomly generated (e.g., a Rorschach inkblot), would appear to be an aspect of creative mentation that is posited to be a property of the non-dominant hemisphere. This explanation can account for the common features of good placebo responders and good hypnotic subjects.

In the second phase (the consolidation phase) of placebo learning, the placebo response may become evident in the right hemisphere, which appears to be the hemisphere mainly involved in the hypnotic or suggestible mode of information processing. I hypothesize that at this stage the same variables that can influence hypnotic responding can also influence placebo responding. I predict that the placebo response can be potentiated through strong implicit or explicit verbal instructions (Wickramasekera, 1976b) if the following hypnosis-potentiating conditions are also systematically manipulated: (1) Low-arousal states, or training procedures (e.g., biofeedback) that induce low arousal, appear to increase hypnotic responsivity temporarily (Arons, 1976; Engstrom, 1976; Schacter, 1976; Wickramasekera, 1971, 1973b, 1977a). (2) Procedures that induce high arousal appear to increase hypnotic responsivity temporarily (Gur, 1974; Wickramasekera, 1972b, 1976a). (3) Sensory deprivation procedures also appear to increase hypnotic responsivity temporarily (Pen, 1963; Sanders & Reyher, 1969; Wickramasekera, 1969, 1970). (4) The subject’s level of attention to relevant stimuli appears to influence hypnotic responsivity (C. Graham & Evans, 1977; Krippner & Bindler, 1974; Mitchell, 1967; Van Nuys, 1973). (5) The baseline suggestibility or hypnotizability of the individual subject (T. X. Barber, 1969; Hilgard, 1965) has a profound effect on hypnotic responsivity.

PARAMETERS OF PLACEBO LEARNING

The Interstimulus Interval (CS-UCS)

Contemporary research (Kimble, 1973) on conditioning and learning clearly demonstrates that interstimulus (CS-UCS) intervals are not immutable, particularly with human subjects, and that they can exceed .5 milliseconds. A positive UCS in the health care situation can be defined as a stimulus that reliably elicits a set of specific therapeutic changes (UCRs) in the verbal-subjective, physiochemical, and motor response systems of a human subject. The UCS alters not only the overt symptoms, but also the pathophysiology of the disease or disorder. The CSs are initially neutral features of the
A Conditioned Response Model

TEMPORAL CONDITIONING

"Temporal conditioning” is a situation in which a specific time interval functions as a CS. A UCS occurs or is presented at regular time intervals, and during the test period the UCS is omitted on a portion of the trials. Under these conditions, a CR will occur at the time the UCS typically occurs. This form of conditioning may occur with some chronic diseases that have a fairly reliable intermittent onset. For example, primary dysmenorrhea may be caused part of the time by physiochemical (endocrine) stimuli (UCSs) of varying magnitude. But the chronic maintenance of severe symptoms of unvarying or increasing intensity may be in part related to psychoneuroendocrine events (CSs), such as temporarily conditioned anticipatory dysmenorrhea responses.

Phenomena of Conditioning

ADAPTATION

Repeated presentations of even potent UCSs can lead to the failure to evoke the UCR and to an absent or extinguishing CR. This phenomena is particularly likely to occur in the treatment of chronic functional problems treated symptomatically. In this instance, even initially potent but nonspecific drugs, such as Valium given for classic migraine headaches, can become less effective over time. For example, the physician and most aspects of his or her practice can lose the ability to elicit conditioned therapeutic responses. The physician has encountered “placebo sag” and becomes a “quack” in the eyes of the patient. Hence, even a careful CS-UCS analysis of the therapy situation would focus attention on the clear and urgent need for therapeutic stimuli to be targeted on the known or presumed etiology of the disorder, and not simply on peripheral symptoms.

SUMMATION

When two or more CSs are presented together, the strength of the CR will be stronger than to either CS alone. This implies that the presence of several “safety signals” or CSs will lead to a stronger placebo response (e.g., not 36% but perhaps 60%). The humane use of diagnostic electrical-medical high technology (e.g., CAT scans) (CSs) and efficacious drugs (UCSs) and/or effective surgical procedures (UCSs) may inflate the size of the placebo component in healing. When high technology and irrelevant (nonspecific) state-of-the-art diagnostic and therapy procedures are used without sacrificing humane patient care, by practitioners even with minimal UCSs, a large placebo component will be found. This situation probably occurs in large and prestigious tertiary care medical centers to which many patients with functional disorders journey over long distances, as if on a pilgrimage to temples of healing.
TWO-COMPONENT RESPONSE

A UCS will always elicit two components, a CR and a UCR. This is predicted because it is probably impossible to deliver a pure UCS isolated from a CS to a conscious vertebrate.

RESPONSE GENERALIZATION

A person who has learned to respond therapeutically to physician A or procedure A has also learned to respond therapeutically to almost equivalent stimuli (e.g., physician B and procedure B). This phenomenon is often clearly observable in the medical management of acute illness. Acute illness is effectively treated by the health care system, and psychosocial factors seldom have enough time to interfere with healing. In the case of chronic illness, however, we often observe attenuated therapeutic effects even to active therapeutic ingredient (UCSs), due to generalization of negative CRs from previous illness episodes or ineffective therapy.

GENERALIZATION OF EXTINCTION

When physicians use ineffective UCSs to treat chronic conditions, we often observe extinction of the placebo response—not only to the original primary care physician, but to all subsequent physicians. This extinction of the placebo component to even an effective UCS may jeopardize even a rational and effective treatment program, because it has been found that the placebo response may not only potentiate or attenuate a UCS (active drug), but may also negate its effects.

THE IMPACT OF EXPLICIT OR IMPLICIT VERBAL INSTRUCTIONS AND “INFORMATION” ON CONDITIONED RESPONSES

There is good evidence that “awareness” of contingency can potentiate the acquisition of CRs (Bandura, 1969). The patient’s conscious recognition of the association between the physician and efficacious UCSs (e.g., penicillin) will enhance the acquisition of learning of placebo responses. Also, information about the physician’s credentials, reputation among colleagues, and therapeutic record can potentiate or attenuate the placebo component of the healing. There is a large, well-established, experimentally based literature documenting the fact that instructions and information can potently influence both respondent and operant conditioning procedures (Bandura, 1969).

PREDICTIONS FROM THE MODEL

The following predictions appear consistent with the CR model of the placebo, and empirical data disconfirming any of these predictions will cast doubt on the theory.

1. Therapists who routinely use active ingredients (UCSs) will get stronger placebo effects (CRs) than those who do not. This procedure creates and reinforces the CS-UCS relationship that optimizes the conditions for “hope” (Frank, 1973). Intrinsic to all interventions with active ingredients (UCSs) is the potential for Pavlovian conditioning, and therefore for placebo learning. Hence, the stronger the active ingredient (UCS) or drug used, the stronger the placebo effect; the weaker the active ingredient or UCS intensity, the weaker the placebo response.

2. The response to any active ingredient (UCS) will come to include two components (CR + UCR): a placebo (CR) and an active component (UCR). In other words, a fraction of the response to a UCS will always include a CR—for example, the response to the sight of the syringe (CS) or the ingestion per se (CS) of the pill. In fact, it is very likely that the fractional anticipatory response (CR) will have a shorter latency than the response (UCR) to the UCS (e.g., morphine). The shorter latency of the CR will be due to the posited central mediation of conditioning effects, as opposed to the initial peripheral mediation of some drug effects.

3. Therapists who frequently use inert or placebo medication or procedures (CSSs) will get weaker placebo responses over time. This is an extinction procedure because withdrawal of the UCS (active ingredient) will eventually lead to extinction of the CR, or “placebo sag.” Therapists who have the “right packaging” (CSSs) but who lack a science or truly efficacious UCSs will eventually collapse under the weight of their own incompetence.

4. Numerous repeated presentations of the UCS in drug therapy can lead to temporary tolerance or habituation. But temporary withdrawal of the UCS will abolish “placebo sag.” CSs alone will not reliably show this recovery feature.

5. Dose-response and time-effect curves for a placebo and an active medication will be similar but not identical. Literature review (Evans, 1974a) supports this prediction. The response to CS is like the response to UCS but of shorter latency.

6. Patients higher on trait anxiety will be stronger placebo responders. It is known that trait anxiety is related to the acquisition and magnitude of CRs (Spence & Taylor, 1951). This model can comfortably embrace the anxiety reduction data reviewed by Evans (1974a).

7. The placebo response is predicted to be stronger under modified double-blind conditions. This implies that neither patient nor therapist should know that an inert or CS procedure is being used. In fact, they should both be told that only an active ingredient or a UCS is used. In general, there will be less inhibition of the expectancy mechanisms when this modified double-blind procedure is used. Credibility will be optimal with this modified double blind. Orne (1974) and Frank (1973) have stressed the role of expectancy and credibility in their analyses of the placebo.
8. The use of several placebo (inert or neutral) stimuli \((CS_1, CS_2, CS_3)\) can lead to a stronger placebo response (higher than the typical 35% rate) than the use of one placebo stimulus \((CS_1)\). It is known that when two \((CS_1 + CS_2)\) or more CSs are presented together, the strength of the CR is often greater than to either CS alone. This phenomenon is called “summation” (Kimble, 1961).

9. In the final analysis, there can be no CR if there are no UCS (active ingredients). Paradoxically, progress in isolating and manipulating active ingredients (UCSs) will inevitably lead to more and stronger placebo effects (CRs). In other words, “faith” will grow with progress in “science,” and it may be increasingly difficult to separate out the effects of CSs and UCSs.

10. If the baseline suggestibility of the patient is mobilized with specific explicit or implicit instructions, then the CR can be potentiated or attenuated.

11. Children, highly hypnotizable adults, and early adolescents can be stronger placebo responders because of their inherently higher baseline suggestibility (Hilgard, 1965).

12. Treatment procedures that use systematic (a) attentional manipulations, (b) induction of low or high arousal, and (c) sensory restriction can potentiate placebo components (CSs) plus any active ingredients (UCSs) in a procedure or substance.

13. Neutral persons, places, and procedures can operate as both positive or negative CSs. This may explain iatrogenic illness and may suggest ways of arranging the conditions for iatrogenic health. Nocebo effects can arise out of associating neutral stimuli with negative UCSs.

14. Patients whose childhood histories combine firm discipline with warm and effective relief of needs, plus an ability to entertain themselves alone, will be the best placebo responders. Patients whose childhood histories include few or no instances of predictable, reliable, and effective (positive or negative) interventions in their environment or on their behalf will demonstrate weak placebo responses to culture-specific, socially sanctioned health rituals. For example, autistic children will be poor placebo responders.

15. Skeptical, critical, analytic modes of thinking or information processing (typical of the dominant hemisphere) will attenuate or negate placebo responding (CR).

16. The placebo response will not occur if the healing ritual involves bypass of consciousness and the CNS.

17. The placebo response will occur maximally under conditions of strong motivation or real personal health deprivation (e.g., escape from life-threatening illness, pain, or fear). In clinical situations with sick patients, the threat to well-being is real, intense, cross-situational, and of unknown duration, whereas with nonpatients in experimental studies, the threat to well-being is superficial, situation-specific, reversible, and of known duration. The magnitude of the placebo response will generally be weaker with nonpatients. In general, the placebo response will be most potent in life-threatening medical situations, and not in personally trivial social-psychological experiments in university laboratories.

**TESTING THE MODEL**

The model must be tested under conditions of ecological validity. “Ecological validity” refers to the extent to which we may generalize from controlled laboratory studies of a phenomenon to similar phenomena in nonexperimental situations (clinical or natural environments). For example, it is well known that the parameters of clinical and experimental pain are different (Melzack, 1973; Sternbach, 1978). The placebo rate in double-blind experimental pain studies is small and ranges between 9% and 16% (Evans, 1974a) whereas the average placebo rate in double-blind clinical pain (postsurgical) studies is 36%, and thus substantially larger (Beecher, 1959). A sick or health-deprived person is in several psychological and physical respects different from a well person in an experimental study. A sick person is often immobilized by his or her symptoms cross-situationally. An experimental subject is only immobilized by experimental pain in a situation-specific (laboratory) sense. An experimental subject exposed to a physical stressor (radiant heat, ischemic pain, etc.) is a voluntary subject involved in an episodic and reversible stressful event, which does not intrude on the rest of the subject’s life. A sick person is immobilized cross-situationally in an involuntary situation, whose outcome is uncertain and which intrudes on all social, personal, and vocational aspects of his or her life. Uncertainty about the consequences of diagnosis and therapy, dependency on others, and lost mobility cause loss of self-esteem over the erosion of important social roles (income provider, caretaker, adult). Sometimes the impatience and progressive withdrawal of loved ones from the patient cause frustration, anger, and depression. These psychological reactions are often superimposed on the pain and physical discomfort caused by the physiological disease process. Therefore, both physically and psychologically, a sick person is not like a typical experimental laboratory subject. The CR model has been developed to predict behavior in a clinical situation and should be tested on sick patients in therapy.

**CONCLUSION**

Since this model of the placebo effect is formulated in terms of experimental psychology and learning, it may have some heuristic value, because it may lead us to the design of experiments that raise different questions about treatment and may lead us to interpret the responses in unexpected ways. This model makes several specific counterintuitive and paradoxical predi-
tions that may be worth testing empirically. A large body of precise and empirically validated principles from learning theory can now be related to the nebulus field of the placebo. This conceptual translation may stimulate new, sharper, and more focused thought and empirical investigation into this neglected psychobiological realm.

This realm includes psychological effects that are powerful but unreliable, rapid but not always durable, and clearly worthy today of investigation in their own right. It may even turn out that this realm includes the only therapeutic effects that are primarily psychological. It is perhaps time that we settled down to the tedious business of making these “nonspecific” effects specific by isolating, explicating, and specifying the type of subject, the type of therapist, and the situational and procedural conditions under which these effects can be negated, attenuated, or potentiated. It seems unlikely that all the phenomena today lumped under the label “placebo effects” can be comprehended within the present CR model. But we can no longer continue to dismiss these effects with impatience and embarrassment as “nonspecific,” “placebo,” or plain “nuisance” effects. It appears to me that these effects reside at and regulate the intersections of all psychobiological actions and transactions.

REFERENCES


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A Conditioned Response Model


A Conditioned Response Model


