The Placebo as a Conditioned Response: With 17 Predictions from the Model*

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A placebo may be defined as a presumably inert or neutral substance or procedure that elicits a therapeutic response.1

Some of the most vivid examples of a placebo effect are often referred to. In the area of clinical pain — the pain of patients — reviews of 26 double-blind studies covering 1,991 patients found that approximately 35 percent of them have severe pain reduced to at least a half of its original intensity by an inert substance or placebo drug. With experimentally induced laboratory pain, however, the placebo rate is considerably lower.2 The discrepancy between the success of a placebo in treating 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 on pain can also include surgical therapies. In a classic paper "Surgery as a Placebo," Beecher3 compared the results of questioning surgeons performing the then popular internal mammary-artery ligation for the pain of angina pectoris against the results of almost universally enthusiastic surgeons. Two independent skeptical teams, using a single-blind procedure, performed a bilateral skin incision on patients under local anesthesia and in randomly selected patients ligated the internal mammary artery. One team,4 found that 100 percent of the nonligated and 76 percent of the ligated patients reported both a decreased need for nitroglycerin (a medication to relieve the pain) and an increased ability to exercise. All nonligated patients showed improvement for more than 6 weeks. Six to 8 months later, those patients available for a follow-up examination had maintained their improvement. Neither the ligated nor the nonligated group showed any improvement in their electrocardiograms. The second team5 found that 6 months after surgery, 5 ligated and 5 nonli-

*This material was originally presented as an invited paper at the San Diego Biomedical Symposium, San Diego, California, November 1977. Later it was presented at a symposium on Non-specific Effects in Biofeedback Society of America, Albuquerque, New Mexico, February 1978. It has been published in abbreviated form in Proceedings of the San Diego Biomedical Symposium, New York: Academic Press, 1977 and the Journal of Clinical Engineering, 1977. I would like to thank G. E. Schwartz for encouraging me to reshape this model for left-brain (critical analytic) consumers, and particularly for his encouragement and critical comments during the review process.
gated patients reported more than 40 percent subjective improvement. Two nonligated patients showed dramatic improvement in their tolerance for exercise, and one nonligated patient even manifested an improved electrocardiogram after exercise. These studies demonstrated that actual ligation of the internal mammary artery produced no better results than a mere skin incision, and that skin incision by itself could generate a dramatic and sustained therapeutic effect.

Placebos may also be useful in the therapy of a wide range of disorders including coughs, headaches, asthma, multiple sclerosis, the common cold, diabetes, ulcers, arthritis, emesis, sea sickness, cancer, and parkinsonism.

Placebo effects are not limited to chemical and surgical treatments. A review of controlled studies of systematic desensitization and a pioneering credible double-blind study of clinical biofeedback have also found equally high rates of placebo response in these psychological treatments. For example, in the double-blind biofeedback study, which appeared in 1977, subjects who received false feedback information (the placebo treatment) improved clinically as much as those who received true feedback. An earlier study in 1968 found that mechanical devices such as medical instruments can also generate placebo effects, and in a paper commenting on the findings of the biofeedback study, I discussed the placebo effect of medical instruments.

It has also been found experimentally that a placebo can increase, attenuate, or negate the active ingredients in a drug; that it can have powerful effects on organic illness and malignancies, and can even mimic the effects of active drugs; that the dose response, the time-effect curves, and the side effects of an active drug and a placebo can all be similar.

When a therapeutic phenomenon such as the placebo occurs across such a wide range of clinical treatments (drugs, surgery, psychotherapies, biofeedback) and physical and mental symptoms (including pain, anxiety, edema, tachycardia, emesis, fever, vasocconstriction, phobias, and depressions), the implication is strong that it must be an ingredient in all clinical situations.

An examination of the placebo literature leads to several conclusions: (1) In any clinical study, a group of patients shows a significant therapeutic response to chemically inert or placebo substances, procedures, and objects. (2) As yet no reliable procedure exists to identify in advance this particular group of patients. (3) From study to study, the same group does not consistently respond to placebos. (4) Under the "right" conditions, any object or procedure offered with therapeutic intent can generate placebo effects. (5) The mechanism of the effect is unknown, and all the "right" conditions are unclear.

Many hypotheses have been advanced to explain the psychological mechanism of the placebo response. Shapiro and Barber appear to favor suggestion, and Evans appears to favor the reduction of trait anxiety. Frank and Strobel have stressed the role of expectancy in encouraging a therapeutic response. I have discussed these hypotheses elsewhere, and for reasons of space will not repeat my analysis here. Instead, I offer in this paper a new model of the placebo response. The model maintains, in short, that all reliably effective interventions, whether physiochemical, behavioral-psychological, or surgical, have the potential to be produced by Pavlovian conditioning and therefore to become placebos.

After this paper was written and submitted for publication, in 1977, one of the reviewers drew my attention to a relevant paper by Gleitman, Gantt, and Teitelbaum. I located and read this paper in July 1979. It was very exciting to note that the authors advanced one of the central components of the present theory more than 20 years ago. Their brief excellent paper summarizes some experiences in conditional reflex studies in dogs that relate placebo reactivity to established learning concepts. The observations are cited in informal anecdotal style and deal with three groups of unpublished studies. The first group "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 is a "miscellaneous one," which pertains to the general state of the organism and the general setting with respect to placebo effects. The authors' thoughts with respect to the first series are almost identical to mine, and with respect to the second and third series, there is substantial implicit agreement. But the paper provides no discussion of hypnotizability, brain lateralization, and the possibility that an unconditioned stimulus can be neurochemical behavioral events.

In October 1979, the editor of Biofeedback and Self-Regulation, Dr. J. Stoyva, drew my attention to a study by R. J. Herrnstein. 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.
I should note that there is no systematic human evidence to support or to disprove the model I advance here, it has not yet been put to the test. But there is some strong controlled animal evidence\textsuperscript{9} that supports the view that neutral stimuli — the nonspecific substances or procedures that sometimes induce a placebo effect — can elicit the complex biological and biochemical changes postulated by the model.

**ORIGINS OF THE MODEL**

Early in 1970, I was using electromyogram biofeedback therapy to help give patients with more than 20 years of chronic and continuous muscle-contraction headaches greater control over the muscles in their head and neck, and I made some observations that puzzled me.\textsuperscript{20} A group of patients reported relief of their headache pain with startling rapidity, often after no more than one or two sessions of EMG feedback therapy and several sessions before they demonstrated any measurable ability to reduce the relevant muscle tension. Since the etiology and mechanisms of muscle-contraction headache is presumed to be sustained contraction of muscles of the head and neck, changes in the verbal report of the intensity and frequency of headache pain should at least correlate with or follow a drop in frontal EMG levels, and certainly not precede it.

I wondered if this very rapid therapeutic response was not a conditioned placebo response to the impressive and highly credible biofeedback instruments, which evoked the anticipation of actual healing. As is well known, conditioned responses, mediated as they are by the central nervous system, occur more rapidly than do an unconditioned response — in this case, the actual reduction in muscle tension levels in the head and neck.

Such considerations led me to regard the rapid therapeutic response of the patients who so quickly reported improvement in their condition as a type of fractional and anticipatory\textsuperscript{21} conditioned response to the electronic medical instruments used in the therapy.\textsuperscript{22} The rapid therapeutic response (a conditioned response) to the sight of the biofeedback instruments (a conditioned stimulus) was like the conditioned response of salivation that Pavlov produced in a dog by a ringing bell (a conditioned stimulus), the salivation being a fractional component of eating that occurs in anticipation of food. (The rapidity of the response also reminded me of the well-known clinical observation that ingestion of aspirin often relieves a headache long before the aspirin's pharmacological effect could occur.) In short, it seemed possible that Pavlovian conditioning could account for a portion of the positive therapeutic outcome in electromyogram feedback therapy for headache. At the time, the mechanism for treating such a condition was thought to be an exclusively operant or Skinnerian conditioning (achieved through reinforcement and reward) that reduced frontal EMG.

This experience plus further speculation brought me to the more general notion that all stimuli in a clinical therapeutic situation (including the therapist and his or her behavior, staff, tools, and procedures, and also the physical environment and its furnishings) could be divided into two classes of events: unconditioned and conditioned stimuli.

Unconditioned stimuli (physiological-chemical or behavioral-psychological) reliably elicit or increase the probability of unconditioned therapeutic responses by altering the mechanisms of pathophysiology. An example of such stimuli would be the behavioral techniques that reduce the elevated frontal EMG levels that presumably are the source of muscle contraction headache pain.\textsuperscript{23} The definitive feature of unconditioned stimuli is their reliability in altering the underlying response mechanism of a disease, dysfunction, or an injury and thus, eventually, the physical and/or behavioral symptoms.

Conditioned stimuli, on the other hand, are initially neutral stimuli that do not elicit a therapeutic response but which, through repeated association with unconditioned stimuli that reliably elicit positive therapeutic responses, can come to inhibit the symptoms and/or the underlying mechanism of a disease. The formerly neutral stimuli elicit at least a fractional component of the unconditioned response and rapidly cause a positive clinical outcome.
The Pavlovian Model

In Pavlov's original experiment the dog salivated as he ate meat, but did not salivate when a neutral tone was presented. However, when the tone preceded the food for several presentations, the tone itself elicited salivation in the dog, i.e., the conditioned stimulus (the tone) evoked the same response as the unconditioned stimulus (food). This is the classical conditioning paradigm—unconditioned stimulus (food) elicits unconditioned response (salivation); conditioned stimulus (tone) originally does not elicit the response, but having been paired with the unconditioned stimulus several times, does produce the unconditioned response. The major concern of conditioning theory has been the understanding of the nature of the connections being made; the substitution of one stimulus for another, or, as it has been called, the signalling process.


Conditioned stimuli may also intensify the healing process by operating as what Mowrer calls safety signals. They mark the reduction of anxiety and the arousal of hope, and indicate that the period of suffering is over, that the patient will be healed. Such phenomena are well established in the laboratory.

I will now cast these observations into an explanatory model of the placebo effect. Part of my aim is to indicate how, using our knowledge of the conditioning process, the so-called non-specific effects of the placebo response can be made specific by isolating, explicating, and identifying the conditions under which these effects can be negated, attenuated, or strengthened.

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 a conditioned stimuli for the alleviation of anxiety, pain, dysfunction, trauma, and disease, if such stimuli have been repeatedly associated with powerful unconditioned stimuli that reliably relieve both the mechanisms and overt symptoms of illness.

Mowrer's notion of a safety signal identifies another way in which neutral stimuli can come to have a positive placebo effect. Insofar as neutral stimuli are associated with the diminishment or the ending of unpleasant symptoms and/or painful disease processes (unconditioned stimuli), they can, as signals, acquire a positive conditioned effect on healing and the reduction of anxiety. Safety-signal stimuli can be objects such as syringes and white coats, behavioral procedures such as physical examinations and ingesting medication, labels such as “hospital” and “clinic,” and — doctors and professors.

Mowrer also describes how neutral stimuli can come to have negative conditioned effects. Because the onset of unfamiliar and unpleasant symptoms such as fever, pain, and insomnia is a naturally occurring (unconditioned) aversive reaction to an underlying (unconditioned) disease process, injury, or dysfunction, neutral stimuli associated with the onset and course of a disease may become negative conditioned stimuli. Such stimuli are called nocebos and the learned response to them a nocebo response. Negative conditioned stimuli can elicit conditioned responses that intensify the disease process, for example by directly or indirectly inhibiting mechanisms of the immune system. For another example, it has been observed that the simple act of changing a patient's physical environment — that is, removing the patient from negative conditioned stimuli — can increase spontaneous remissions. This phenomenon is most often noted with hospitalized mental patients who return home.

Thus, positive conditioned stimuli can be produced in at least two ways: first, by association with an active ingredient for healing (like morphine, insulin, nitroglycerin, penicillin); and second, by association with diminishing the symptoms of an unfamiliar, unpleasant,
and painful disease or injury. In contrast, neutral stimuli associated with the onset of a painful (unconditioned) disease process may come to elicit such negative effects as conditioned anxiety and/or a fractional anticipatory component of the disease.

This analysis leads to three predictions: (1) Conditioned psychological responses that were previously relegated to the realm of nonspecific factors can reliably come to attenuate or enhance health and illness. (2) Initially neutral stimuli can come to influence the underlying physiochemical and cellular mechanisms of health and illness, either directly or indirectly. (3) Theoretically, the influence of such variables on the symptoms and mechanisms of disease can be demonstrated in appropriately controlled double-blind studies in which the active chemical ingredient (the unconditioned stimulus) is withheld.

Therapeutic theory regularly singles out the active ingredients in a drug or procedure as the specific remedy for a condition. For example, according to therapeutic theory, penicillin is the active ingredient for pneumococcal pneumonia because the disease is caused by pneumococcus, which is sensitive to penicillin. The notion of specific activity in medicine has meant that (a) the therapeutic mechanism of action was exclusively a physiochemical one, that (b) the action of the active ingredient was logically related to the presumed etiology of the disease, and that the therapeutic effect was both (c) reliable and (d) durable.

The conditioned response analysis of the placebo effect (as well as the new psychobiological models of disease and dysfunction\(^7\)) render the 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 to the possibility that every unconditioned disease process has a conditioned component and is therefore psychophysiological in nature. Illness and disease mechanisms are not insulated from conditioning effects. To the contrary, these effects are inevitable given an intact complex central nervous system.

The literature of respondent conditioning clearly demonstrates that the response to an unconditioned stimulus — nitroglycerine, for example — will inevitably involve two components. The first component will be an unconditioned (nonplacebo) response elicited by the active unconditioned ingredient (nitroglycerine). The second component will be a conditioned response or learned functional component of the unconditioned response, elicited by formerly neutral events surrounding the delivery of the drug. For all practical purposes, it is inconceivable to imagine a disease process that does not have a psychological or placebo element. It similarly follows that all effective interventions (physiochemical, surgical, or behavioral) have the potential for Pavlovian conditioning and thus for triggering a placebo response.

**COMPONENTS OF THE CONDITIONED PLACEBO RESPONSE**

The elements of the placebo response in healing is unknown today. The sparse available evidence suggests that it is a complex psychophysiological response that is a composite of cognitive-verbal, motor, and physiochemical components.\(^8\)

The cognitive-verbal component of the placebo response may be recognized subjectively as an emotion such as hope.\(^9\) But this hope need not be conscious. There is now evidence from several converging experimental-empirical sources that an individual can process an important amount of cognitive and emotional information without conscious awareness.\(^10\) It is an unconscious process that appears to take place in the conditioned placebo response.

The motor component of the placebo response is probably strongly controlled by the patient’s mood (emotions) and by elements of support and reinforcement in the environment. For example, is the patient treated as someone who is helpless or someone who is still active and competent? Reinforcement contingencies may sometimes override mood and alter motor behavior prior to stable and positive changes in emotion. But generally, as the patient starts to feel better and as the inhibition of motor activ-
Possible Determinants of Placebo Response: A List
Leonard White, Bernard Tursky, and Gary E. Schwartz

One of the difficulties facing an integrative theory of health is the number of variables that have been nominated as determinants of the placebo response. The following list of nominees, drawn from the literature, consists of concepts associated with cultural influences, social psychological theory, cognitive theory, classical conditioning, and psychophysiology. It is arranged from the most general to the most specific, from macrolevel to microlevel.

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ity by emotions like pain and depression recede, the resumption of normal adaptive activities refill the temporal and behavioral vacuums created by maladaptive uncertainty, fear, pain, and depressive ruminations, all of which probably intensified the unconditioned components of the disease or injury.

This analysis may be particularly relevant to chronic diseases and functional disorders such as low back pain, diabetes, cardiovascular disorders, musculoskeletal disorders, and cancer, in which the long-term and intermittent reinforcements of the unconditioned disease process, injury, or dysfunction increase the probability of negative conditioned effects that sustain the disorder. In such cases, the chronic intermittent activation of the disease mechanisms by unconditioned physiochemical causes may lead to increasingly strong aversive anticipatory responses that inhibit the motor system even when the unconditioned stimulus is inactive. It is a well-established fact that intermittent reinforcement by unconditioned stimuli will make a maladaptive response maximally resistant to improvement.

The physiochemical component of the placebo response involves at least both the psychoneuroendocrine and the psychoneuroimmunologic systems. As to the first, it now appears that there are pain-inhibitory pathways descending from the medical brain stem to the dorsal horn of the spinal cord. These pathways may involve both opiate and nonopiate mechanisms. The opiate mechanisms can be
activated by the endogenous morphine-like substances termed endorphins and apparently also by electrical stimulation of certain brain sites (for example, the periaqueductal gray matter). It appears further that the opiate mechanism can be activated within seconds of stimulating the central nervous system, 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 is possible that the activation of the endorphin system may be a primary chemical mechanism of pain reduction in the placebo response. However, other psychoneuroendocrine pain systems that are cognitively initiated but chemically mediated — hypnogic analgesia is an example — may also exist.

In addition, there is good evidence that depression adds to chronic clinical pain, and it has been suggested that decreased activity in the endogenous opioid system may be a result of the pathophysiology of depression. Both sensitivity to pain and susceptibility to depression may be mediated through the catecholamines serotonin, norepinephrine, and dopamine, which are known to alter opiate action. Hence, one rapidly activated psychoneuroendocrine mechanism through which a placebo stimulus may reduce both depression and pain is by stimulating the endorphin system.

As for the psychoneuroimmunological system, there is now evidence that the immune system, the primary mechanism of healing, is not totally independent of the central nervous system and the psychosocial environment. At least 3 types of general evidence (hypothalamic lesions that affect immunocompetence, the effects of the adrenocorticotropic hormone and the adrenal cortical axis on immune functioning, and classical conditioning of immune responses) suggest that events originating in the central nervous system can potentially and reliably alter the immune system. More specifically, there is now evidence that anxiety and depression can inhibit the immune system. The evidence on classical conditioning of immune responses shows that Pavlovian conditioning procedures can modestly but reliably reduce immunocompetence. Theoretically, respondent conditioning procedures may also be able to enhance immunocompetence, but this remains to be demonstrated experimentally.

EXPERIENCES THAT HELP ESTABLISH THE CONDITIONED PLACEBO RESPONSE

How does an individual come to associate certain neutral stimuli with the phenomena of health or disease? In other words, how does an individual learn the placebo response?

The Historical Perspective. Developmentally, the child or immature organism, being 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. Thus, in the developmental history of the immature organism, the effective and reliable satisfaction of needs may come to be associated with features of people (height, weight, color), behavioral styles (authoritarian, permissive), and places. The objective ability of an adult consistently to reduce or bring about discomfort, uncertainty, fear, and pain in the individual, the tribe, or the physical environment is the original basis, ultimately, of the notion of specific, active ingredients that reliably produce predictable consequences.

This analysis has several powerful implications. So long as an adult can maintain unconditioned control, then neutral features of the adult will continue to function as conditioned stimuli. The conditioned stimuli depend on the unconditioned. Once the latter begins to fade, the former will too.

For example, an aging dominant adult baboon who loses his teeth or an aging president who loses his wits are each likely to be eventually pushed aside by younger, stronger, and more intelligent members of the group who can more reliably punish or reward the older, weaker, and less intelligent group members. Sharp teeth and sharp wits, in this analysis, are both unconditioned stimuli. Thus the toothless baboon and the increasingly witless president will gradually encounter “placebo sag” as their once active ingredients (teeth, muscles,
claws, I.Q.) fade and become inert. Without at least intermittent demonstrations of their unconditioned strength and intelligence, the potency of their conditioned features — their "packaging" — cannot be sustained.

Hence, baboons, presidents, and therapists who come to lean increasingly on their conditioned stimuli, their packaging, will inevitably come to be seen as imposters and will be identified as quacks. Whereas the baboons, presidents, and therapists who primarily use their active strengths (or unconditioned stimuli), paradoxically will get stronger placebo effects than quacks, will enjoy escalating credibility, and will be seen as miracle men — when in fact perhaps only half of their miracles can be traced to their active ingredients while the other half is a function of the anticipatory (or conditioned) response elicited by their conditioned features.

This analysis casts a rather new light on science. It emerges as a uniquely human quest to identify, isolate, and manipulate unconditioned stimuli, to make our environments more predictable, reliably controllable, and explainable.

It follows too that general intelligence emerges as a potent and, in evolutionary terms, a new behavioral unconditioned stimulus. General intelligence can produce specific and reliable changes in both physiochemical and psychological domains. Coupled with pertinent information, it can be an unconditioned behavioral stimulus on par with other active physiochemical ingredients and just as capable of producing conditioning effects.

**Acquisition Phase of the Conditioned Placebo Response.** For infants and young children the entry and intervention of the parents is usually associated with the reliable diminution of aversive events (danger and deprivation) and the onset of positive events (food, protection from danger and pain). In this way, parental figures and, by association, such people as doctors and priests, acquire the properties of safety signals that inhibit fear and anxiety and release an attitude of hope.

During this acquisition phase, the to-be-conditioned placebo stimulus and response probably involves the parents' implicit awareness of both active (unconditioned) stimuli such as medical interventions, and reinforcing (conditioned) contingencies such as giving the child extra attention; implicit or explicit verbal reference to the reinforcing contingencies; and implicit or conscious awareness by the child of such culture-specific safety signals as rattles, syringes, pills, potions, wands, stethoscopes. The safety signals thus become conditioned stimuli that can inhibit worry, doubt, and skepticism, and in this way can make a patient, young or old, more receptive to the healing instructional suggestions given by a physician or therapist.

**Consolidation Phase of Placebo Learning.** After the placebo response is well established through repeated association with potent unconditioned stimuli, it probably takes on the following characteristics: becomes increasingly abbreviated, involves minimal or no awareness, becomes rapid and automatic, bypasses the verbal or dominant left hemisphere, and preferentially involves the minor right hemisphere. The importance of bypassing the dominant hemisphere is that it makes the response relatively independent of the critical, skeptical analytic mode of information-processing that is typical of this hemisphere. The response thus can occur before doubt and skepticism ("noise") inhibits or attenuates it. Stimulus events can directly elicit physiological-chemical or visceral changes without the interference of the dominant hemisphere's analytic filtering. This process may be similar to the profound visceral and neuroendocrine changes that can occur in response to the registration of an event on the central nervous system when there is an inhibition of critical analytic brain functions (for example, being charged by a lion in a dream).

Developmentally, the placebo response may begin as what Spence and Taylor have called a V form of classical conditioning, but it then most likely develops into a C form of conditioning. The basis of this distinction is the degree of verbal mediation and volition involved in the conditioned response. The placebo response is probably most effective when it is in the C, or second, stage of conditioning,
and is sufficiently rapid and automatic to be labelled an unconscious response.

THE CHARACTERISTICS OF PLACEBO RESPONDING

What factors encourage an individual to respond to a placebo? We have already noted one element that contributes to a placebo response — being dependent. In terms of health and disease, the physical and psychological immobilization of an organism (by injury, infection, tissue damage, high fever, disorientation, unpleasant and unusual symptoms, fear and depression) creates the prerequisite dependency and the opportunity for conditioning.

I would argue that hypnotic suggestibility is an important second element that encourages an individual to respond to a placebo.

Not all research findings correlate placebo responding and hypnotic susceptibility. Shapiro has pointed out that laboratory tests show an unreliable relationship between these two phenomena. Several other analyses have also cast doubt on the existence of a reliable relationship between hypnotizability and the placebo response. I would suggest that these findings may be due to the fact that other moderating variables (the credibility, empathy, or authoritarianism of the hypnotist; the subject’s levels of attention and arousal; the potency of the instructional signals) were not systematically manipulated.

The strongest evidence to date showing a lack of relationship between hypnotizability and placebo responding is a study of experimental pain by McGlashan, Evans, and Orne. This study, which dealt with arm pain caused by restricted blood circulation, found the degree of hypnotizability to be unrelated to the magnitude of the placebo response. However, there are two problems with generalizing to a clinical situation from this laboratory study. First, the study was an investigation of experimental pain, and as I noted at the outset, the parameters of experimental and clinical pain do not overlap. Second, the study failed to use strong, extended, and specific instructions to mobilize fully the potential of the highly hypnotizable subjects in the placebo-analgesia session.

Other studies have produced contrary findings. In one study, presenting a rationale for a “drug” (placebo) mobilized the hypnotic ability of the patient and functioned as a hypnotic induction. A study by Glass and Barber found that a placebo administered as a hypnosis-inducing drug was as effective as an actual trance induction in eliciting enhanced suggestibility. A recent study of experimental pain by Knox and Gekoski has shown clearly that an individual’s level of hypnotizability is related to the placebo response. Evans reviewed 2 non-patient (laboratory) and 5 patient (clinical) studies on the relationship between suggestibility and placebo responding. He did not find a positive relationship between suggestibility and placebo responding in either of the non-patient studies, but did find a relationship in 4 of the 5 patient studies.

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

Good placebo responders will 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. Like good hypnotic subjects, they are likely to embroider or elaborate on the properties of a drug, enhancing its potency out of their own subjective repertoires.

Shapiro describes placebo nonresponders as “rigid and stereotypic and not psychologically minded.” There is a striking similarity between this description and the description of a poor hypnotizable subject. Increasing evidence shows that hypnotizability or suggestibility is predominantly a right-hemisphere function for right-handed people. Right-hemisphere functions include holistic and imaginative mentation with diffuse, relational, and simultaneous processing of information. The tendency to see some relationship or meaning even in randomly generated data (like a
Rorschach inkblot) would appear to be an aspect of creativity that probably is a property of the nondominant hemisphere.

In the consolidation phase of placebo learning, the placebo response may become located in the right hemisphere. 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 enhanced through strong, implicit or explicit verbal instructions\(^\text{47}\) if the following hypnosis-enhancing conditions are systematically manipulated: low arousal states or low arousal induction training procedures (for example, biofeedback),\(^\text{38}\) high arousal induction procedures (which also appear temporarily to increase hypnotic responsivity),\(^\text{38}\) sensory deprivation procedures,\(^\text{34}\) a subject's level of attention to relevant stimuli,\(^\text{55}\) and the baseline suggestibility or hypnotizability of the individual subject.\(^\text{56}\)

PARAMETERS OF Placebo LEARNING

Forms of Conditioning

I have spoken generally about how a neutral stimulus can come to be associated with an unconditioned stimulus. Here I will examine several ways this can occur. In my examples, I will focus on the role of the doctor.

1. Simultaneous Conditioning. Both conditioned and unconditioned stimuli occur simultaneously, beginning and ending at precisely the same time. This situation is unlikely to occur, except perhaps if a neutral stimulus is associated with the relief of acute pain through a powerful, fast-acting analgesic.

2. Delayed Conditioning. The conditioned stimulus appears before the unconditioned stimulus and lasts at least as long. An example would be the arrival of a physician prior to the onset of spontaneous remission and the departure of the physician with the onset of the physiochemical (unconditioned) events that precede or correlate with symptomatic improvement. Historically speaking, this was a fairly likely scenario, since for hundreds of years physicians had observed and tracked the natural invariable symptomatic course of several common diseases. Thus, physicians could predict or prophecy the sequential progression and resolution of symptoms long before doctors could control them. It is entirely probable that sagacious physicians once timed their arrivals and departures (conditioned stimuli) to coincide with visible symptomatic changes in a patient. On a simple correlational basis, this before-the-event appearance could be a dramatic demonstration of a physician's therapeutic power. But, of course, whatever a patient thought, prediction and correlation are not control. It would be control only if the physicians could have turned the disease process on and off at will. Fortunately for the early physicians, they were not asked "do that again."

3. Trace Conditioning. The conditioned stimulus comes and goes briefly before the onset of the unconditioned stimulus. When a physician has a very detailed and confident knowledge of the course of an illness, he or she could arrive "late," stay briefly, and leave long before the onset of a spontaneous remission, nonetheless accurately prophesying the course of a patient's symptoms. Before the physician left, he or she might order the performance of some inert rituals, confidently asserting a cure within a specified time interval.

4. Backward Conditioning. The conditioned stimulus follows the unconditioned stimulus—the physician arrives after the recovery has started. It is unlikely that many smart early physicians used this conditioning procedure. They likely understood intuitively, as we now know, that such a situation leads to weak and unreliable conditioning.

5. Temporal Conditioning. An unconditioned stimulus occurs at regular time intervals and then, for a while, does not appear. A conditioned response develops during these interim periods. This form of conditioning may take place with regard to chronic diseases that have a fairly reliable intermittent pattern. For example, for a part of the time, primary dysmenorrhea may be caused purely by physiochemical (unconditioned) stimuli of varying magnitude. But the chronic maintenance of severe symptoms of unvarying or increasing intensity may
also be related to temporarily conditioned anticipatory psychoneuroendocrine responses.

**Phenomena of Conditioning**

Here I will consider the situational factors that affect the strength and durability of a conditioned response.

1. Repeated presentations of even potent unconditioned stimuli can lead to the failure to evoke the unconditioned response and to the extinguishing of the conditioned response. This phenomenon is particularly likely to occur when chronic functional problems are treated symptomatically. For example, even initially potent but nonspecific drugs like valium, given for classic migraine headaches, can become less effective over time. When this happens, as I noted earlier, the physician also loses the ability to elicit conditioned therapeutic responses. The physician has encountered “placebo sag.” In such a situation, there is a clear and urgent need for therapeutic stimuli to be aimed at the known or presumed etiology of the disorder and not simply on peripheral symptoms.

2. When two or more conditioned stimuli are presented together, the strength of the conditioned response will be stronger than it would have been to either stimulus alone. This implies that the presence of several safety signals (or conditioned stimuli) will lead to a stronger placebo response, and be present in perhaps 60 percent of the patients rather than 36 percent. When practitioners who employ even a minimal amount of unconditioned stimuli use high technology and nonspecific state-of-the-art diagnostic and therapy procedures without sacrificing humane patient care, a large placebo component will be present. 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. (Today, the university medical center is the new temple of healing.)

3. A person who has learned to respond therapeutically to physician A or procedure A has also learned to respond therapeutically to *almost equivalent stimuli*. This phenomenon, called response generalization, is often clearly observable in the medical management of acute illness, which is effectively treated by the health care system, so that negative psychosocial factors seldom have enough time to interfere with healing. In the case of chronic illness, however, we often observe attenuated therapeutic effects, even with regard to active therapeutic ingredients, because of negative conditioned responses from previous illness episodes or ineffective therapy.

4. When physicians use ineffective unconditioned stimuli to treat chronic conditions, we often observe the extinction of the placebo response not only to the original primary care physician but to all subsequent physicians. This development may jeopardize even a potentially effective treatment program by a negative placebo response (a nocebo) can negate the effects of a useful unconditioned response.

5. There is good evidence that a patient’s ability to create links and associations can encourage the acquisition of conditioned responses. A patient’s conscious recognition of the association between his or her physician and the physician’s efficacious unconditioned stimuli (for example, penicillin) will enhance the acquisition or learning of placebo responses. Also, information about a physician’s credentials, therapeutic record, and reputation among colleagues can strengthen 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 potentially influence both Pavlovian and Skinnerian conditioning procedures.

**PREDICTIONS FROM THE MODEL**

To recapitulate the main points of my argument, I offer the following 17 predictions, some of which have been noted before, and all of which appear consistent with the conditioned response model of the placebo. Empirical data that disprove any of these predictions will cast doubt on the model. I should note, however, that any test of the model should occur in the appropriate situation with appropriate subjects. As we have seen, an individual who is actually sick is different in major aspects from a person in an experimental study. This model
was developed to predict behavior in a clinical situation and should be tested on patients in therapy.

1. Therapists who routinely use effective active ingredients will get stronger placebo effects than those who do not! The routine use of effective active ingredients reinforces the relationship between conditioned and unconditioned stimuli, thereby optimizing the conditions for hope. As we have seen, intrinsic to all interventions with active ingredients is the potential for Pavlovian conditioning, and therefore placebo learning. Hence, the stronger the active ingredient, the stronger the placebo effect. The weaker the active ingredient, the weaker the placebo response.

2. The response to any active ingredient will come to include two components: a placebo and an active component. In other words, a fraction of the response to an unconditioned stimulus will always include a conditioned response.

3. Therapists who frequently use inert or placebo medication or procedures will get weaker placebo responses over time. Withdrawal of active ingredients will eventually lead to extinction of the conditioned response, to “placebo sag.” Therapists who have the “right packaging” but who are deficient in their grasp of science and of truly efficacious active ingredients will eventually collapse under the weight of their own incompetence.

4. Numerous repeated presentations of an unconditioned stimulus in drug therapy can lead to temporary tolerance or habituation. But temporary withdrawal of the stimulus will abolish “placebo sag.” The use and withdrawal of a conditioned stimulus 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. A review of the literature supports this prediction. The response to a conditioned stimulus is like the response to an unconditioned stimulus, but it happens more rapidly.

6. Patients higher on trait anxiety will be stronger placebo responders. It is known that trait anxiety is related to the rate of acquiring conditioned responses and to their magnitude. This model thus, can comfortably embrace the anxiety-reduction data reviewed by Evans.

7. The placebo response is predicted to be stronger under strengthened double-blind conditions. That is, neither the patient nor the therapist should know that any inert procedure is being used. In fact, both should be told that only an active ingredient is being used. In general, there will be less inhibition of the expectancy mechanism with this strengthened double-blind procedure, and there will be the optimal level of credibility. Orne and Frank have stressed the role of expectancy and credibility in their analyses of the placebo.

8. The use of several placebo stimuli can lead to a stronger placebo response than the typical 35 percent rate that accompanies the use of one placebo stimulus. It is known that when two or more conditioned stimuli are presented together, the strength of the conditioned response is often greater than it is to either stimulus alone.

9. In the final analysis, there can be no conditioned response if there is no unconditioned stimulus (active ingredients). Paradoxically, progress in isolating and manipulating active ingredients will inevitably lead to more and stronger placebo effects. In other words, “faith” will grow with progress in “science,” and it may be increasingly difficult to separate out the effects of conditioned and unconditioned stimuli.

10. If the baseline suggestibility of a patient is mobilized with specific explicit or implicit instructions, then the conditioned response can be either strengthened or attenuated.

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

12. Treatment procedures that systematically use attentional manipulations, low or high arousal induction, and sensory restriction can strengthen both placebo components and the effects of any accompanying active ingredients.
13. Neutral persons, places, and procedures can operate as negative as well as positive conditioned stimuli. This may explain iatrogenic illness and suggest ways of negating the conditions for iatrogenic health. Nocebo effects can arise out of associating neutral stimuli with negative unconditioned stimuli.

14. Patients whose childhood histories combine firm discipline with the warm and effective relief of their needs, and also an ability to entertain themselves alone, will be the best placebo responders. On the other hand, children who have few or no instances of predictable, reliable, and effective interventions in their environment or on their behalf will demonstrate weak placebo responses to culture-specific, socially sanctioned health rituals.

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

16. The placebo response will not occur if the healing ritual bypasses consciousness and the central nervous system.

17. The placebo response will occur maximally under conditions of strong motivation, which is to say, a state of being severely deprived of one's health. In clinical situations with sick patients, the threat to well-being is real, intense, not connected to a limited situation, and of unknown duration, whereas with nonpatients in experimental studies the threat to well-being is superficial, specific to a limited situation, reversible and of known duration. The magnitude of the placebo response will generally be weaker with non-patients. In general, the placebo response will be most potent in life-threatening medical situations and not in individually trivial social-psychological experiments in university laboratories.

CONCLUSION

Since this model of the placebo effect is formulated in terms of experimental psychology and learning, it may, at the minimum, have a heuristic value in leading to the design of experiments that raise new questions about treatment. In particular, this model makes several specific counterintuitive and paradoxical predictions that may be worth testing empirically.

Further, I believe that the model helps relate a large body of precise and empirically validated principles from learning theory to the nebulous field of the placebo. The result may be new, sharper, and more focused thought and empirical investigations in this unfairly neglected psychobiological realm.

As we have seen, this realm includes psychological effects that are powerful but unreliable, rapid but not always durable. But it may turn out to include the only therapeutic effects, which are primarily psychological.

It is unlikely that all the phenomena today lumped under the label placebo effect can be comprehended within the present conditioned-response model. But we can no longer continue to dismiss these effects with impatience and embarrassment. I believe that they reside at and regulate the intersections of all psychobiological actions and transactions.

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References


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