The Placebo Effect

illness and interpersonal healing

Franklin G. Miller,* Luana Colloca,† and Ted J. Kaptchuk‡

ABSTRACT The placebo effect has been a source of fascination, irritation, and confusion within biomedicine over the past 60 years. Although scientific investigation has accelerated in the past decade, with particular attention to neurobiological mechanisms, there has been a dearth of attention to developing a general theory of the placebo effect. In this article, we attempt to address this gap. To set the stage, we review evidence relating to the reality and clinical significance of the placebo effect. Next we investigate the scope and limits of the placebo effect by examining the hypothesis that the placebo effect operates predominantly by modifying the experience and perceptions of illness symptoms, such as pain, anxiety, and fatigue, rather than by modifying the pathophysiology of disease. Based on this background, we characterize the placebo effect as a form of interpersonal healing, as distinct from spontaneous natural healing and from technological healing dependent on physiologically active pharmaceuticals or procedures. Finally, we argue that research on the placebo effect has the potential to revitalize the art of medicine.

*Department of Bioethics, National Institutes of Health.
†Department of Neuroscience, University of Turin Medical School, Italy.
‡Osher Research Center, Harvard Medical School.
Correspondence: Franklin G. Miller, Ph.D., Department of Bioethics, Clinical Center, National Institutes of Health, Building 10, Room 1C118, Bethesda, MD 20892-1156.
E-mail: fmiller@nih.gov.

The opinions expressed are those of the authors and do not necessarily reflect the position or policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.

The authors thank Howard Brody, Reidar Lie, and four anonymous reviewers for helpful comments on previous versions of this paper. Research for this paper was supported by the Intramural Research Program of the Clinical Center, NIH (FGM), a grant by Regione Piemonte (LC), and NIH grant No. K24 AT004095 from the National Center for Complementary and Alternative Medicine (TJK).

Perspectives in Biology and Medicine, volume 52, number 4 (autumn 2009):518–39

WRITING OVER A DECADE AGO, Ader (1997) noted that "There has been relatively little systematic exploration of the scope of placebo phenomena, a fact that may reflect the lack of any theoretical position(s) within which to organize existing data and upon which to base the design of new research" (p. 138). Recently, scientific investigation of the placebo effect has flourished, yielding substantial progress in understanding psychological and neurobiological mechanisms (Benedetti 2009). Nevertheless, the poverty of theory has continued to characterize placebo research. We suggest that lack of adequate attention to theory has hindered scientific investigation of the placebo effect and translation of scientific research into improved clinical practice. The concept of theory generally has been applied narrowly within the literature on the placebo effect to refer to various mechanistic theories of how the placebo effect works: for example, expectation, conditioning, and anxiety reduction. In this article we develop a broader theoretical account of the placebo effect with particular emphasis on the concept of "interpersonal healing," which is especially able to modify the perceptions and experience of illness symptoms.

Healing is a causal process. Accordingly, before we explicate the concept of the placebo effect as a form of interpersonal healing, we set the stage by examining two questions: (1) can placebo effects produce clinically significant outcomes?; and (2) what is the scope and limits of healing by means of the placebo effect? After this discussion, we offer a conceptualization of placebo effects understood as interpersonal healing, primarily targeting the experience of illness, with the aim of contributing to translating scientific understanding into improvements in patient care.

CLINICAL SIGNIFICANCE OF PLACEBO EFFECTS

There is no standard definition of the "placebo effect." As a clinical phenomenon, the "placebo effect" is a generic name for beneficial effects that derive from the context of the clinical encounter, including the ritual of treatment and the clinician-patient relationship, as distinct from therapeutic benefits produced by the specific or characteristic pharmacological or physiological effects of medical interventions. Although the "inert" placebo (such as a sugar pill or saline injection) is a tool for scientific understanding of the placebo effect, a placebo intervention is not necessary to elicit it. The placebo effect may accompany and enhance the effectiveness of medical interventions with demonstrated specific treatment efficacy. Moreover, the communicative interaction of practitioners with patients, both verbal and nonverbal, may produce placebo effects even without the use of discrete treatments.

Evidence of placebo effects derives mainly from two types of experimental research: randomized placebo-controlled clinical trials of drugs and procedures, and laboratory experiments specifically aimed at evaluating the placebo effect. Patients in the placebo arm of randomized clinical trials often show substantially

improved outcomes as compared with their pretrial baseline (Beecher 1955; Bendsten et al. 2003; Dorn et al. 2007; Kaptchuk 1998; Walsh et al. 2002). At best, however, this only suggests the possibility of a placebo effect—improvement *caused* by the placebo intervention and its surrounding clinical context—for patients may have improved as a result of the natural history of their condition or regression to the mean (Hrobjartsson 2002; Kienle and Kiene 1997; Miller and Rosenstein 2006). A placebo effect cannot be demonstrated without comparing a placebo group with a no-treatment control group, or comparing two or more placebo interventions under different contexts, which are not typical for randomized trials.

Even when no-treatment control groups are included, randomized clinical trials have distinctive limitations in evaluating placebo effects. Because these experiments are typically designed to evaluate treatment efficacy, as measured by the difference between treatment and placebo groups, trialists have an interest in minimizing placebo effects. Most importantly, the double-blind design, in which patients are told that they may get a drug or a placebo masked to appear indistinguishable, likely creates a lower expectation of benefit from the placebo intervention than when placebos are presented (deceptively) as a known beneficial treatment (Vase, Riley III, and Price 2002). Some experimental evidence aimed at evaluating responses to placebos under different informational contexts supports this point (Geers et al. 2006; Kirsch and Weixel 1988; Pollo et al. 2001). Consistent with these methodological limitations, a landmark meta-analysis by Hrobjartsson and Gotzsche (2001) of 114 randomized clinical trials including placebo and no-treatment groups, with 8,525 patients across a wide range of medical conditions, found no evidence of placebo effects for objective and binary outcomes and only a small, and doubtfully clinically relevant, effect for continuous subjective outcomes, such as pain.

In contrast to the lack of evidence of clinically significant benefit from placebo interventions in this meta-analysis of randomized trials, the results of several recent acupuncture trials conducted in Germany indicate clinically significant benefit from interventions that appear to work by virtue of the placebo effect (Brinkhaus et al. 2006; Haake et al. 2007; Linde et al. 2005; Melchart et al. 2005; Witt et al. 2005). This series of three-arm randomized trials compared traditional Chinese acupuncture, sham acupuncture (superficial needling at non-acupuncture points), and either no-treatment (wait-list) groups or those receiving usual clinical care. Conditions studied included migraine, tension headaches, chronic low back pain, and osteoarthritis of the knee. Generally, across the various trials, no difference was detected between verum and sham acupuncture, but patients receiving either of these interventions experienced substantially greater symptom improvement than no-treatment and usual care control groups. For example, in a trial of over 1,100 patients with chronic low back pain receiving 10 30-minute acupuncture sessions over five weeks (Haake et al. 2007), the response rate after six months was 48% for verum acupuncture and 44% for sham

acupuncture, as compared with 27% for patients receiving usual care (physiotherapy plus as-needed pain medication).

The results of these trials suggest that traditional acupuncture lacks specific efficacy for the conditions investigated—that is, there is nothing specific to the needling characteristic of traditional acupuncture that contributes to therapeutic benefit. This conclusion is bolstered by a recent systematic review of 13 randomized trials of 3,025 patients with pain conditions that included acupuncture, sham acupuncture, and no-treatment groups (Madsen, Gotzsche, and Hrobjartsson 2009). A small effect favoring acupuncture was detected, but this was not considered clinically significant and could easily be attributed to bias created by patients in the unblinded no-treatment groups. While it may be premature to infer with confidence that acupuncture is no better than a placebo intervention, the accumulated evidence strongly points in this direction.

Does it follow that acupuncture produces clinical benefit by virtue of the placebo effect? It is possible that the repetitive physical stimulus common to real and sham acupuncture is responsible for observed analgesic effects by means of some physiological mechanism (Haake et al. 2007). There is, however, evidence that expectation influences the clinical benefit associated with acupuncture in both verum and sham groups. In an analysis of four of the German acupuncture trials, Linde and colleagues (2007) found that the odds ratio for a clinical response to real or sham acupuncture was twice as high among those patients reporting a positive expectation of benefit. In general, sham devices may produce distinct or especially large placebo effects as compared with placebo pills (Kaptchuk et al. 2000, 2006). More research will be needed to clarify the placebo response to acupuncture, but these trials at least suggest that this type of invasive but safe intervention, characterized by an elaborate treatment ritual and frequent clinician-patient interaction, may be a potent method of interpersonal healing by means of the placebo effect (Kaptchuk 2002). Interestingly, more recent acupuncture trials using more sophisticated non-invasive sham needles have obtained similar results to the German trials' sham superficial needling (Cherkin et al. 2009; Goldman et al. 2008; Lembo et al. 2009).

Hrobjartsson and Gotzsche have recently updated their meta-analysis of randomized trials including placebo and no-treatment groups, with a data set now encompassing 234 trials and 16,570 patients (Hrobjartsson, personal communication 2009). They found essentially the same pooled results: modest effects of placebo on continuous, subjective outcomes, most notably with respect to relief of pain and nausea. The increased sample size, however, permitted more powerful subgroup analyses. Placebo effects were significantly larger for physical placebos as compared with pill placebos, for patient-reported outcomes as compared with observer-reported outcomes, when patients were not informed about the possibility of receiving a placebo intervention, and when the trials were explicitly designed to study placebo effects.

Independently of randomized clinical trials, the reality of placebo effects has

been demonstrated repeatedly in laboratory experiments over the past 60 years, starting with Stuart Wolf's (1950) pioneering experiments. In the last 30 years, these studies have shown that placebo interventions can elicit quantifiable changes in neurotransmitters, hormones, and immune regulators (Benedetti 2009). During the past decade, numerous studies have investigated the neurobiological mechanisms underlying placebo effects by means of brain imaging techniques (Colloca, Benedetti, and Porro 2008; Faria, Fredrikson, and Furmark 2008). Nevertheless, despite impressive progress in understanding the placebo effect, the clinical significance of findings from laboratory placebo mechanism experiments remains open to question. Most of these studies have enrolled healthy volunteers, who were administered experimental manipulations aimed at understanding placebo analgesia. Although suggestive, the relevance of these experiments to placebo effects in clinical pain conditions is unclear. Those mechanistic studies that have enrolled patients with various medical conditions have, with a few exceptions, examined very short-term effects of placebo interventions, lasting from several minutes to a few hours to, on occasion, a few days in duration. Especially lacking and needed is translational placebo research involving patient-subjects, aimed at understanding clinical implications of placebo effects over time and at testing hypotheses relating to how placebo effects can be tapped and enhanced in service of patient care.

A noteworthy recent clinical experiment identified components of the placebo effect and their impact on therapeutic outcomes (Kaptchuk et al. 2008). Patients with irritable bowel syndrome were randomized to two placebo acupuncture interventions that varied in the intensity and quality of communicative interaction between practitioner and patient; and both groups were compared with a no-treatment waiting-list group. Patients received sham acupuncture during a run-in phase of a randomized trial comparing verum and sham acupuncture (consisting of a device with a non-penetrating retractable needle that creates the illusion of needling). Patients received sham acupuncture twice a week for three weeks. In the "limited" arm, communication between practitioner and patient was "business-like" and reduced to a minimum. Patients in the "augmented" arm had a 25-minute conversation relating to their condition with the practitioner at the initial visit (as compared with five minutes in the limited arm), which was structured to be supportive and empathic and to promote positive expectations from acupuncture therapy. At three weeks, 62% of the patients in the augmented group reported adequate symptom relief, as compared with 44% in the limited group and 28% in the waiting list, a difference that was sustained for the three-week follow-up.

This experiment suggests that the simulation of treatment, as reflected in the sham acupuncture intervention, by itself contributes to therapeutic benefit. When augmented by supportive communication, the ritual of treatment produces an enhanced and sustained placebo response in a difficult-to-treat patient population.

The Healing Power of Placebo Effects in Relation to Illness and Disease

In light of the emerging evidence suggesting the potential for the placebo effect to produce clinically significant benefit, what are the scope and limits of the placebo effect as a mode of healing? The distinction between *disease* and *illness*, described by various commentators over the past 30 years, may help in defining the healing power of the placebo effect (Eisenberg 1977; Kleinman 1988). Disease consists of biological dysfunction of the human organism—the primary focus of diagnosis and treatment within biomedicine. Illness is the experience of detriments to health, including the symptomatic manifestations of disease. Disease adversely affects the organism; illness adversely affects the person. The body is the locus of both disease and illness, but the impact on the body is understood differently in these two domains. Disease is understood scientifically in terms of pathophysiology; illness is understood phenomenologically, as lived experience (Carel 2008). Diseases can occur without illness when they are asymptomatic; conversely, people can suffer from illness without any diagnosable disease. Despite these differences between disease and illness, they are not mutually exclusive categories. The pathophysiology of diseases produces characteristic symptoms, often experienced as illness. Commonly for a sick person, illness and disease coexist in a dynamic relationship.

Part of why the placebo phenomenon has been relatively neglected within biomedicine is that the predominant paradigm focuses on a biological conception of disease that is treated by technological interventions (including drugs, medical procedures, implanted devices, and surgery), with relatively less attention to illness relieved by the context of the medical encounter, including the doctor-patient relationship. As Frank (1973) notes: "scientific medicine . . . while paying copious lip service to the doctor-patient relationship, in actuality largely ignores it" (p. 47). Yet relief of suffering is a major goal of medicine. From a historical and cultural perspective, the response to illness by healers is a universal phenomenon. Although traditional forms of medicine lacked a scientific understanding of disease and had few treatment interventions with any specific efficacy, much of the success of traditional medicine can be attributed to the placebo effect, operating on illness.

Spiro (1997) suggested that placebo effects have the power to ameliorate illness but not to cure or control disease. Considerable scientific evidence supports this hypothesis. The most studied and well-understood area of placebo research concerns placebo effects on pain and related forms of distress, which primarily belong to the experience of illness (Benedetti 2009). As reviewed above, the best evidence for placebo effects derives from two situations. First, laboratory experiments have demonstrated short-term symptomatic relief, especially pain. Second, patients with chronic conditions marked by pain or distress have obtained significant and lasting symptomatic relief following sham acupuncture, as compared with no-treatment and usual care control groups. There is little reliable

evidence that the placebo effect can cure or control disease by modifying pathophysiology. This absence of solid evidence of placebo interventions producing objective benefit in treating disease *beyond* its distressing symptomatic manifestations is most visible in the meta-analysis mentioned earlier of trials that included placebo and no-treatment controls (Hrobjartsson and Gotzsche 2001). In this study, placebo treatment was found superior to no-treatment control groups only for continuous subjective outcomes, such as pain.

Unfortunately, there is a dearth of systematic reviews of placebo outcomes in particular medical conditions restricted to trials with no-treatment controls. Yet an examination of meta-analyses and systematic reviews of the observed responses in the placebo arms of randomized controlled trials supports the hypothesis that the placebo effect is limited to providing symptomatic relief. For example, the substantial placebo response in gastrointestinal disease for such symptoms as pain, emesis, bloating/fullness, and early satiety does not correlate with pathophysiological changes in motility or gastric hypersensitivity (Mearin et al. 1999; Reingard et al. 2004). When objective changes occur in the placebo arm of trials with more serious gastrointestinal conditions, such as ulcerative colitis and Crohn's disease (which alternate between intermittent acute exacerbation and remission), the dominant interpretation seems to be that these are not genuine placebo responses, but likely represent "spontaneous" natural improvement (Garud et al. 2008; Meyers and Janowitz 1989; Su et al. 2004, 2007). Absent evidence from clinical trials with no-treatment control groups, claims that placebo interventions cure ulcers or other gastrointestinal conditions are suspect. Another example is urinary symptoms, such as overactive bladder and voiding problems, which typically improve in patients randomized to placebo; however, these outcomes are rarely, if ever, accompanied by detectable changes in pathophysiology (McConnell et al. 1998; Moyad 2002; van Leeuwen et al. 2006).

Laboratory experiments have demonstrated short-term objective improvement with placebo treatment in Parkinson's disease (Benedetti et al. 2004; de la Fuente-Fernandez 2001); however, claims that placebo treatment produces lasting changes in objective measures of Parkinson's disease (Goetz et al. 2000, 2008) have never been tested with no-treatment groups to control for normal fluctuations. A meta-analysis of randomized trials that included 213 patients with sleep disorders treated with placebo for two weeks found subjective improvement but no changes in objective measures such as polysomnographic sleep latency (McCall, D'Agostino, and Dunn 2003). The evidence for objective changes in hypertension produced by placebo interventions is equivocal, at best. Although high placebo responses have been reported in hypertension randomized trials (Materson et al. 1993), large trials including no-treatment controls generally have not shown any difference between placebo and no-treatment groups (e.g., Gould et al. 1981; MRC Working Party 1977). Several meta-analyses of observed placebo response rates in other cardiovascular conditions have shown changes in both symptoms and pathophysiology, but these trials have not controlled for natural

history (Archer and Leier 1992; Bienenfeld, Frishman, and Glasser 1996; Olshansky 2007). For oncological diseases, a systematic review of randomized trials found that placebo treatment is associated with improvement in subjective complaints like pain and appetite (Chvetzoff and Tannock 2003). Slight rates of tumor response in placebo-treated patients were attributable to changes normally associated with "spontaneous remission."

A recent randomized trial in 601 asthmatic patients with poor symptom control, using a factorial design, allocated subjects to an established drug or placebo, with neutral or enhanced messages relating to expectation of benefit. After four weeks, no differences were found in objective measures of peak expiratory flow or lung function; however, patients randomized to placebo under enhanced expectation had significant improvements in patient-reported symptoms and asthma control (Wise et al. 2009). Again, the placebo effect seems to represent what Wilson (1999) calls "a response shift" to biological disease, rather than modification in pathophysiology.

Some randomized trials have detected an association between compliance with placebo interventions and mortality (Simpson et al. 2006). Does this suggest that the placebo effect can improve survival? Although this possibility cannot be ruled out, it seems doubtful that merely taking placebo pills faithfully, and expectations associated with taking them, can have any impact on mortality. More plausible is the hypothesis that compliant patients engage in health-promoting behavior, which itself may influence survival. In discussing their meta-analysis of adherence and mortality, Simpson and colleagues note that "The observed association between adherence to placebo and mortality supports the premise of a healthy adherer effect, where adherence to drug therapy may be a surrogate marker for overall healthy behavior" (p. 15).

This cursory examination of observed placebo responses in randomized trials without solid and consistent evidence of objective improvement in disease outcomes could easily be extended. Nevertheless, we cannot rule out the possibility that placebo interventions may produce beneficial (and lasting) modification of disease beyond symptomatic relief, especially in the context of classical conditioning (Ader 1997). Classical conditioning, pairing an immunosuppressive drug with a neutral stimulus, can produce a conditioned response that enhances survival in mice with a lupus-like disease (Ader and Cohen 1982). Giang and colleagues (1996) produced decreased peripheral leukocyte counts in patients with multiple sclerosis following a conditioning experiment with cyclophosphamide and a flavored syrup. More recently, investigators have demonstrated conditioned immunosuppression in healthy human volunteers (Goebel et al. 2002). These studies suggest the disease-modifying potential in substituting placebo interventions for drugs in conditioning paradigms, though the efficacy of such paradigms in treating disease with therapeutic outcomes has yet to be demonstrated in humans (Benedetti 2009). In any case, until evidence to the contrary is consistently produced, we suggest that placebo effects that derive

from other psychological mechanisms may inherently lack the potential to produce therapeutic benefit beyond symptomatic relief. Better understanding of the scope and limits of clinically relevant placebo effects awaits further investigation.

In evaluating the hypothesis that the placebo effect predominantly relieves illness rather than cures or controls disease, it is important to avoid presuming that illness is an exclusively mental or subjective phenomenon. Illness concerns the way in which the body presents itself to the suffering person. Heartburn is experienced as pain in the chest, and fatigue is felt as a lack of energy in the body. Although pain is an inherently subjective phenomenon, the pain behavior it elicits can be detected by others. In addition, areas of the brain related to pain can be imaged with fMRI and PET in the context of placebo analgesia experiments that administer pain stimuli and placebos described to human subjects as pain-relieving agents (Craggs et al. 2008; Kong et al. 2006; Petrovic et al. 2002; Wager et al. 2004; Zubieta et al. 2005). As the symptomatic manifestation of disease, illness has subjective and objectively measurable dimensions, both of which may be modified by placebo effects. For example, reduced arthritic pain from a placebo effect may also be associated with improved mobility. Accordingly, the thesis that the placebo effect predominantly operates on illness does not imply that it is "all in the mind" or that it only involves subjective outcomes, based entirely on patient reports.

The Placebo Effect and Interpersonal Healing

Understanding the placebo effect is hampered by its connection with the confusing concept of the placebo (Grunbaum 1986; Miller and Kaptchuk 2008a). Especially problematic for understanding the placebo effect and its therapeutic potential are a variety of negative and muddled characterizations of the placebo, which at best are half-truths, if not complete distortions. The placebo is thought to be merely "inert," nothing at all. Whatever effects are produced by placebo interventions are "non-specific." In clinical practice, the placebo treatment—typically an "impure" placebo consisting of an active agent without specific efficacy for the patient's condition (Tilburt et al. 2008)—is given just to please or placate; it is a fake treatment that is mediated by deceptive verbal suggestions. Within randomized controlled trials, the "gold standard" of evidence-based medicine, the placebo effect is merely noise or a nuisance variable that needs to be factored out in order to detect the real effects of real treatments.

Moerman (2002) has advocated the "meaning response" as a better characterization of the placebo effect and related phenomena, because it avoids the misleading language associated with the placebo concept. This conceptualization has the merit of emphasizing one component that is important to the placebo effect as a mode of healing. This is the communication to the patient of an intelligible account that explains the illness and provides a credible rationale for the potential efficacy of treatment. As Frank (1973) observes: "Naming something is the

first step toward controlling it" (p. 65). Brody and Waters (1980) argue that diagnosis may itself be a form of therapy. Elaborating on this meaning component within "nonmedical healing," Frank also remarks that "Another source of the patient's faith is the ideology of the healer or sect, which offers him a rationale, however, absurd, for making sense of his illness and treatment procedure, and places the healer in the position of transmitter or controller of impressive healing forces" (p. 73). This is no less true of scientific medicine.

The "meaning response," however, has limitations as a descriptive label for the placebo effect. First, meaning is a pervasive feature of human life, as all forms of human communication involve the perception and expression of meaning. Hence the "meaning response" is too broad a label to specifically characterize healing connected with the contexts of the clinical encounter. Second, and most significantly, this term is question begging. As Ader (1997) observes: "Some definitions of the placebo effect . . . include a phrase that presumes the means by which the effect occurs" (p. 139). The "meaning response" implies an explanatory hypothesis relating the placebo effect to perception of symbolic meaning. While attention to meaning—especially the hope and expectation for relief based on contextual features of the clinical encounter—plays a prominent role in eliciting placebo effects, there is abundant evidence that this phenomenon may be evoked by classical conditioning (Siegel 2002).

Although expectation and conditioning are not mutually exclusive, at least in some cases conditioned placebo responses are likely independent of perceived meaning (Amanzio and Benedetti 1999; Stewart-Williams and Podd 2004). Also, nonhuman animals can manifest placebo effects, which cannot be explained in reference to grasping symbolic meaning (McMillan 1999). In connection with a conditioning experiment in rats, Hernstein (1962) noted that "Viewed as conditioning, the placebo effect is merely a particular instance of a phylogenetically widespread behavioral phenomenon, and not a manifestation of man's special symbolic capacities" (p. 678). Third, responses to meaning in clinical contexts can be positive or negative. However, the placebo effect has been understood primarily as referring to beneficial effects, in contrast to the nocebo effect, which involves adverse consequences of clinical communication.

Although the placebo concept is fraught with confusion, the terminology of the "placebo effect" and the "placebo response" is entrenched in the language of biomedicine and unlikely to be abandoned in the near future. We suggest that progress in conceptualizing the placebo effect and in probing its clinical significance can be promoted by seeing it as a set of related causal processes within "interpersonal healing," by means of which the context of the clinical encounter and the relationship between a healer and a patient produce therapeutic benefit. Compared with the "meaning response," "interpersonal healing" as an orienting concept is more specific (though still very broad), neutral between explanatory hypotheses for how the clinician-patient encounter promotes healing, and focused on positive therapeutic outcomes.

To explicate interpersonal healing and to locate the role of the placebo effect within interpersonal healing, it is important to distinguish this from two other forms of healing: spontaneously self-generated "natural healing" and what we call "technological healing." Natural healing is the spontaneous or automatic response of the body to disease or injury, exemplified by internal mechanisms of fighting infections and wound healing. Technological healing consists of the full array of medical and surgical treatments that have pharmacological or physiological properties capable of promoting cure, disease control, or symptomatic relief. It encompasses everything from a herbal remedy in traditional medicine that has specific efficacy for treating a particular condition to heart transplantation accompanied by immunosuppressive drugs.

All three modes of human healing often work in tandem. For example, surgery repairs a lesion but creates a wound that heals naturally. While the pain that accompanies surgery may be treated by prescribed analgesics, their activity is enhanced, or the need for them is reduced, by therapeutic benefit deriving from the context of the clinical encounter and associated expectations.

One obvious, but significant, way in which interpersonal healing differs from both natural and technological healing is that the former, but not the latter, requires a conscious patient, aware of stimuli that may contribute to promoting healing. In contrast, both natural healing and technological healing can occur with unconscious patients. Indeed, at the extreme, wound healing occurs in "brain dead" patients maintained on mechanical ventilation—patients who have permanently lost the capacity for higher brain function (Truog 1997). Not only does interpersonal healing require an alert patient, but some measure of the patient's attention to the context of the clinical encounter is typically necessary in order to produce interpersonal healing by means of the placebo effect. This is demonstrated by illuminating experiments comparing open and hidden administration of drugs, showing a substantially greater effect of open administration, presented to an alert patient in a ritual of treatment accompanied by a communicated expectation of benefit (Colloca et al. 2004). For example, the substantial difference between patient responses to pain in the open and hidden administrations of analgesic drugs represents the placebo effect component of treatment outcome, without the use of a placebo intervention. Moreover, some of the psychological mechanisms of various types of interpersonal healing via the placebo effect may involve alterations in patient attention—for example, distraction from a pain or reduction in anxiety, leading to a diminished tendency of morbid attention to bodily dysfunction (Allen and Siegel 2002; Geers et al. 2006; Wilson 1999). Nevertheless, the fact that elements of alertness and attention must be involved to generate the placebo effect does not exclude aspects of placebo responses that might happen through direct sensory or affective perception outside of conscious awareness, as hypothesized by anthropological theories of "embodied experience" or "performative efficacy" (Kaptchuk et al. 2009; Thompson, Ritenbaugh, and Nichter 2009).

Another major difference between interpersonal and technological healing relates to the role of the patient. In technological healing, the patient is essentially a passive recipient of treatment interventions administered or prescribed by clinicians. Healing happens *to* the patient. In interpersonal healing, the relationship between clinician and patient promotes healing; it happens *between* them.

As suggested above, the distinction between these three modes of healing by no means implies that they are mutually exclusive. Interpersonal healing may often work by activating, facilitating, or enhancing natural healing. Technological healing primarily occurs within the context of the clinician-patient relationship, and thus will often be assisted by interpersonal healing. However, the scientific and medical emphasis on technological interventions focuses attention on the specific efficacy of the technology in promoting health and its mechanisms of action and downplays the interpersonal context of healing.

It is worth noting that the three types of healing each have their opposing, negative dimensions. Autoimmune disorders are pathological developments of natural healing. Technological healing produces iatrogenic illnesses and side effects from treatment interventions. The clinician-patient relationship can give rise to nocebo effects.

The rubric of interpersonal healing might be disputed as a theoretical focus for the placebo effect, as not all placebo effects are related to healing (or contrary to healing, as in the nocebo effect): for example, placebo effects that mimic the rewarding effects of drugs of abuse, that produce enhanced performance in sports, or that stimulate alertness and arousal, as in placebo caffeine (Benedetti, Pollo, and Colloca 2007; Fillmore, Mulvihill, and Vogel-Sprott 1994; Mitchell, Laurent, and de Wit 1996; Volkow et al. 2003). Nevertheless, the major impetus to studying placebo effects is to understand how contextual factors relating to the clinical encounter can promote health (Miller and Kaptchuk 2008a), making it reasonable to conceptualize the area of interest as interpersonal healing. The nocebo effect is also relevant in this context, as it interferes with interpersonal healing. Another potential objection to locating the placebo effect within interpersonal healing is the possibility that individuals can obtain a beneficial placebo response to a drug or herbal remedy obtained over the counter without access to a clinician. However, the extent to which individuals acting alone can access therapeutic placebo effects is unknown. Moreover, this is probably derivative from past interpersonal forms of taking medicine provided by parents to children and prescribed by physicians. Both of these points indicate that the placebo effect should not be seen as exclusively a phenomenon of interpersonal healing, but they also do not challenge the salience or utility of invoking interpersonal healing as an orienting focus for inquiry into the placebo effect.

Pulling these threads together, we submit that the "placebo effect" within health care should be understood as a generic name for the various direct causal pathways from clinician-patient interaction to therapeutic outcomes relating predominantly to symptomatic relief and coping with illness. It works by diverse

mechanisms, which may include response expectancies, classical conditioning, learning, anxiety reduction, or reward on the psychological level; and release of various endogenous mediators, such as opioids, dopamine, or serotonin, and antagonism of cholecystokinins on the neurobiological level (Benedetti 2009). On the cultural level, the placebo effect may be activated by diverse behaviors of healers (for example, gaze, touch, empathic witnessing, an opportunity for catharsis), meaningful and evocative symbols and rituals, and processes of social support, all embedded in the patient-healer relationship (Kaptchuk et al. 2009). As a form of interpersonal healing, the placebo effect also differs from natural self-healing that does not require contact with a healer and from technological healing by means of interventions with specific treatment efficacy administered or prescribed by physicians. Yet it is related to these other forms of healing insofar as the placebo effect potentiates natural healing and accompanies and enhances technological healing. In sum, the distinctive features of seeing the placebo effect as a mode of interpersonal healing are that it locates this phenomenon within the clinician-patient relationship and the context of the clinical encounter; it denotes a causal connection between this context and therapeutic outcomes; and this theory hypothesizes that the predominant, if not exclusive, impact of the placebo effect is to relieve illness, rather than to modify disease beyond symptomatic relief.

Consistent with locating the placebo effect within interpersonal healing, Kleinman (1988) advocates an informal process of medical psychotherapy as a basic component of care focusing on the illness experience of chronically ill patients:

> It is of the utmost importance that physicians achieve the highest possible placebo effect rates. To do this, doctors must establish relationships that resonate empathy and genuine concern for the well-being of their patients. . . . The chief sources of therapeutic efficacy are the development of a successful therapeutic relationship and the rhetorical use of the practitioner's personality and communicative skills to empower the patient and persuade him toward more successful coping. (pp. 245–47)

The Evolution of the Placebo Effect

An inquiry into the evolution of the placebo effect bolsters the understanding of this phenomenon as a form of interpersonal healing. Why does the placebo effect exist? Any answer is necessarily speculative, especially as there has been scant attention to the placebo effect from an evolutionary perspective.

We begin this inquiry by noting that various important self-healing functions work automatically, without needing to be elicited by our psychological dispositions or our interactions with others, including homeostatic mechanisms such as fighting infection and wound healing. We know that human beings have inter-

nal pain-relieving mechanisms via release of endogenous opioids (and other non-opioid mediators), and that to some extent placebo analgesia works by means of these mechanisms (Benedetti 2009). Why doesn't this happen automatically in response to pain?

One reason is that pain serves an important biological function, signaling a threat to the physical integrity of the organism. As Humphrey (2002) explains: "The main function of your feeling pain is to deter you from incurring further injury, and to encourage you to hole up and rest" (p. 265). Moreover, the exception to this defense function of pain proves the rule that pain serves survival. In some circumstances of acute and extreme stress, such as in battle, injured people may not feel pain, likely because of endogenous opioid release (Beecher 1956; Willer and Albe-Fessard 1980), and this serves survival in the face of immediate threats to life. In this case, the signaling function of pain is overridden, owing to the stronger survival-oriented need to be free of pain. But the question remains why internal mechanisms of analgesia don't kick in to relieve pain spontaneously when the organism is at rest and is doing what is needed to avoid further damage to itself. Why does it so often take the intervention of a healer (or a parent, in the case of young children) to relieve the pain?

Humphrey (2002) poses the right question about the social dimension of the placebo effect: "If placebos *can* make such a contribution to human health, then *what are we waiting for?* Why should it be that we often need what amounts to *outside permission* [the intervention of others] before taking charge of healing our own bodies?" (p. 259). He suggests that we need the emotional trigger of hope for relief in order to activate internal healing mechanisms to counteract the otherwise biologically useful defense mechanisms of pain and anxiety. For example, he states that "when it's known that the threat posed by the cause of the pain is soon to be lifted, there's much less need to feel the pain as a precautionary defence" (p. 274). But why does hope for relief *require* the intervention of others, rather than self-generated cognitive/emotional responses?

Although one can only speculate regarding an answer, it appears that in the face of illness-related distress, it is difficult to generate hope for relief by personal strategies. The illness itself impedes hoped-for relief. Typically, in the throes of suffering from illness, especially if worried about mortality or serious morbidity, we can't think, wish, or will the expectation that relief is in store. It takes the intervention of an authoritative or protective figure to promote hope and expectation for relief, leading to the placebo effect. Moreover, as social animals, we are attuned from infancy to look to authoritative or protective figures—initially, our parents—to intervene to relieve distress. Adler and Hammett (1973) describe the healer as "a culturally sanctioned parental figure." From a psychodynamic perspective, the healer's authority and ability to comfort may be a projection of parental care, operating by a process of transference (Brody 1980). Both conditioning from prior exposures to healers and expectations, as well as anxiety reduction,

generated by the healer are likely to activate the placebo effect. In any case, the placebo effect probably contributes to the emergence of the healer role and the profession of medicine by underlying the efficacy of interpersonal healing.

If we are correct that the placebo effect operates predominantly on illness rather than disease, then it may not be favored directly by natural selection. Instead, it may be a byproduct of the prolonged nurturance of human infants and the social solidarity of early human communities, both of which have survival value. Viewed as interpersonal healing, the placebo effect may be explainable in terms of ontogenesis, in which neocortical structures are crucial in processing language, social attitudes, and elements of interpersonal context. Additionally, the propensity to be conditioned and the potential for placebo interventions to modify disease by means of classical conditioning are part of our biological heritage. In the future, genetic research may improve our knowledge of evolutionary meanings and advantages of placebo effects by clarifying if and how specific polymorphisms are transmitted from one generation to the next (Furmark, Appel, and Henningsson 2008).

Why Placebo Research Matters: Revitalizing the Art of Medicine

The goal of translating placebo research into improved patient care, via "harnessing the placebo effect," has been repeatedly articulated (Benson and Friedman 1996). Nevertheless, this remains, so to speak, an attractive business plan that has failed to yield substantial profit. We suggest that it is fruitful from a theoretical perspective to consider the placebo effect, in the context of interpersonal healing, as a central tool of the art of medicine. Placebo research has the potential to bridge the chasm between the science and the art of medicine, but in order to make optimal use of this tool in the service of patient care, placebo research should be oriented to providing scientific insight and experimental guidance towards enhancing the art of medicine.

Traditionally, clinical medicine was, at best, an art of healing, with minimal scientific foundation. Whatever genuine therapeutic success physicians achieved was likely due to placebo effects or natural healing, rather than benefit produced by the active ingredients of treatment agents (Shapiro and Shapiro 1997). As science transformed clinical practice, first with respect to diagnostic technology and later with powerful drug treatment, commentators remarked on a disjunction between the art and the science of medicine (Armstrong 1977; Reiser 1978). Concerns were raised that the art of healing, based on intuitive clinical judgment and the physician-patient relationship, was being eclipsed by the science and technology of medicine.

The advent and ascendancy of the randomized controlled trial has further eroded the status of the art of medicine. The randomized trial focuses on outcomes in groups of patients administered treatment interventions according to

specified protocols. Therapeutic benefit deriving from the clinical encounter is a confound that needs to be eliminated or minimized in order to detect "specific" treatment efficacy. Under evidence-based medicine, the randomized trial is the arbiter of medical value—the gold standard for evaluating medical interventions. Commenting on the implications of the methodology of randomized controlled trials for the practice of medicine, Sullivan (1993) remarks: "Medical scientists set themselves apart from the doctor-patient relationship in order to obtain a knowledge that is stripped of personal elements. This allows the development of a context-independent expertise and therapeutic technology that can be delivered by a profession to its patients" (p. 227). This biomedical orientation puts a premium on the clinical value of discrete medical therapies, demonstrated to be effective in randomized trials, leaving the art of medicine outside the purview of evidence-based medicine, and thus in danger of becoming merely a cultural relic.

Indeed, the very distinction between the science and the art of medicine, when hardened into a rigid dichotomy, contributes to the marginalized status of the art of medicine and to interpersonal healing as a basic component. It suggests that the art of medicine is impervious to scientific inquiry. Accordingly, it discourages devoting scientific investigation to the therapeutic potential of the clinical encounter, with the aim of promoting improved, evidence-based, outcomes for patients. In contrast, placebo research offers promise in breaking down this dichotomy by directing scientific investigation to techniques of ameliorating illness, thus enhancing both the art of medicine and patient care.

It is reasonable to suppose that discrete patterns of interaction between clinicians and patients have the potential to promote optimal therapeutic outcomes. These patterns can be evaluated by rigorous, hypothesis-based experimental inquiry. However, in pursuit of the goal of providing evidence-based support and guidance for the art of medicine via therapeutically oriented research on the placebo effect, many important questions remain to be answered. The following seem especially pertinent for experimental inquiry:

- What components of the clinical encounter contribute to or detract from interpersonal healing?
- What communicative techniques can clinicians adopt to optimize relief of suffering from illness and enhance patient care?
- Is the ritual of treatment necessary to make optimal use of the placebo effect?
- What types of treatment interventions that lack specific efficacy are effective in promoting clinically significant placebo effects?
- Does this include openly administered placebo pills without pharmacologically active agents, provided with non-deceptive communication of positive expectation?
- Do complementary and alternative medical interventions produce clin-

ically relevant placebo effects (as compared with no-treatment or usual care groups)?
- What are the best scientific and ethical methods of evaluating placebogenic treatments?
- How should clinical trials be optimally designed to evaluate clinically significant placebo effects?
- What types of well-controlled laboratory experiments have the most promise for guiding translational placebo research?
- How do interpersonal and contextual effects interact with natural and technological healing?
- Can placebo interventions be used to reduce the doses of medically indicated treatments, such that adverse side effects are reduced without decreasing treatment efficacy?

CONCLUSION

We suggest, using the language of Kuhn (1970), that scientific research on the placebo effect has taken the shape of "normal science" without guidance by any systematic theoretical paradigm. To begin to address this gap in theory development, we have offered a series of interconnected themes that locate the placebo effect within the concept of interpersonal healing and that show its connection with the key distinction between disease and illness. Given the limited rigorous evidence relating to the clinical significance of placebo effects, we recommend experimental inquiry aimed at translating the scientific understanding of the placebo effect into improved patient care. This will be the ultimate test of a theoretical paradigm for the placebo effect: its fruitfulness in guiding future patient-centered research.

REFERENCES

Ader, R. 1997. The role of conditioning in pharmacotherapy. In *The placebo effect: An interdisciplinary exploration*, ed. A. Harrington, 138–65. Cambridge: Harvard Univ. Press.

Ader, R., and N. Cohen. 1982. Behaviorally conditioned immunosuppression and murine systemic luypus erythematous. *Science* 215:1534–36.

Adler, H. M., and V. B. O. Hammett. 1973. The doctor-patient relationship revisited: An analysis of the placebo effect. *Ann Intern Med* 78:595–98.

Allen, L. G., and S. Siegel. 2002. A signal detection theory analysis of the placebo effect. *Eval Health Prof* 25:410–25.

Amanzio, M., and F. Benedetti. 1999. Neuropharmacological dissection of placebo analgesia expectation-activated opioid systems versus conditioning-activated specific subsystems. *J Neurosci* 19:484–94.

Archer, T. P., and C.V. Leir. 1992. Placebo treatment in congestive heart failure. *Cardiology* 81:125–33.

Armstrong, D. 1977. Clinical sense and clinical science. *Soc Sci Med* 11:599–601.

Beecher, H. K. 1955. The powerful placebo. *JAMA* 159:1602–6.
Beecher, H. K. 1956. Relationship of significance of wound to pain experienced. *JAMA* 161:1609–13.
Bendsten, L., et al. 2003. Placebo response in clinical randomized trials of analgesics in migraine. *Cephalalgia* 23:487–90.
Benedetti, F. 2009. *Placebo effects: Understanding the mechanisms in health and disease*. Oxford: Oxford Univ. Press.
Benedetti, F., A. Pollo, and L. Colloca. 2007. Opioid-mediated placebo responses boost pain endurance and physical performance: is it doping in sport competitions? *J Neurosci* 27:11934–39.
Benedetti, F., et al. 2004. Placebo-responsive Parkinson patients show decreased activity in single neurons of subthalamic nucleus. *Nat Neurosci* 7:587–88.
Benson, H., and R. Friedman. 1996. Harnessing the power of the placebo effect and renaming it "remembered wellness." *Annu Rev Med* 47:193–99.
Bienenfeld, L., W. Frishman, and S. P. Glasser. 1996. The placebo effect in cardiovascular disease. *Am Heart J* 132:1207–21.
Brinkhaus, B., et al. 2006. Acupuncture in patients with chronic low back pain: A randomized controlled trial. *Arch Intern Med* 166:450–57.
Brody, H. 1980. *Placebos and the philosophy of medicine*. Chicago: Univ. of Chicago Press.
Brody, H., and D. B. Walters. 1980. Diagnosis is treatment. *J Family Practice* 10:445–49.
Carel, H. 2008. *Illness: The cry of the flesh*. Stocksfield, U.K.: Acumen.
Cherkin, D. C., et al. 2009. A randomized trial comparing acupuncture, simulated acupuncture, and usual care for chronic low back pain. *Arch Intern Med* 169:858–66.
Chvetzoff, G., and I. F. Tannock. 2003. Placebo effects in oncology. *J Natl Cancer Inst* 95: 19–29.
Colloca, L., F. Benedetti, and C. A. Porro. 2008. Experimental designs and brain mapping approaches for studying the placebo analgesic effect. *Eur J Appli Physiol* 102:371–80.
Colloca, L., et al. 2004. Overt treatment versus covert treatment for pain, anxiety, and Parkinson's disease. *Lancet Neurol* 3:679–84.
Craggs, J. G., et al. 2008. The dynamic mechanism of placebo induced analgesia: Evidence of sustained and transient regional involvement. *Pain* 139:660–69.
de la Fuente-Fernandez, R., et al. 2001. Expectation and dopamine release: Mechanism of the placebo effect in Parkinson's disease. *Science* 293:1164–66.
Dorn, S. D., et al. 2007. A meta-analysis of the placebo response in complementary and alternative medicine trials of irritable bowel syndrome. *Neurogastroenterol Motil* 19: 630–37.
Eisenberg, L. 1977. Disease and illness: Distinctions between professional and popular ideas of sickness. *Cult Med Psychiatry* 1:9–23.
Faria, V., M. Fredrikson, and T. Furmark. 2008. Imaging the placebo response: A neurofunctional review. *Eur Neuropsychoparmacol* 18:473–85.
Fillmore, M. T., L. E. Mulvihill, and M. Vogel-Sprott. 1994. The expected drug and its expected effect interact to determine placebo responses to alcohol and caffeine. *Psychopharmacology* 115:383–88.
Frank, J. D. 1973. *Persuasion and healing: A comparative study of psychotherapy*. Baltimore: Johns Hopkins Univ. Press.
Furmark, T., L. Appel, and S. Henningsson. 2008. A link between serotonin-related gene

polymorphisms, amygdale activity, and placebo-induced relief of social anxiety. *J Neurosci* 28:13066–74.

Garud, S., et al. 2008. Meta-analysis of the placebo response in ulcerative colitis. *Dig Dis Sci* 53:875–91.

Geers, A. L., et al. 2006. Expectations and placebo response: A laboratory investigation into the role of somatic focus. *J Behav Med* 29:171–78.

Giang, D. W., et al. 1996. Conditioning of cyclophosphamide-induced leucopenia in humans. *J Neuropsychiatry Clin Neurosci* 8:194–201.

Goebel, M. U., et al. 2002. Behavioral conditioning of immunosuppression is possible in humans. *FASEB J* 16:1869–73.

Goetz, C. G., et al. 2000. Objective changes in motor function during placebo treatment in PD. *Neurology* 54:710–14.

Goetz, C. G., et al. 2008. Placebo response in Parkinson's disease: Comparisons among 11 trials covering medical and surgical interventions. *Mov Disord* 23:690–99.

Goldman, R. H., et al. 2008. Acupuncture for treatment of persistent arm pain due to repetitive use: A randomized controlled clinical trial. *Clin J Pain* 24:211–18.

Gould, B. A., et al. 1981. Does placebo lower blood-pressure? *Lancet* 2:1377–81.

Grunbaum, A. 1986. The placebo concept in medicine and psychiatry. *Psychol Med* 16: 19–38.

Haake, M., et al. 2007. German Acupuncture Trials (GERAC) for chronic low back pain: Randomized, multicenter, blinded, parallel-group trial with 3 groups. *Arch Intern Med* 167:1892–98.

Hernstein, R. J. 1962. Placebo effect in the rat. *Science* 138:677–78.

Hrobjartsson, A. 2002. What are the main methodological problems in estimation of placebo effects. *J Clin Epidemiol* 55:430–35.

Hrobjartsson, A., and P. C. Gotzsche. 2001. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med* 344:1594–1602.

Humphrey, N. 2002. Great expectations: The evolutionary psychology of faith healing and the placebo effect. In *The mind made flesh: Frontiers of psychology and evolution*, 255–85. Oxford: Oxford Univ. Press.

Kaptchuk, T. J. 1998. Powerful placebo: The dark side of the randomized controlled trial. *Lancet* 351:1722–25.

Kaptchuk, T. J. 2002. The placebo effect in alternative medicine: Can the performance of a healing ritual have clinical significance. *Ann Intern Med* 136:817–25.

Kaptchuk, T. J., et al. 2000. Do medical devices have enhanced placebo effects? *J Clin Epidemiol* 53:786–92.

Kaptchuk, T. J., et al. 2006. Sham device verus inert pill: Randomized controlled trial of two placebo treatments. *BMJ* 332:391–97.

Kaptchuk, T. J., et al. 2008. Components of placebo effect: Randomised controlled trial in patients with irritable bowel syndrome. *BMJ* 336:999–1003.

Kaptchuk, T. J., et al. 2009. "Maybe I made up the whole thing": Placebos and patients' experiences in a randomized controlled trial. *Cult Med Psychiatry* 33:382–411.

Kienle, G. S., and H. Kiene. 1997. The powerful placebo effect: Fact or fiction? *J Clin Epidemiol* 50:1311–18.

Kirsch, I., and L. J. Weixel. 1988. Double-blind versus deceptive administration of a placebo. *Behav Neurosci* 102:319–23.

Kleinman, A. 1988. *The illness narratives: Suffering, healing and the human condition*. New York: Basic Books.

Kong, J., et al. 2006. Brain activity associated with expectancy-enhanced placebo analgesia as measured by functional magnetic resonance imaging. *J Neurosci* 26:81–88.

Kuhn, T. S. 1970. The structure of scientific revolutions, 2nd ed. In *The international encyclopedia of unified science*, vol. 2, ed. O. Neurath, R. Carnap, and C. Morris, 53–272. Chicago: Univ. of Chicago Press.

Lembo, A. J., et al. 2009. A treatment trial of acupuncture for IBS patients. *Am J Gastroenterol* 104:1489–97.

Linde, K., et al. 2005. Acupuncture for patients with migraine: A randomized controlled trial. *JAMA* 293:2118–25.

Linde, K., et al. 2007. The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. *Pain* 128:264–71.

Madsen, M. V., P. C. Gotzsche, and A. Hrobjartsson. 2009. Acupuncture treatment for pain: Systematic review of randomized clinical trials with acupuncture, placebo acupuncture, and no acupuncture groups. *BMJ* doi: 10.1136/bmj.a3115.

Materson, B. J., et al. 1993. Singe-drug therapy for hypertension in men: A comparison of six antihypertensive agents with placebo. *N Engl J Med* 328:914–21.

McCall, W. V., R. D'Agostino, and A. Dunn. 2003. A meta-analysis of sleep changes associated with placebo in hypnotic clinical trials. *Sleep Med* 4:57–62.

McConnell, J. D., et al. 1998. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplastia. Finasteride Long-term Effiacy and Safety Study Group. *N Engl J Med* 338: 557–63.

McMillan, F. D. 1999. The placebo effect in animals. *JAVMA* 215:992–99.

Mearin, F., et al. 1999. Placebo in functional dyspepsia: Symptomatic, gastrointestinal motor, and gastric sensorial responses. *Am J Gastroenterol* 94:116–25.

Melchart, D., et al. 2005. Acupuncture in patients with tension-type headache: Randomised controlled trial. *BMJ* 331:376–82.

Meyers, S., and H. D. Janowitz. 1989. The "natural history" of ulcerative colitis: An analysis of placebo response. *J Clin Gastroenterol* 11:33–37.

Miller, F. G., and T. J. Kaptchuk. 2008a. The power of context: Reconceptualizing the placebo effect. *J R Soc Med* 101:222–25.

Miller, F. G., and D. L. Rosenstein. 2006. The nature and power of the placebo effect. *J Clin Epidemiol* 59:331–35.

Mitchell, S. H., C. L. Laurent, and H. de Wit. 1996. Interaction of expectancy and the pharmacological effects of d-amphetamine: Subjective effects and self-administration. *Psychopharmology* 125:371–78.

Moerman, D. 2002. *Meaning, medicine and the "placebo effect."* Cambridge: Cambridge Univ. Press.

Moyad, M. A. 2002. The placebo effect and randomized trials: Analysis of conventional medicine. *Urol Clin North Am* 29:125–33.

MRC Working Party. 1977. Randomised controlled trial of treatment for mild hypertension: Design and pilot trial. Report of MRC Working Party on Mild to Moderate Hypertension. *BMJ* 1:1437–40.

Olshansky, B. 2007. Placebo and nocebo in cardiovascular health. *J Am Coll Cardiol* 49: 415–21.

Petrovic, P., et al. 2002. Placebo and opioid analgesia: Imaging a shared neuronal network. *Science* 295:1737–40.

Pollo, A., et al. 2001. Response expectancies in placebo analgesia and their clinical relevance. *Pain* 93:77–84.

Reingard, B. K., et al. 2004. Acupuncture has a placebo effect on rectal perception but not on distensiblity and spatial summation: A study in health and IBS. *Am J Gastroentroenterol* 99:1990–97.

Reiser, S. J. 1978. *Medicine and the reign of technology*. Cambridge: Cambridge Univ. Press.

Shapiro, A. K., and E. Shapiro. 1997. *The powerful placebo*. Baltimore: Johns Hopkins Univ. Press.

Siegel, S. 2002. Explanatory mechanisms for placebo effects: Pavlovian conditioning. In *The science of the placebo: Toward an interdisciplinary research agenda*, ed. H. A. Guess, et al., 133–57. London: BMJ Books.

Simpson, S. H., et al. 2006. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ* 333:15.

Spiro, H. Clinical reflections on the placebo effect. In *The placebo effect: An interdisciplinary exploration*, ed. A. Harrington, 37–55. Cambridge: Harvard Univ. Press.

Stewart-Williams, S., and J. Podd. 2004. The placebo effect: Dissolving the expectancy versus conditioning debate. *Psychol Bull* 130:324–40.

Su, C., et al. 2004. A meta-analysis of the placebo rates of remission and response in clinical trials of active Crohn's disease. *Gastroenterology* 126:1257–59.

Su, C., et al. 2007. A meta-analysis of the placebo rates of remission and response in clinical trials of active ulcerative colitis. *Gastroenterology* 132:516–26.

Sullivan, M. D. 1993. Placebo controls and epistemic control in orthodox medicine. *J Med Philos* 18:213–31.

Thompson, J. J., C. Ritenbaugh, and M. Nichter. 2009. Reconsidering the placebo response from a broad anthropological perspective. *Cult Med Psychiatry* 33:112–52.

Tilburt, J. C., et al. 2008. Prescribing "placebo treatments": Results of a national survey of U.S. internists and rheumatologists. *BMJ* 337:a1938.

Truog, R. D. 1997. Is it time to abandon brain death? *Hastings Cent Rep* 27(1):29–37.

van Leeuwen, J. H. S., et al. 2006. The placebo effect in the pharmacologic treatment of patients with lower urinary tract symptoms. *Eur Urol* 50:440–52

Vase, L., J. L. Riley III, and D. D. Price. 2002. A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain* 99:443–52.

Volkow, N. D., et al. 2003. Expectation enhances the regional brain metabolic and the reinforcing effects of stimulants in cocaine abusers. *J Neurosci* 23:11461–68.

Wager, T. D., et al. 2004. Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science* 303:1162–67.

Walsh, B. T., et al. 2002. Placebo response in studies of major depression: Variable, substantial, and growing. *JAMA* 287:1840–47.

Willer, J. C., and D. Albe-Fessard. 1980. Electrophysiological evidence for release of endogenous opiates in stress-induced analgesia in man. *Brain Res* 198:419–26.

Wilson, I. B. 1999. Clinical understanding and clinical implications of response shift. *Soc Sci Med* 48:1577–88.

Wise, R. A., et al. 2009. Randomized trial of the effect of drug presentation on asthma

outcomes: The American Lung Association Asthma Clinical Research Centers. *J Allergy Clin Immunol* doi:10.1016/j.jaci.2009.05.041.

Witt, C., et al. 2005. Acupuncture in patients with osteoarthritis of the knee: A randomised trial. *Lancet* 366:136–43.

Wolf, S. 1950. Effects of suggestion and conditioning on the action of chemical agents in human subjects: The pharmacology of placebos. *J Clin Invest* 29:100–109.

Zubieta, J. K., et al. 2005. Placebo effects mediated by endogenous opioid activity on m-opioid receptors. *J Neurosci* 25:7754–62.