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Ideas and Commentary

A Conditioned Response Model of the Placebo Effect

Predictions from the Model[1]

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A model of the placebo response as a conditioned response (CR) is presented and predictions from this model are listed. Through association with active ingredients (UCS), neutral (CS) places, persons, procedures, and things can come to acquire the ability to reduce pain, anxiety, and depressive responses. One major counterintuitive prediction from the model is that therapists who routinely use active ingredients (UCS) or powerful drugs will get stronger placebo effects than those who routinely use "inert" ingredients (CS) or weak drugs. Developmentally, placebo responding appears to involve two successive conditioning stages, which may involve first the left and later the right hemisphere in right-handed subjects. The relationship between placebo responding and hypnotizability is discussed.

It is known that the administration of an inert chemical substance (a placebo) can be associated with a therapeutic response (Beecher, 1959; Shapiro, 1971; Evans, 1974a,b). Reviews (Beecher, 1959; Evans, 1974a) of 26 double-blind studies covering 1,991 patients found that approximately 35%

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of patients have severe clinical pain reduced by one-half of its original intensity by a placebo drug. Placebo effects are not limited to chemical treatments; psychological treatments can have "active" and placebo components. A review of controlled studies of systematic desensitization (Kazdin & Wilcoxon, 1976) and an important double-blind study of clinical biofeedback (Cohen, Graham, Fotopoulos, & Cook, 1977) have also found an equally high rate 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. A study by Schwitzgebel and Traugott (1968) found that mechanical devices can also generate placebo effects.

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 the above 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.

PLACEBO EFFECT

It has been found that a placebo can potentiate 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, 1974b).

Clearly we are dealing with a real effect that has been regarded as a "nuisance" for several reasons previously discussed (Wickramasekera, 1976a, 1977a,b) and 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 paper 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 other active ingredients are used in routine clinical practice.

Many hypotheses have been advanced to explain the mechanisms of "nonspecific" effects and the placebo response. Shapiro (1971) and Barber (1959) appear to favor a suggestion hypothesis, and Evans (1974b) appears to favor a trait anxiety reduction hypothesis. Frank (1973 has stressed the role of expectancy in potentiating therapeutic response. For reasons of brevity these analyses will not be presented here and are discussed elsewhere (Wickramasekera, 1976a, 1977a,b). The following paper offers a new[3],[4] model of the placebo response, traces the predictions from this model, and presents the relevant subject, therapist, and procedural variables. This analysis points out that intrinsic to all effective interventions (chemical, psychological, or surgical) is the potential for Pavlovian conditioning (Pavlov, 1927) and therefore placebo learning. 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.

[3]After this paper was written and submitted for publication, one of the reviewers drew my attention to a relevant paper by Gleidman, Gantt, 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 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 points two and three, there is substantial implicit agreement. But there is no elaboration with respect to hypnotizability, brain lateralization, and the possibility that the UCS can be nonchemical behavioral events.

[4]After this paper was written and accepted for publication, the editor of *Biofeedback and Self-Regulation,* Dr. J. Stoyva, drew my attention (on 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.

THE PLACEBO AS A CONDITIONED RESPONSE

I propose that a placebo (inert ingredient) per se, the ritual of its administration, the place it is administered, and the administrator himself can come to function as conditioned or discriminitive stimuli for the alleviation of discomfort or pain. Vicarious (Bandura, 1969) or in vivo respondent and operant conditioning can through association with active ingredients (UCS) establish neutral places, things, procedures, and persons as conditioned stimuli (CS) for the relief of discomfort or pain (Wickramasekera, 1977a,b). These neutral (CS) or inert stimuli may have been associated with powerful active (UCS) ingredients (e.g., penicillin, morphine, demerol) for the relief of pain or discomfort. Therefore, the response to any UCS will include two components. The first component will be a CR (placebo response) and the second component a UCR (e.g., specific effect of a drug). The latency of the placebo component (CR) will be shorter due to central mediation of conditioning effects. This short latency learned component (placebo response) may be further reinforced by information in the mass media and tacit shared belief systems in the culture (Wickramasekera, 1976a, 1977a,b) and peer group.

It is also possible that certain apparently neutral (CS) features of people (height, color, etc.) and response styles (permissive or authoritarian) may have been associated in the history of the immature organism with active (UCS) ingredients (e.g., strength or intelligence) used on behalf of the immature organism. This ability to *effectively* and *reliably* intervene to reduce uncertainity and fear, or to produce specific changes in the individual, the tribe, or the environment, is the original basis of the notion of active ingredients or UCS. For example, a dominant baboon who loses his teeth or a senile chairman who looses his wits due to senility are both likely to be pushed aside by a younger, stronger, and brighter member of the group who can more effectively and reliably consequate (positively or negatively) the behavior of group members. Both the dominant baboon and the chairman will eventually encounter "placebo sag" (Wickramasekera, 1977a,b) or "credibility" extinction as their active (teeth, wits) ingredients (UCS) fade with senility. The potency of their packaging or neutral features (appearance or CS) cannot be sustained without intermittent demonstrations of strength and/or intelligence (UCS). In this analysis, intelligence emerges as a potent and highly generalizable new (on the evolutionary scale) active ingredient on par with other active ingredients (e.g., chemical) and capable of producing classical conditioning effects. High *credibility* in this analysis refers to the ability to effectively and reliably produce specific observable changes for one's own benefit or the benefit of others. Hence

baboons, therapists, and chairmen who come to depend increasingly on their inert ingredients (CS alone) will inevitably encounter "placebo sag," will be discovered as imposters, and historically may be identified as "quacks," whereas those who routinely use active ingredients (UCS) will inevitably enjoy escalating placebo effects and may be seen as "miracle men"—When, in fact, perhaps only one-half of their "miracles" can be traced directly to their science.

The nature of the conditioned placebo response is unknown but it is probably a complex patterned psychophysiological response (Schwartz, 1976), which may be recognized subjectively as an emotion like hope (Mowrer, 1960; Frank, 1973). Components of this psychophysiological response can dissipate pain, uncertainty, depression and fear, and disinhibit adaptive behavioral and biological (e.g., immune response) resources. A recent study (Levine, Gordon, & Fields, 1978) and two extensive literature reviews (Verebey, Volavka, & Clouet, 1978; Basbaum & Fields, 1978) suggest that the endorphin system may chemically mediate some of these changes. There is also evidence that psychological states like depression and anxiety can inhibit the immune system (Rogers, Dubey, & Reich, 1979) and increase susceptibility to disease. As inhibitory emotions (fear, depression) recede, the patient's behavioral-motor repertoire is expanded (returns to work, resumes copulation) to occupy the previous behavioral vacuums that were occupied by pain, fear, and depressive cognitions. This analysis may apply particularly to chronic stress-related medical and psychological complaints where there are few or no physical findings.

Contemporary research on conditioning and learning demonstrates that interstimulus intervals (CS-UCS) are not immutable, particularly with human subjects (Kimble, 1973), and that they can exceed .5 milliseconds. An unconditioned stimulus can be defined as a stimulus that is *reliably* associated with a set of *specific* changes (UCR) in the verbal-subjective, physiological, or motor response system or systems of an experimental subject. The UCS or active ingredient is associated with a specific change or UCR in the subject. If neutral (CS) or inert stimuli were repeatedly associated with a UCS or active ingredient in the subject's history of reinforcement, then the CS, "inert," or "placebo" stimulus may come to evoke an anticipatory fractional component of the UCR. This fractional anticipatory component of the UCR can be called a conditioned or placebo response. The anticipatory fractional component can be elicited by neutral physical objects (empty syringes), places (hospitals), procedures (cleaning the skin), or cognitive verbal labels (e.g., "medical," "scientific") that have been associated with the UCS or active ingredients. The labels ("scientific," "medical," professor, doctor), rituals (measuring, graphing),

and places (laboratories, consulting rooms, emergency rooms) of *credible* culture specific healing can acquire conditioned properties.

DEVELOPMENTAL ASPECTS OF CONDITIONED PLACEBO RESPONSE

Acquisition Phase

In the acquisition or credibility formation phase the conditioned placebo response probably involves (a) awareness of the response-reinforcement contingency, (b) implicit or explicit verbal mediation, and (c) several culture-specific socially learned credible signals or discriminitive stimuli. These S_d or CS may influence the rate of acquisition through potentiating attention and arousal conditions. These credible signals can be quite diverse. (1) The labeling of the therapist (e.g., doctor, swami) can influence his attention or arousal value in a given culture. (2) The credibility of the therapeutic setting (e.g., hospital, temple, park bench), (3) the credibility of the placebo per se (e.g., size, shape, color, taste), (4) the credibility of the administration ritual (e.g., oral vs. injection, abstinence), and (5) the nature of the relationship between patient and therapist (e.g., accurate empathy, authoritarianism) can all influence the attention and arousal properties of these events. The attention and arousal value of these CS can be directly related to the extent to which they have been previously reliably associated with specific and effective interventions on behalf of the immature organism or some aspect of his environment.

In the acquisition of any new material or task it is likely that sequential specification of component responses and verbal mediation of these components can reduce error. During this first phase, large individual differences related to a given subject's history of learning or his context of learning (specific culture) can influence learning through the determination of what is a "credible" CS for that subject (Wickramasekera, 1978).

Consolidation Phase

After the placebo response is well established through repeated associations with UCS or active ingredients, it probably (a) becomes increasingly abbreviated, (b) involves minimal or no awareness, (c) becomes very rapid and automatic, (d) involves a bypass of the verbal or dominant hemisphere, (c) is processed mainly in the minor hemisphere as hypnosis

appears to be (Bakan, 1969; Lachman & Goode, 1976), and (f) can therefore be potentiated or attenuated by the same variables that determine suggestibility or hypnosis.

Developmentally, the placebo response may begin like what Spence and Taylor (1951) and others (Cerekwicki, Grant, & Porter, 1968; Grant, 1972) 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 conditioned response. The mechanism of the placebo probably is 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 supports the position that the registration of perceptual stimulation can occur outside of conscious awareness (Erdelyi, 1974; Dixon, 1971) and may be consciously recognized only as an emotional change. There is also some evidence that the nondominant hemisphere is more closely related to emotional arousal (Safer & Leventhal, 1977; Schwartz, Davidson, & Maer, 1975).

There is no systematic human evidence to support the above model. But there is some strong controlled animal evidence (Goldberg, & Schuster, 1967, 1970; Drawbraugh & Lal, 1974; Siegel, 1978; Schuster & Thompson, 1969; Wilker & Pesor, 1970) presented elsewhere (Wickramasekera, 1977a) that supports the view that neutral stimuli can elicit complex biological and biochemical changes as postulated by the conditioned response model of the placebo.

PLACEBO RESPONDING AND HYPNOTIZABILITY

Shapiro (1971) has pointed out that laboratory tests of hypnotic susceptibility show an unreliable relationship to placebo responding. Also, several good analyses have cast doubt on the existence of a reliable relationship between hypnotizability and the placebo response (Thorn, 1962; Evans, 1969; Moore & Berk, 1976; Katz, 1974). It is possible that the above unreliability is due to the activity of other moderating variables (e.g., credibility, accurate empathy, authoritarianism, levels of attention and arousal, potency of instructions), where were not systematically manipulated in the above 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.

A single study by McGlashan, Evans, and Orne (1969) has been used to promote the view that hypnotic susceptibility and placebo responding are unrelated. At present, this study provides the most direct test of the relationship between hypnosis and the placebo response. However, there are several problems with making inferences and generalizing to a clinical situation from the above laboratory study, and therefore, their conclusions may be premature: (1) The McGlashan et al. 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 stuidy to the phenomena of clinical pain. (2) In the McGlashan et al. study there was a failure to use strong extended, and specific instructions of dominant arm analgesia to fully mobilize the potential of the highly hypnotizable subjects in the placebo-analgesia session. The presentation of a rationale for a "drug" (placebo) can function as a hypnotic induction (Wickramasekera, 1976a).

I predict that with increased attention to those variables mentioned above that moderate 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 characteristic of the dominant verbal hemisphere. Good placebo responders will tend to be individuals who are prone to see relationships between events that seem randomly distributed to others. Like good hypnotic subjects, they are likely to embroider or elaborate on the barren stimulus properties of the world, out of their own rich subjective repertoires.

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

In phase two, the placebo response may become regnant 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, 1976a) if the following hypnosis-potentiating conditions are also systematically manipulated. (1) *Low arousal* states or low arousal induction training procedures appear to temporarily increase hypnotic responsivity (Wickramasekera, 1971, 1973, 1977c; Engstrom, 1976; Arons, 1976; Schacter, 1976). (2) *High arousal* induction procedures appear to temporarily increase hypnotic responsivity (Wickramasekera, 1972, 1976b; Gur, 1974). (3) *Sensory deprivation* procedures also appear to temporarily increase hypnotic responsivity (Pena, 1963; Wickramasekera, 1969, 1970; Sanders & Reyher, 1969). (4) The subject's level of *attention* to relevant stimuli appears to influence hypnotic responsivity (Krippner & Bindler, 1974; Graham & Evans, 1977; Mitchell, 1967; Van Nuys, 1973). (5) The *baseline* suggestibility or hypnotizability of the individual subject (Hilgard, 1965; Barber, 1969) has a profound effect on hypnotic responsivity.

PREDICTIONS FROM CONDITIONED RESPONSE MODEL OF PLACEBO

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

1. Therapists who routinely use active ingredients (UCS) will get stronger placebo effects (CR) than those who do not. This procedure associates and reinforces the CS–UCS relationship, that optimizes the conditions for "hope" (Frank, 1973). Intrinsic to all interventions with active ingredients (UCS) is the potential for Pavlovian conditioning, and therefore 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): (1) a placebo (CR) and (2) 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 intial peripheral mediation of some drug effects.

3. Therapists who frequently use inert or placebo medication or procedures (CS) 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" (CS) but who lack a science will eventually collapse under the weight of their own incompetence. 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." CS alone will not reliably show this recovery feature.

4. Dose response and time-effect curves for a placebo and an active medication will be similar. Literature review (Evans, 1974b) supports this prediction. The response to CS is like the response to UCS.

5. Patients higher on trait anxiety will be stronger placebo responders. It is known that trait anxiety is related to the rate of acquistion and magnitude of conditioned responses (Spence & Taylor, 1951). This model can comfortably embrace the *anxiety* reduction data of Evans (1974b).

6. 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 UCS is used. In general there will be less inhibition of the *expectancy mechanism* 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.

7. The use of several placebo (inert or neutral) stimuli can lead to a stronger placebo response (higher than typical 35% rate) than the use of one placebo stimulus. It is known that when two or more CS are presented together, the strength of the CR is often greater than to either stimulus alone. This phenomenon is called summation (Kimble, 1961).

8. In the final analysis, there can be no CR if there were no UCS (active ingredients). Paradoxically, progress in isolating active ingredients (UCS) will inevitably lead to more and stronger placebo effects (CR). In other words "faith" will grow with progress in "science" and it may be increasingly difficult to separate out the effects of CS and UCS.

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

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

11. Treatment procedures that use systematic (a) attentional manipulations, (b) low or high arousal induction, and (c) sensory restriction can

potentiate placebo components (CS) plus any active ingredients (UCS) in a procedure or substance.

12. Placebo persons, places, and procedures can operate as both positive or negative CS. This may explain iatrogenic illness and suggest ways of arranging the conditions for iatrogenic health.

13. Patients whose childhood histories have few or no instances of reliable and effective (positive or negative) interventions in the child's environment or on the child's behalf will demonstrate weak placebo response to culture-specific, socially sanctioned health rituals.

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 design experiments that raise different questions about treatment and lead us to interpret the responses in unexpected ways. This model makes several specific counterintuitive and paradoxical predictions that may be worth testing empirically. A large body of precise and empirically validated priciples from learning theory can now be related to the nebulous 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, but clearly worthy today of investigation in their own right. It may even turn out that this realm includes the only therapeutic effects, which 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 subject, the therapist, and the situational and procedural conditions under which these effects can be negated, attenuated, or potentiated. It seems unlikely that all the phenomena lumped under the 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 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.

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