Discussion

Placebo and health—II

The following two selections continue the discussion of the placebo and its role in health that began in the Winter 2000 issue. The discussion in that issue had two parts: eight responses to the proposition, “True or false: The placebo effect as seen in drug studies is definitive proof that the mind can bring about clinically relevant changes in the body,” and a report on a National Institutes of Health Conference on Placebo and Nocebo (December 1996). “Toward a research agenda on placebo” by Daniel E. Moerman and Wayne B. Jonas. The selections here focus on models to explain the placebo response. In “How to produce not only powerful but, more importantly, reliable placebo healing and analgesia,” Ian Wickramasekera presents a conditioned response model replete with testable predictions. He writes: “I propose that by combining the behavioral technology of Pavlovian conditioning with high hypnotic ability, we will increase both the potency and reliability of placebo effects.” In “Three perspectives on the placebo response: Expectancy, conditioning, and meaning,” Howard Brody (with Daralyn Brody) offers a broad overview of the evidence and arguments to support three different, though not necessarily mutually exclusive, frameworks to explain placebo effects. He writes: “Each perspective addresses important findings of studies seeking to establish a scientific understanding of the placebo response.”

How to produce not only powerful but, more importantly, reliable placebo healing and analgesia

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Yes, the placebo effect in drug studies refers to powerful but unreliable physiological and subjective changes (for example, pain, anxiety, or fear perception) induced by a physiochemically inert substance or drug (Shapiro 1971). I propose that by combining the behavioral technology of Pavlovian conditioning (Ader 1995; Ader & Cohen 1982; Wickramasekera 1977a, 1980, 1985) with high hypnotic ability, which is the active ingredient in all hypnotic procedures (Wickramasekera 1977a, 1980, 1985), we will increase both the potency and reliability of placebo effects, at least to start with, in people of high hypnotic ability. Highly credible and stable beliefs are essential and sufficient conditions for rapid, powerful, and durable placebo responding. Building on the above findings, we will be able to alter, even if only temporarily, baseline hypnotic ability in the general population (Wickramasekera 1977b).

In earlier papers (Wickramasekera 1977a, 1977b, 1980, 1985) I have proposed a memory-based or Pavlovian learning mechanism of the placebo effect. Active treatments (for example, morphine,
penicillin) and active diagnostic procedures are unconditioned stimuli, but the vehicles in which they are delivered (for example, pills, capsules, syringes, biomedical instruments) are conditioned stimuli. The medical treatments and diagnostic procedures that people experience during their lives constitute conditioning trials during which the vehicles of delivery are paired with active ingredients (which include accurate and valid medical information). Thus, these pairings (Ader 1988, 1995; Wickramasekera 1977a, 1977b, 1980, 1985) endow the vehicles of pills, capsules, syringes, and biomedical instruments with the capacity to elicit the memories of therapeutic clinical effects as learned or conditioned responses.

The conditioned response model of placebo responding that I propose involves the elicitation of implicit (unconscious) and explicit (conscious) psychophysiological memories of actual prior healing experiences in childhood or adolescence and the credible expectation of future healing. Central to this conditioned response model is the hypothesis that the elicitation-through-memory of the behavioral, autonomic, neuroendocrine, and immune components of prior healings is the crux of the placebo effect. Conditioning and learning are probably the most reliable and powerful method of installing and eliciting complex mind-body memories and expectations in humans and animals.

Much about the placebo effect is unknown but beliefs constructed from memories seem central. Theoretically, alterations in cognitions, emotions, and beliefs induced by a placebo drug that is believed to have healing properties can directly alter physiology. Beliefs may also indirectly alter physiology through behavioral mechanisms (for example, exercise, diet, etc.). Unfortunately, many double-blind studies testing placebo effects do not have an additional control group to control for the natural course of pain or disease remission nor do they use placebos with side effects (Fisher & Greenberg 1989) that sufficiently mimic the side effects of the active drugs (for example, antidepressants) to which they are compared. Consequently, we do not know if the healing associated with a placebo is due to the spontaneous remission of a disease or if the reduced potency of a placebo drug occurs because patients are alerted by the lack of side effects that they are receiving a placebo rather than an active drug.

The degree of belief or faith in the potency of a drug appears to be a powerful factor in placebo efficacy (Roberts et al. 1993), and belief may also be a powerful factor in the initiation of psychophysiological disease (Wickramasekera 1979, 1986, 1988, 1998) particularly in people of high hypnotic ability. In one large nonblind review study (n = 6, 931), the mean magnitude of the placebo effect was found to be 70% when both the patient and doctor believed in the efficacy of drugs or surgical therapies, drugs and therapies that later research proved to have no active physiochemical mechanism of action (Roberts et al. 1993). The studies in this review resemble actual clinical practice, which uses drugs that both patients and physicians believe are effective (whether or not they ultimately prove to be) and which does not use double-blind instructions (which research shows reduce mean placebo efficacy by 50% [Wickramasekera 1999]). The powerful "top-down" (Sperry 1980) or placebo effects in natural clinical settings may leave only 30% of variance to be determined by genes and germs in some chronic diseases!

On the other hand, even when potent alterations in physiology and clinical symptoms are possible, placebo responding in double-blind drug studies is notoriously unreliable within and across subjects. For example, Turner et al (1994) have shown that while the mean magnitude of subjective pain reduction in placebo analgesia drug studies is often reported to be 33%, it can vary widely from 10 to 90%.

It appears that a learning or conditioned-response mechanism model of the placebo effect is the most effective method of installing reliable response expectancies in the general population (Ader 1995; Voudouris, Peck & Coleman 1989, 1990; Wickramasekera 1977a, 1980, 1985). Placebos constructed by conditioned responses probably operate by producing learned physiochemical changes similar to but generally of lesser magnitude than changes produced by active drugs or unconditioned stimuli (Ader 1988, 1995; Ader & Cohen 1982; Wickramasekera 1977a, 1980).

Because of the notorious difficulty of investigating whether people can be persuaded to select a placebo, the powerful placebo is now a "faith healing" ability (Buck 1979). The conditioned or automatic placebo response is not more powerful than do people's "self-healing ability" (Sperry 1980; Webb 1969, 1988).

The conditioned response model (Wickramasekera 1977a, 1977b) suggests that people who believe in their ability to heal and administer it to themselves can actually act upon their belief in a way that predicts the placebo response. The continuous reinforcement that accompanies the high hypnotic ability of the placebo is the durable physiological change that eventually leads to the production of a placebo response. Availing ourselves of these ances could be an adequate way to develop a placebo that works, as opposed to the placebo that is controlled for by its administration of empirically shown to be effective.

It is worth noting that it is possible to limit the placebo effect by using physiological or psychological methods to reduce subject distress (Evans 1979; Sperry 1980). Incongruence between the source of the mind-body experience and the possible beneficial outcome (Wickramasekera 1989) may be the treatment of choice for conditions in which psychotherapy is not possible.
Because alterations in physiology and clinical symptoms induced with placebo drugs are notoriously unreliable, it is crucial in the initial investigation of this conditioned-response model to select subjects in whom mind-body effects occur powerfully and reliably. People high on hypnotic ability (Barber 1969, Hilgard 1965) rapidly acquire conditioned responses both voluntarily (the autonomic nervous system) and operantly (the central nervous system), and they overlearn or automatize conditioned responses more quickly than do people of low to moderate hypnotic ability* (Das 1982a,b; King & McDonald 1976; Webb 1962; Wickramasekera 1976, 1980, 1985, 1988).

The conditioned-response model of the placebo (Wickramasekera 1976, 1977a, 1980, 1985) predicts that people of high hypnotic ability and a respondent conditioning model of drug administration will produce the most rapidly acting and reliable placebos. More specifically, it predicts that a partial (rather than a continuous) reinforcement acquisition procedure used with high hypnotic ability people will produce the most durable placebos. For example, when the patient is eventually switched to a strictly placebo schedule of delivery, this acquisition procedure will also generate the greatest resistance to the extinction of placebo responding.

Available studies so far do not provide an adequate test of these two predictions. I know of no double-blind placebo drug studies of clinical pain, as opposed to experimental pain, with good controls for measured hypnotic ability. The only empirical study of placebo responding to date that controlled for hypnotizability used experimental

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*It is worth noting that even in people of high hypnotic ability, it is possible to find inconsistencies between self-reported results and physiological measurements, such as strong verbal reports of reduced subjective distress but only moderate alterations in electrophysiological and autonomic nervous system measures of distress (Evans & Paul 1971; Hilgard & Hilgard 1978). Incongruities between explicit or conscious beliefs and biology are often at the crux of psychophysiological disease—"secrets kept from the mind but not from the body or behavior" (Wickramasekera 1979, 1986, 1988, 1988). This level of analysis, presented in full elsewhere (Wickramasekera 1988), is crucial for both the diagnosis and the treatment of chronic psychophysiological diseases treated by psychotherapy, drugs surgery, or even placebos.

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Pain induction (McGlashan et al. 1969), and it appears (Evans 1974) that mean placebo rates in experimental pain studies are significantly lower (11%) than in clinical pain studies (36%), the reason probably being that the long-term consequences and meaning of clinical pain (for example, surgical pain) are vastly more serious for the patient than is the temporary unpleasantness of radiant heat or ischemic pain for subjects in experimental placebo pain studies. The ultimate power of placebo or "top-down" healing is most likely to be manifested under conditions of massive emotional arousal (Frank 1965) in skillfully managed life-threatening clinical situations, as in the Greek drama of the surgical operating theater where surgeons, the robed and masked high priests of the medical establishment, perform surgical rituals (Cobb et al. 1959; Diamond et al. 1958). In such surgical placebo studies, the mean placebo rates were as high as 90%.

The model predicts that the second best way to induce powerful and reliable placebo analgesia and healing is to induce psychophysiological alterations with conditioning procedures in people with real clinical conditions (for example, people treated with steroids or morphine) who are highly hypnotizable.

The model also predicts that progress in isolating physiochemically active ingredients (such as morphine and antibiotics) and psychologically active ingredients (such as hypnotic ability, accurate empathy and warmth) or unconditioned stimuli for healing will be associated with more powerful placebo effects because of the inevitable learned or conditioned response component in all active drug and physiological effects (Wickramasekera 1980, 1985). According to the model, reliable mechanisms of pathophysiology (for example, infections by germs or virus) with clearly and sharply defined onsets and offsets can operate as unconditioned stimuli, from which it follows that chemicals and procedures that reliably and clearly turn on or off such pathophysiology can also operate as unconditioned stimuli for human and animal learning. Living organisms, human or animal, can learn and can interact with any
Discussion
Wickramasekera

psychophysiological active ingredient (for example, insulin, morphine, warmth, accurate empathy, hypnotic ability) or unconditioned stimulus for healing or toxic disease in their environment. Microbiologists are starting to realize this, and it was recently bluntly stated in Science (Bull & Levin 2000) that even mice are not "simply furry petri dishes." There are major differences between drug experiments done in test tubes and those done in animals that can learn and can interact with drugs. In sum, the mechanisms of both disease and healing may not be insulated from conditioning effects. Further, the unconditioned response is a function not only of the unconditioned stimuli but also of any associated conditioned stimuli. Important here too is the "vulnerability" of the animal or the patient: The symptomatically immobilized and dependent patient in a state of health deprivation (not unlike food deprivation) is an ideal candidate for conditioning and learning.

Counterintuitively, then, this model predicts that therapists who use active ingredients or unconditioned stimuli (morphine, high hypnotic ability, etc.) will get stronger placebo effects than those who use inert ingredients (saline or professional detachment) or neutral stimuli. The model also paradoxically predicts that biomedical progress in isolating active ingredients will inevitably lead to both more and stronger placebo effects (Wickramasekera 1980, 1985, 1988). Put another way, the more effective the medicine, the stronger the placebo effects of anything associated with the delivery of the medicine (a bitter irony, no doubt, for biomedical practitioners, who tend to be contemptuous of the placebo). I say this in view of the very powerful placebo effects documented best in the life-threatening skilful surgical theater (Cobb et al 1959, Diamond et al) and in early life-threatening nausea and vomiting studies (Wolf 1950). Naive human experimentation committees or institutional review boards can be obstacles to the composition of placebo control groups that are necessary to separate out the learned or mind component in, for example, popular and expensive surgical procedures. As one instance, there is need for more careful studies of the magnitude of the placebo or learned component in coronary bypass surgery. But unlike the 1950s, today double-blind surgical research (with both patient and clinical evaluator blind) is hard if not impossible to do on presumably ethical grounds. Today only cases of "surgical misadventures" can hint at the magnitude of placebo efficacy in surgery.

While there is no systematic human evidence to support the conditional response model, some strong controlled animal evidence (Ader 1981; Drawbrough & Lal 1974; Goldberg & Schuster 1967, 1970; Schuster & Thompson 1969; Siegel 1978; Wilker & Poffer 1970) supports the view that neutral stimuli can elicit complex biological and biochemical changes, as postulated by the model. There is also good and growing evidence (Wickramasekera 1988, 1999; Wilson & Barber 1993) that in people of high hypnotic ability "beliefs can have biological consequences" (Wickramasekera 1979).

The practical implications of this learned or memory-based conditioned response model of the placebo is that people currently on high and lifetime doses of hypertensive medications, insulin, or ritalin may be able to control their hypertension, diabetes, or attention deficit disorder with only half of their current dose if their drug (unconditioned stimulus) is delivered on an intermittent reinforcement schedule in a vehicle that makes active drug indistinguishable from a placebo drug (conditioned stimulus) and that mimics the side-effects of the active drug. This reduction in medication usage may not please the drug industry but may enable patients to control their symptoms with less medication and less toxic side-effects of drugs.

In short, the above theoretical analysis (Ader 1995, Wickramasekera 1977a, 1980, 1985), which remains to be empirically tested in humans (O'ness & Ader 1992) with drugs (and also with surgery), strongly suggests that the mind, through learning mechanisms, can alter the body both physiochemically and behaviorally.

References


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Response by Broom

Placebo and health—II
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Ian Wickramasekera

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Howard Brody with Daralyn Brody

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