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 comprehensive theory of the placebo effect. In this article, we attempt to address this gap by reviewing evidence relating to the reality and clinical significance of the placebo effect. We suggest the hypothesis that the placebo effect operates predominantly by producing symptomatic relief of illness, such as pain, anxiety, and fatigue, rather than by modifying the pathophysiology of disease. The placebo effect as a clinical phenomenon is characterized as representing the interpersonal component of healing, as distinct from spontaneous natural healing and technological healing dependent on physiologically active pharmaceuticals or procedures. Speculations regarding the evolution of the placebo effect are entertained. Finally, we argue that research on the placebo effect has the potential to revitalize the art of medicine and discuss ethical issues relating to the use of placebo interventions in clinical practice and in research on the placebo effect. We hope that this preface to developing a theory of the placebo effect will provoke debate and alternative conceptualizations and theoretical hypotheses in service of promoting a deeper and more fruitful understanding of this elusive phenomenon.
theory, offering a preface to development of a theory of the placebo effect, with emphasis on conceptual and normative dimensions.

A theory of the placebo effect needs to pose and explore several questions:

- What is the placebo effect?
- Does the placebo effect exist as a clinically significant phenomenon?
- What type of healing is produced by the placebo effect?
- Why does the placebo effect exist?
- What psychological and neurobiological mechanisms account for the placebo effect?
- Why does the placebo effect matter?
- How can placebo effects be optimized and nocebo effects minimized within clinical practice, consistent with respect for patients’ rights?

In articulating a preface to a theory of the placebo effect we can do no more than briefly address these questions. We devote the least attention to the mechanisms of the placebo effect, because this is the most extensively addressed aspect of the placebo effect in the scientific literature and has recently been summarized comprehensively by Benedetti (2009).

**Investigation of the Placebo Effect**

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, there is no need for the use of a placebo intervention 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 relating to symptoms of their disorder as compared with their pretrial baseline (Beecher 1955; Kaptchuk 1998; Walsh et al. 2002; Bendsten et al. 2003; Dorn et al. 2007). However, at best, 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 (Kienle and Kiene 1997; Hrobjartsson 2002; Miller and Rosenstein 2006). Without comparing a placebo group with a no-treatment control group, which is not typical for randomized trials, a placebo effect cannot be demonstrated.

Even when no-treatment control groups are included, randomized clinical trials have distinctive limitations in demonstrating 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 et al.
2002). Some experimental evidence aimed at evaluating responses to placebos under different informational contexts supports this point (Pollo et al. 2001; Kirsch and Weixel 1988; Geers et al. 2006). Consistent with these methodological limitations, a 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 show evidence of clinically significant benefit from interventions that appear to work by virtue of the placebo effect (Linde et al. 2005; Melchart et al. 2005; Witt et al. 2005; Brinkhaus et al. 2006; Haake et al. 2007). This series of 3-arm 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. (It is noteworthy that the sham acupuncture was described to research participants not as a placebo intervention but as a non-traditional form of acupuncture shown to be beneficial in previous clinical trials, thus enhancing expectations of benefit for participants randomized to verum or sham interventions under double-blind conditions.) 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 1100 patients with chronic low back pain receiving ten 30-minute acupuncture sessions over 5 weeks (Haake et al. 2007), the response rate after 6 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 3025 patients with pain conditions that included acupuncture, sham acupuncture, and no treatment groups (Madsen et al. 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 absolute 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). However, there is 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; Kaptchuk et al. 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 (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 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 sub-group 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 involving a janitor with a stomach fistula and two pregnant women. In the last 30 years, as reviewed comprehensively and in depth by Benedetti (2009), laboratory studies have shown that placebo interventions can elicit quantifiable changes in neurotransmitters, hormones, and immune regulators. During the past decade, numerous studies have investigated the neurobiological mechanisms underlying placebo effects by means of brain imaging techniques (Colloca et al. 2008; Faria et al. 2008). As Benedetti (2009, p.75) notes, mechanistic research on the placebo effect, beginning with experiments in the late 1970s indicating that placebo analgesia is mediated by release of endogenous opioids, gave “scientific credibility to the placebo phenomenon by unraveling the underlying biological mechanisms.” This scientific credibility is particularly important in light of the dismissive and confusing characterization of the placebo phenomenon within biomedicine.

Nevertheless, despite impressive progress in understanding the fascinating interactions of mind and body in connection with the placebo effect, the clinical significance of findings from placebo mechanism experiments remains open to question. Most of these studies have enrolled healthy volunteers administered experimental manipulations aimed at understanding placebo analgesia. The relevance of these experiments to placebo effects in clinical pain conditions is unclear. Those studies that have enrolled patients with a variety of medical conditions have, with a few exceptions, examined very short term effects of placebo or placebo-like 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 recent clinical experiment is noteworthy in attempting to identify 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 waiting list group without the sham acupuncture. All patients received sham acupuncture during a run-in phase of a randomized trial comparing verum and sham acupuncture. Different from the German trials, this study used a validated sham acupuncture intervention consisting of a device with a retractable needle that does not penetrate the skin but retracts into the handle, creating 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 45 minute conversation relating to their condition with the practitioner at the initial visit (as compared with 5 minutes in the limited arm), which was structured to be
supportive and empathic and to promote positive expectations from acupuncture therapy. Patients in the augmented arm had superior outcomes of symptom relief and quality of life to those in the limited arm, which in turn had better outcomes than those in the waiting list control arm. For example, at 3 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 3-week follow up.

This experiment suggests that the simulation of treatment, as reflected in the sham acupuncture intervention administered in the limited arm, by itself contributes to therapeutic benefit. When enhanced by supportive communication, the ritual of treatment produces a dramatic placebo response over a 3-week period and continued in the 3-week follow-up in a difficult-to-treat patient population.

The Placebo Effect 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 is the scope and limits of the placebo effect as a mode of healing? The distinction between illness and disease, described by various commentators over the past 30 years, may be fruitful for locating the placebo effect within the domain of healing (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 manifestation of disease. Disease adversely affects the organism; illness adversely affects the person. The body is the locus of both disease and illness; however, 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 illness and disease, they are not mutually exclusive categories. The pathophysiology of diseases produce characteristic symptoms, which are often experienced as illness. Commonly for a sick person, illness and disease co-habit in a dynamic and not necessarily stable relationship.

Part of why the placebo phenomenon has been relatively neglected, and often maligned, within biomedicine is that biomedicine conceptually 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, p.47) notes, “scientific medicine … while paying copious lip service to the doctor-patient relationship, in actuality largely ignores it.” Yet relief of suffering (from illness) 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 know virtually nothing about disease from a scientific perspective and may have 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.

The scientific evidence relating to placebo effects in clinical situations suggests the hypothesis that placebo effects are salient predominantly in ameliorating illness, as distinct from curing or controlling disease. The most studied and well-understood area of placebo research concerns placebo effects on pain and related forms of distress, which are primary manifestations 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 associated with mechanisms such as release of endogenous opioids and dopamine. 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 play a role in curing or controlling 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 114 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 is suggestive. For example, the substantial placebo response in gastrointestinal disease for such symptoms as pain, emesis, bloating/fullness, and early satiety does not correlate to pathophysiological changes in motility or gastric hypersensitivity (Mearn 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 (Meyers and Janowitz 1989; Su et al 2007; Garud et al 2008; Su et al 2004). In the absence of evidence from clinical trials with no-treatment control groups, any claims that placebo interventions cure ulcers or other gastrointestinal conditions are suspect. While urinary symptoms, such as overactive bladder and voiding problems, typically improve in patients randomized to placebo, these outcomes are rarely, if ever, accompanied by detectable changes in pathophysiology (van Leeuwen et al 2006; Moyad 2002; McConnell et al 1998).

While very short-term laboratory experiments have demonstrated objective improvement with placebo treatment in Parkinson’s Disease (Benedetti et al 2004, de la Fuente-Fernandez 2001), claims that placebo treatment produces lasting changes in objective measures of Parkinson’s Disease (Goetz et al 2000; Goetz et al. 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 et al 2003); however, a subsequent laboratory within-subject experiment with 10 subjects who were deceptively told that they were taking a new hypnotic found both subjective and objective changes from placebo treatment compared to no treatment controls (Fratello et al 2005).

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., Report of MRC Working Party on Mild to Moderate Hypertension 1977; Gould et al 1981). In contrast, one very small trial comparing placebo and no treatment demonstrated significant effects of placebo on systolic blood pressure, diastolic blood pressure, and mean arterial pressure (Asmar et al. 2001). 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; Olshansky 2007; Bienenfeld et al 1996). 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 “spontaneous remission.”
Some randomized trials have detected an association between compliance with placebo interventions in randomized trials and outcomes such as mortality (Simpson et al. 2006). Does this suggest that the placebo effect can have an impact on mortality from disease? It is highly doubtful that 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.

This cursory examination of meta-analyses of observed placebo responses in randomized trials without solid and consistent evidence of objective improvement in disease outcomes could easily be extended. Nevertheless, we do not dispute 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). There is experimental evidence that 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, pp. 157–9). In any case, if placebo interventions in deliberate conditioning paradigms have the power to modify disease, this therapeutic potential is, so to speak, borrowed from the known-effective drugs with which they are paired. Placebo effects that derive from other psychological mechanisms may inherently lack the potential to produce therapeutic benefit beyond relief of symptoms of illness. Understanding 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 the presumption 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 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 in the context of placebo analgesia experiments that administer pain stimuli and placebos described to human subjects as pain-relieving agents (Petrovic et al. 2002; Wager et al. 2004; Zubieta et al. 2005; Kong et al. 2006; Craggs et al. 2008). 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.

Whereas placebo effects can rarely be demonstrated in individual cases, the following historical example is instructive concerning the potential impact of the placebo effect on illness. William James, who suffered from angina, consulted “mind cure” therapists to obtain relief. After a visit with such a healer, he noted in his diary in 1907, “Remarkable improvement in moral and physical ‘tone’—and what was unlooked for in my power to walk without angina” (Myers 1986, p. 388). Assuming that James experienced a placebo response, it both reduced his pain and improved his ability to walk. Yet it is unlikely that this symptomatic relief (in both subjective and objective dimensions) had any impact on the underlying pathophysiology and progression of his heart disease.
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, which 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—the diagnosis within medicine—and provides a credible rationale for the potential efficacy of treatment. As Frank (1973, p.65) observes “[n]aming something is the first step toward controlling it.” Brody and Walters (1980) argue that diagnosis may itself be a form of therapy. Elaborating on this meaning component within “nonmedical healing,” Frank remarks that “[a]nother 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” (Frank 1973, p.73). This is no less true of scientific medicine.

The “meaning response,” however, has distinctive 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, p.139) observes, “[s]ome definitions of the placebo effect … include a phrase that presumes the means by which the effect occurs.” The “meaning response” implies an explanatory psychosocial 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 et al 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, p.678) 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.” 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 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: 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 an herbal remedy in traditional medicine that has specific efficacy for treating a particular condition to heart transplantation accompanied by immunosuppressive drugs. To a large extent, the contrast between technological healing and interpersonal healing tracks two important and related distinctions that are central to understanding the latter and its role within medicine: the distinction between the science and the art of medicine and between disease and illness (discussed above). Technological healing is a major focus of the science of medicine—the development and testing of technological interventions to successfully treat disease and symptoms of illness. Interpersonal healing concerns the art of medicine, oriented therapeutically towards relief of suffering—the illness component of disease and injury. A theory of interpersonal healing will need to illuminate why and how the clinical encounter independently contributes to healing, separate from (though often associated with) natural healing and technological healing.

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: e.g., distraction from a pain or reduction in anxiety, leading to a diminished tendency of morbid attention to bodily dysfunction (Wilson 1999; Allan and Siegal 2002; Geers et al 2006).

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” (Thompson et al. 2009; Kaptchuk et al. 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.

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 focus on technological interventions concerns the specific efficacy of the technology in promoting health and its mechanisms of action.

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); e.g., placebo effects that mimic the rewarding effects of drugs of abuse (Mitchell et al. 1996; Volkow et al. 2003), that produce enhanced performance in sports (Benedetti et al. 2007), that stimulate alertness and arousal, as in placebo caffeine (Fillmore 1994), etc. Nevertheless, the major impetus to studying placebo effects is to understand the mind-body connection in health and illness, making it reasonable to focus on the placebo phenomenon as it relates to health and 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 a marginal source of placebo effects and 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 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, or reward on the psychological level; and release of various endogenous mediators, such as opioids, dopamine, or serotonin, and antagonism of cholecystokinin on the neurobiological level (Benedetti 2009). As a form of interpersonal healing, the placebo effect also differs from natural healing that does not require contact with a healer and 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 context of the clinician-patient relationship; 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, p. 245) 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.” He adds that “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” (Kleinman 1988, p.247).

The Evolution of the Placebo Effect

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 by entertaining the hypothesis that the placebo effect activates self-healing functions of the organism—what Brody (2000) has called “the inner pharmacy.” Various important self-healing functions work automatically, without needing to be elicited by our psychological dispositions or our interactions with others: e.g., homeostatic mechanisms such as fighting infection and wound healing. We know that human beings have internal 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, p.265) 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.” 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 (Beecher 1956), likely because of endogenous opioid release (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 the “inner pharmacy” doesn’t kick in to relieve pain when the organism is at rest and is doing what is needed to avoid further damage to the organism? Why does it so often take the intervention of a healer (or a parent in the case of young children) to relieve the pain?

In contrast, there is some internal mental capacity to relieve anxiety—also a biological defense mechanism—without the therapeutic/placebogenic interventions of others. Anxiety serves to signal threat of impending danger to the organism; and cognitive appraisal of the alarming stimulus (e.g., a startling sound) as not in fact threatening can make the anxiety go away. To be sure, to some extent, it may be possible for the individual to divert attention from a mild acute painful stimulus, and thus to relieve the pain; but as pain become more severe or chronic this does not work. Also, anxiety relating to illness may be difficult to relieve without attention from a healer.

Humphrey (2002, p. 259) 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?” 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” (Humphrey
2002, 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 we can’t think, wish, or will the expectation that relief is in store. It takes the intervention of an authoritative 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, np.596) 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, p.20). 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.

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.

In any case, the placebo effect probably contributes to the emergence of the healer role and the profession of medicine, by underlaying the efficacy of interpersonal healing. In addition, the healer role is supported by natural human bias and fallacious reasoning—in particular, the fallacy of post hoc ergo propter hoc. We are inclined to attribute recovery from disease to the ministrations of healers when, in point of fact, it is often due to self-limiting diseases and the automatic natural healing of the organism.

**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 conceive the placebo effect, in the context of interpersonal healing, as a central tool of “the art of medicine.” To make optimal use of this tool in service of patient care, however, requires breaking down the traditional dichotomy between the art and the science of medicine. Placebo research has the potential to bridge the chasm between the science and the art of medicine. To realize this potential, it 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 in accordance with 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, p.227) remarks that “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.” 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 the art of medicine and patient care.

We do not suggest, however, that the art of medicine can be reduced to a set of evidence-based rules for the clinical encounter. Physicians necessarily rely on individualized judgments about how to relate to particular patients. The art of medicine can never be rule-governed in a mechanical way. Nevertheless, it is reasonable to suppose that discrete patterns of interaction between clinicians and patients are more or less likely to promote optimal therapeutic outcomes; and these patterns can be evaluated by rigorous, hypothesis-based experimental inquiry. Many important questions remain to be answered 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. The following questions 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 that are not better than placebo controls produce clinically 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 (by means of conditioning, expectation, or anxiety reduction) to reduce the doses of medically indicated treatments, such that adverse side effects are reduced without decreasing treatment efficacy?

Ethics and the Placebo Effect

From the perspective of bioethics, the placebo effect has a tainted history, as it is associated with the paternalistic and deceptive practice of physicians prescribing inert agents or “impure” placebos (Brody 1982). These concerns remain relevant to contemporary clinical practice. Recent surveys have shown that physicians continue to prescribe or recommend “placebo treatments,” which are believed to lack specific pharmacological efficacy for the patient’s condition (Tilburt et al 2008). There is reason to be on guard against invoking the placebo effect, building on public fascination and enthusiasm for mind-body interactions in the domain of health, as a rationalization for paternalistic and unprofessional practices. Promoting the placebo response is not the same as merely trying to please the patient. To be sure, there may be situations in which it is appropriate to satisfy patient expectations of receiving a medicinal treatment and thus to support the physician-patient relationship (e.g., recommending vitamins to treat fatigue for conditions without a medical diagnosis); however, these do not include, for example, the prescription of antibiotics for viral infections. The latter practice is objectionable owing to the side effects of antibiotics and the public health risk of promoting drug-resistant bacteria. On the other hand, it is possible that prescribing benign treatments to “please” or placate the patient may also promote a genuine placebo response.

Two questions are particularly salient to the ethics of prescribing treatments genuinely aimed at promoting a placebo response: (1) can this be done without deception, and thus compatible with informed consent? and (2) is there adequate evidence of clinically significant benefit? Empirical research is needed to address both these questions.

These ethical concerns do not arise in the case of efforts to tap the placebo effect solely by means of clinician-patient interaction, without a placebo treatment (Brody 1982). A therapeutic alliance, based on listening, empathy, reassurance, and therapeutic optimism, constitutes good clinical practice. Scientific investigation of the placebo effect derived from the clinician-patient relationship holds promise for improving patient care in service of the fundamental goal of relief of suffering.

However, concerns about paternalism and informed consent are relevant to the nocebo effect—especially, adverse effects on patients of clinical communication (Barsky et al. 2002). The fact that informing patients of side effects of drugs may itself, by means of expectation or anticipatory anxiety, produce these adverse effects does not license withholding material information from patients. Likewise, concern that communicating grim prognostic information may, by means of “the self-fulfilling prophecy,” demoralize patients with life-threatening conditions and adversely affect clinical outcomes does not justify withholding information relevant to patients’ choices of goals of care and treatment regimens (Christakis 1999). The “therapeutic privilege,” which traditionally has permitted physicians to withhold potentially
harmful clinical information from patients, has been rejected by the law and bioethics in the United States (Berg et al. 2001, pp. 79–85). Although pertinent to patient care, research on the nocebo effect does not warrant rehabilitating this paternalistic doctrine. Whereas information material to patient decision-making should not be withheld from patients, the way in which this is communicated is very important. In this regard, research on the placebo and the nocebo effects has the potential to guide methods of communication that are respectful and minimize adverse outcomes.

Research methods for investigating the placebo effect also pose ethical issues. Deception in study design is often necessary in order to create a credible placebo intervention. For example, in placebo analgesia research inert placebos are typically described to subjects as a powerful pain-relieving medication (Miller et al. 2005). In addition, subjects typically are not informed that the purpose of the research is to investigate the placebo effect, in order to avoid biasing subject responses to experimental manipulations. Although necessary or desirable to promote scientific validity, such use of deception violates informed consent and respect for the autonomy of research subjects (Miller et al. 2005). Debriefing is typically employed in deceptive research: at the end of study participation subjects are informed of the true purpose of the research and the nature of research procedures. This, however, does not cancel the ethical problem with research that deviates from informed consent (Miller et al. 2008).

The use of “authorized deception,” alerting subjects before study enrollment to the use of deception without disclosing how they will be deceived, has been recommended as a way to eliminate or minimize the ethical concern with use of deception (Wendler and Miller 2004; Miller et al. 2005). Subjects are thus given a fair opportunity to decide whether they are willing to volunteer for research that involves deception. Some experimental evidence indicates that authorized deception does not bias research results (Weiner and Erker 1986), but this has not been examined systematically. Moreover, the potential for authorized deception to compromise scientific validity has not been evaluated in the context of placebo research. From an ethical perspective, it is an urgent priority to conduct experiments comparing undisclosed deception with authorized deception in research on the placebo effect.

Finally, published reports of research on the placebo effect have not been sufficiently transparent about the way in which deception deviates from informed consent (Miller et al. 2005; Miller and Kaptchuk 2008b). Typically, research reports of studies involving initially undisclosed deception assert that informed consent was obtained from research participants. Signing consent documents, however, does not mean that subjects have given informed consent when the disclosure about the study fails to provide an accurate description of its purpose or the nature of research procedures. Published scientific articles should forthrightly report deviations from informed consent and the use of remedial procedures, such as debriefing and the offer to subjects to withdraw their data during the debriefing process.

**Conclusion**

We suggest that, using the language of Kuhn (1970), 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 sketched the contours of a theory of the placebo effect. Our aim has been to suggest a series of interconnected themes by locating the placebo effect within the concept of interpersonal healing and in connection with the key distinction between disease and illness. In addition to promoting conceptual clarity regarding the placebo effect, we have noted the limited rigorous evidence relating to its clinical significance and recommended experimental inquiry aimed at translating the scientific understanding of the placebo effect into improved patient care. This is the ultimate test of a theoretical paradigm for the placebo effect—its fruitfulness in guiding future patient-centered
Finally, we have highlighted ethical issues that need to be addressed in optimizing placebo effects and minimizing nocebo effects within clinical practice and in conducting justifiable research on placebo effects.

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The Hole in the Heart of Medicine

The Placebo Effect

There is a hole in the heart of the science of medicine. It is the placebo effect. The placebo effect is the technical name for the mind’s power to heal the body without obvious physical intervention. Sometimes the effect is triggered by administering a fake drug, often in the form of a pill made from a chemically inert substance. Such a pill is known as a placebo—from the Latin “to please.”

We say that the placebo effect is a hole in the heart of scientific medicine because every time a new drug or other treatment is tested it has to be run against the placebo effect. That is, the placebo effect is taken to be so powerful that unless the effect of the drug is compared to the effect of a placebo it is almost impossible to tell whether improvements in health are due to the biological effects of the drug or the psychological effects of the encounter with one or more of the medical personnel, their paraphernalia, and the “medicines” or other “treatments” they supply. What this means is that every time a new drug or treatment is successfully tested, the members of the medical profession effectively proclaim two things simultaneously:

1 They proclaim, “We are such skillful medical scientists that we can invent new drugs and treatments,” and they back up this claim by testing the new treatment and revealing its positive effects.
2 They proclaim, “We are such poor medical scientists that we cannot understand how the mind and the body interact,” and they reveal how poor they are by factoring out the effect of the mind in the only way they know how: by comparing the effect of their new invention with the effect of a fake version of it.

Furthermore, in spite of all the medical science that goes into the preparation of new drugs and treatments, on an embarrassingly large number of occasions the fake is just as good or better than the real thing.

The Placebo Effect and Its Near Relations

Unfortunately, the placebo effect and its near relations are a lot more complicated than the above paragraphs suggest. To know where medical science stands today with the placebo effect we have to undertake an excursion through a fascinating but disorienting hall of mirrors. We are going to have to distinguish between the “real placebo effect” and the “fake placebo effect” and navigate a way through expectancy effects and reporting biases. Here we go.

Experimenter Reporting Effects

Consider those who carry out the drug trials. The experimenters have certain hopes and expectations about how the trials will work out. Wherever the results of experiments are marginal, experimenters’ “reading” of their results tends to be influenced by what they want to see. In the 1960s psychologists showed that this had a dramatic influence, threatening the whole basis of experimental work in their subject. But that was just an extreme instance of the unconscious reporting bias that is present in all sciences, including the physical sciences. In the previous volumes of the
Golem series we gave examples of the way that the results of physics and other experiments are contested and interpreted in widely different ways by competing scientists. Though the reasons for different interpretations can sometimes be varied and subtle, the aspect that concerns us in the case of drug trials can be referred to as “experimenter reporting bias.” Reporting bias differs from the placebo effect because it is, as it were, the effect of the mind on the mind (the mind of the experimenter), rather than the effect of the mind on the body (the body of the experimental subject). Reporting bias does not change the body; it merely changes the extent to which the experimenters think the body has changed.

To some extent reporting bias can be avoided if the person who does the analysis of the results of an experiment does not know what outcome to expect. The analyst, in other words, should be “blind” to the meaning of the experiment; this is usually arranged by sorting the subjects into randomly assigned groups for treatment and placebo and keeping the key to the membership of the groups hidden from the analyst.

**Patient Reporting Effects: False and True Placebo Effects**

Now imagine that a drug is being tested for its effect on depression. Depression is a subjective state, and the effect of the drug is likely to be measured by some kind of report made by the patients: the patients will say whether the drug made them feel better or not, probably recording their changed feelings on a form that encourages them to go into considerable detail. Here is another opportunity for a reporting effect to enter the equation. If some patients believe they have been treated with a powerful depression-relieving drug, whereas others think they have been given a neutral substance, then there is likely to be a biasing effect on the way the patients report their feelings. If they think the drug will make them better, they are likely to think they feel better—even if the drug has had no physiological effect at all. We can call this “patient reporting bias,” as opposed to experimenter reporting bias. If there is no actual physiological effect on the patient we can call this the false placebo effect.

Of course, if the patient expects the drug to produce an improvement in health, it might actually produce such an improvement, because the state of the mind—for example a state of relaxed optimism—can affect the state of the body. This is the true placebo effect. The true placebo effect will often be actually or potentially measurable by physiological changes, such as an increased level of endorphins—euphoria-inducing chemicals—in the brain, an enhancement of the immune system, or improved healing of an injury. It is hard to say whether an increase in mobility in, say, a case of arthritis, which follows from a decrease in felt pain, should be described as physiological (due to increased endorphins), or psychological: the boundary between the two is not clear. The overall point remains, however, that the reports of patients given a placebo who believe it to be a potent drug can be affected by a false placebo effect (which is a true reporting bias), or a true placebo effect.

**When is the Subjective Objective?**

Of course, in the case of an illness such as depression, reporting bias and the placebo effect are not easy to separate. For example, if, as a result of reporting bias alone, a patient in a depression trial thinks he feels better does this not mean that they actually do feel better? Isn't thinking you feel better actually feeling better even if there is no physiological evidence that you do? This is one of the problems of measuring the efficacy of psychoanalysis and the like where there are no physiological correlates of the progress of the treatment.

One might think this problem can be avoided in those cases where the effect of a treatment is measured more directly than by a self-report. For example, patient's lung capacity might be tested before and after a test by asking them to blow into a device; or the
length of time patients can walk on a treadmill might be used as a
criterion of success in treatment for the lungs, or some such. Even
in the case of these tasks, however, expectations about one’s own
performance can have an effect on actual performance in the
absence of underlying physiological change. The amount of effort
the patient puts into inflating the bag or walking the treadmill is,
as it were, a self-report on their confidence in the effectiveness of
the treatment even in the absence of a real placebo effect.¹

Expectancy Effects

To confound things further, experimenters and human sub-
jects cannot be thought of as independent groups. In the 1960s
psychologists showed that school pupils’ performance, as mea-
sured by outsiders, was affected by the teacher’s expectations. If a
teacher expected students to do well, they tended to do better than
if the teacher expected poor results, even if reporting bias was
eliminated by blinding. In this case it was the subjects of the ex-
periments who were affected by the teacher’s attitude—encour-
gagement leads to higher expectations in the pupil and higher
achievement. Let us call this the “expectancy effect.”

The expectancy effect will apply to medical treatments too. If
the person who administers the treatment is evidently optimistic
about its potential, the optimism will transmit itself to the patient,
reinforcing both patient reporting bias and real placebo effect.

There are, then, four effects that can lead to a positive outcome
in a test of what is, according to medical science, a physiologically
inactive substance or treatment. The four effects are

1. experimenter reporting bias;
2. the false placebo effect—in other words, patient reporting bias;
3. the true placebo effect in which the mind affects the physiology of
   the patient; and
4. the expectancy effect of the experimenter on the patient, which en-
   hances 2 and 3.

Because of these four influences, when human subjects are in-
volved in experiments, both the subjects and the experimenters
need to be “blinded.” For example, in drugs trials, to avoid effect 2,
the patients must not know whether they are taking the real drug
or the fake; to avoid effect 4, those administering the experiment
must not know whether they are providing the real drug or the
fake to any one patient; and to avoid effect 1, those analyzing the
experiment must not know which patients were administered real
drugs and which fakes. When all these precautions are taken we
have what is called a “double-blind” experiment—both experi-
menters and subjects are blind to the meaning of the experiment
until it is over. Typically, in a double-blind test only after the effect
of the treatment on each individual has been measured are the
random codes which assigned subject to experimental and placebo (control) groups revealed.

Physiological Efficacy

For the sake of completeness and clarity in the subsequent discussion we must not forget that there is a fifth way in which a drug or treatment may affect the well-being of a patient: it may have the effect designed or discovered by medical science. We will describe this as a “direct chemical or physical effect,” or sometimes, “direct physiological effect.” This we will contrast with “indirect chemical, physical/physiological effects” which are the result of the mind’s influence over the body even when this influence is mediated by something physical, such as an increase in endorphins in the brain or a boost to the immune system. In the classification above we can note that categories 1 and 2 involve no physical or chemical effects either direct or indirect, and category 3 involves indirect chemical or physical effects, which category 4 can boost.

Is the Placebo Effect a Fiction?

The placebo effect has been taken to be a scientifically established part of modern medicine at least since the 1950s. Studies suggest that between about 20 and 70 percent of patients seem to benefit from the administration of placebos. Perhaps most striking is placebo surgery, where the appropriate anesthetic is administered and an incision made in the skin, but there is no significant surgical intervention; this is reported to be highly effective. Indeed, the mock surgery sometimes seems to be more effective than the real surgery. For example, it appears to work for certain kinds of heart pain and back pain. In the mid-1990s, it was shown to work for arthritis of the knee; patients whose knees were merely stabbed recovered just as well as those whose knees were internally scraped and washed out—the standard treatment that had been thought to be highly effective.

Unfortunately these seemingly straightforward findings are themselves contested. Now we have to traverse a still more disorientating wing of the hall of mirrors: unwell people can get better even if they have no treatment at all, and it is just possible that patients treated with placebos and those undergoing extensive medical intervention recover spontaneously at about the same rate. In other words, it could be that the patients given placebos or placebo treatments are not getting better because of the placebo effect, but recovering spontaneously, while the medical treatment is equally ineffective and the patients who undergo significant surgery are also recovering spontaneously. In this case, instead of there being a placebo effect which is as good as the real surgery, the placebo effect is no better than the real surgery and both are ineffective.

To find out that there really is a placebo effect, a different kind of experiment must be done. What must be compared are groups who are given a placebo on the one hand and no treatment at all on the other. For a placebo effect to reveal itself in these circumstances, the placebo patients would have to improve more than the untreated patients.

In 2001 two Danish doctors (Hrobjartsson and Gotzsche), analyzed all the articles they could find in which patients who were entirely untreated were compared with those given placebos. There are few experiments that are designed to test placebos directly, and most of the 114 trials the doctors examined had three groups: patients given medical treatment, patients given placebo treatment, and patients given no treatment all. They found that overall there was no significant difference between the placebo patients and the untreated groups in terms of improvement in the condition being treated.

That sounds decisive, and on first reading the report by the Danish doctors is convincing. The number of studies they analyzed and the number of patients involved were large. The study seems to overturn a huge raft of conventional wisdom. Careful ex-
amination of the cautionary remarks toward the end of the paper, however, makes the conclusion more resistible.

First, there are indications within the data of small effects of placebos on the experience of pain, and there is also room for large effects on some small subset of patients or conditions, if not all. These small effects and small numbers could easily be masked within the aggregate statistical approach taken by the Danish researchers. More worrying is the following rather complex piece of logic, the exposition of which will demand an increasing use of exclamation marks at the end of sentences.

A test of some treatment, placebo or otherwise, versus no treatment at all cannot be carried out blindly! Both the patients and those who are treating them will know who is not being treated; the fact that you are not being treated cannot be disguised or it would be not "no treatment" but, by definition, the administration of a placebo.

Now it gets complicated: if the doctors and patients know who is not being treated, one would think that would produce an expectancy effect and reporting effects that would make the difference between placebo and no-treatment patients even more marked than if the placebo worked! In other words, the nontreatment patients ought to feel pessimistic about their prospects, and those who are treating them ought to expect no improvement at all in that group, so one would think that there would be a strong reporting effect from both treaters and treated, and that this would be reinforced by an expectancy effect. In sum, the crucial point is that even if there is no placebo effect, then in these nonblinded experiments there ought to appear to be a placebo effect because of negative reporting and expectancy effects on the untreated groups. In this Alice in Wonderland world this kind of experiment should not be able to fail! Whether it was really there or not, it should appear that there was a placebo effect!

Now, since there was no apparent placebo effect in these experiments, there could not have been any expectancy and reporting effects, and this suggests there was something wrong with the experiments!!! Like Mendel's famous experiments on the inherited characteristics in peas, the results were so good that it looked as though they must have been false!

The Danish authors argue in reply that because in the majority of the experiments there were three groups, not two, neither patients nor analysts would have been concentrating on the difference between placebo and untreated patients and that this may have minimized reporting and expectancy effects. But this argument seems thin.

In any case, there is a quite different and opposite reason for distrusting the conclusions even if the absence of expectancy and reporting effects is not decisive. Inevitably, as we have argued, the untreated group would know they were receiving no treatment. Now, if their illnesses were serious, they might have decided that since they were getting no treatment within the study, they should treat themselves in ways which had nothing to do with the study (see chapter 4 for a similar claim in respect of vitamin C trials). This would not apply to the placebo groups, because they thought they were being treated. This difference in self-treatment could be responsible for the lack of difference in success rate between the groups.

Putting the two arguments against the Danish analysis together leaves us, as so often in difficult statistical sciences, not quite sure where we are, except that we know we cannot take the existence of a placebo effect as being quite as established as we once thought it was, but we are still far from being sure that it does not exist. What we need to settle the issue is a double-blind experiment between placebo groups and nontreatment groups—but we can't have one, by definition (and we'll have to end with yet another exclamation mark)!

Irrespective of the academic arguments, the drug companies, the agencies that administer the tests carried out by the drug com-
panies, and the critics of the drug companies all treat the placebo effect as real. The critics point out that the so-called double-blinding does not work because patients can often guess whether they have been given the real thing or the placebo depending on whether the drug has any side effects, such as dizziness or a dry mouth. This means that even when a drug beats a placebo in a randomized control trial, it might be only because the drug, having side effects, also has a stronger placebo effect.

The drug companies and their agents treat the placebo effect as so real that they actually rate the placebo susceptibility of the patients they enroll in their trials. They try to avoid patients who are very susceptible to suggestion (covert psychotherapy) and the like. And this is where we can leave the question of the existence of the placebo effect: in terms of its consequences for how we think about medicine, the placebo effect is real.

**One More Complication**

Consider tests of some drug or treatment that has long been known to be effective, such as hormone replacement therapy (HRT). Now suppose some doubts about its safety arise and it is thought prudent to test its efficacy again with a new double-blind control trial. In such a trial the patients, whether on the real drug or the placebo, have good grounds for belief that the drug has proven physiological efficaciousness. There is likely to be a very strong placebo effect because the patients will have a high expectation that if the drug they are taking is real, it will have a marked effect. In short, the strength of the placebo effect is partly a function of the strength of the patient’s belief in the effectiveness of the real drug, and this, in turn, may be because of long experience by those who have taken the drug. In that case, if the trial reveals no difference between placebo and control group, this may be not because the real drug is not effective, but because its effectiveness has generated strong expectations in the placebo-takers. Any conclusion drawn from a negative result might, in these circumstances, be incorrect.

**Placebos and the Three Main Themes**

The placebo effect certainly reveals the uncertainties at the heart of modern medicine. But it also poses a fascinating dilemma. If the placebo effect works, why not use it in a systematic way?

One answer to this is immediately apparent. Let us suppose you ask the patient, “Which would you prefer, real treatment or a placebo?” The patient has to say “real treatment,” because as soon as you tell a patient it’s a placebo, it’s no longer a placebo; it is no treatment. Any attempt to offer a choice is self-defeating. (This is the logical complement of what we argued above: if you fool a patient into thinking that no treatment is a treatment, then it isn’t no treatment; it’s a placebo!) Doctors, however, may, and indeed do, dispense placebos in good faith so long as they keep it secret from their patients. A good doctor, wishing to offer some help in the case of an illness for which there is no scientifically accepted means of alleviation, should offer a placebo while concealing from the patient that there is no recognized treatment. But the efficacy of the treatment turns on the patient not being offered a genuine choice: “Would you like this placebo or not?” The doctor has to dissemble, and a dupe cannot make a genuine choice. The same applies to any agency that is responsible for the collective health of a population; placebos are a useful and important part of the armory of treatment, but “more placebos in medical treatment” is not something you can ask a population to vote for. Or can you?

**Medicine as Science or Succor? Alternative Medicine and the Placebo Effect**

Alternative medicine comprises all those cures, some traditional, some new, that are not recognized or supported, or rarely supported, by the main part of the medical science establishment.
To define the borderline between orthodox and alternative medicine is difficult because the uncertainty in medical science leaves lots of room for the borderline to shift. For example, acupuncture is less readily dismissed than it was a couple of decades ago (see chapter 4 on alternative medicine). Luckily, at this point we are not discussing the physiological potency of alternative medicine, and for the purpose of the analysis of the placebo effect we can simply assume that there is a subset of such treatments that have no physiological potency. Indeed, that is not much of an assumption—it is almost bound to be true. It is almost bound to be true because there are many orthodox treatments that have no potency, and it would be very odd if all the alternative treatments worked.

Let us call the subset of alternative medicines that have no physiological efficacy “empty treatments.” We will make no attempt to identify them. The point is that even if empty treatments have no direct physiological power, a very large number of people think they benefit from them. Thus 42 percent of Americans use alternative medicine and so do 20 percent of British people. It is possible that all of these people gain nothing from the expenditure of such large aggregate sums of money except the certainty that they have left no stone unturned in their search for cures, but it is more likely that, at worst, they improve because of placebo effects, some of which will be mediated by real physiological change. Indeed, if the placebo effect is going to be significant anywhere, it is likely to be significant in the area of alternative medicine, which usually stresses care and optimism in respect of “the whole person” and almost never employs the cold and mechanical procedures that can be found in orthodox medicine. If the placebo effect cures, then alternative medicine, including the empty treatments, may be the best place for at least a proportion of the population to find it in its most concentrated and effective form.

And yet, the purveyors of alternative medicine resist the idea that its effectiveness is due to the placebo effect. They are like the medical profession proper in wanting professional recognition for the scientific, physiological, basis of what they do. And they must do this for the reasons we have described above; as soon as a treatment is announced as a placebo it ceases to be a placebo and becomes no treatment.

Let us go over this again by stepping outside the whole debate for a moment and imagining we could achieve an “Archimedean point” where we have the power to separate direct physiological efficacy from physiological change brought about by the placebo effect. Let us suppose that from this vantage point we can see that neither alternative medicine as practiced in Western societies nor the equivalents that are practiced in other societies, such as witch-doctoring, shamanism, voodoo, and the like, have direct physiological effects—they are all empty treatments—but that they can cure, often via indirect physiological changes, because of the placebo effect. In the case of “primitive” societies we can see that an outsider claiming that the rituals have no direct physiological effect would do little harm to their potency, since the medium of the cure is taken to be magical rather than chemical or physical. In large parts of Western society, however, the basis of sound intervention is taken to be chemical or physical. The placebo effect is fragile in our society just to the extent that our society is informed by a scientific worldview.

Here, then, is the tension between medicine as science and medicine as succor in a clear form. The state, in Western societies, generally leans toward medicine as science. For example, in today’s British National Health Service (NHS) there is a growing emphasis on so-called evidence-based medicine. Drugs and treatments will be offered only if they have been proved in randomized control trials or something similar. But the very idea of a randomized control trial is an affirmation of the science-based way of life of our society, and, therefore, the discourse of evidence-based medicine is, by its very existence, something that reduces the effectiveness of placebo-based cures.
It is the view of the authors of this book that for a whole raft of reasons going well beyond medicine the scientific worldview is the one they want to see endorsed at the level of society, even though one has to accept that the health of at least some people will be indirectly damaged by it in the way just described. Here, then, is a way in which the tension between the individual good and the collective good is played out. An individual desperately seeking help for an ailment that orthodox medicine cannot cure and that alternative medicine cannot cure directly might be helped by taking advantage of an empty treatment via the placebo effect. To the extent that the government or any other agency responsible to the collective takes it to be its duty to foster a scientific worldview (and we think that is what such agencies should be doing), the chances of help coming from such a source are reduced. Governments can damage medicine as therapy even while improving it as science, but, nevertheless, they cannot choose to do otherwise.

The Scientific Gold Standard and Broken Bones

As explained, the existence of the placebo effect makes it necessary to use randomized control trials to test new drugs or other interventions, and the RCT has become the gold standard for scientific medicine. This, as we pointed out, has the ironic consequence that medicine's gold standard is itself a celebration of medical ignorance. We can show just what this means with a thought experiment.

Let us invent an ailment and call it Undifferentiated Broken Limb, or UBL. With UBL you know that one of the patient's four limbs is badly damaged, but you don't know which one. Let us imagine that someone invents a new experimental treatment for UBL, and this treatment is a cast on the left leg—a CLL. We do a randomized control trial in which a control group is fitted with a cast around the neck to act as a placebo while each member of the experimental group is given a CLL. We can imagine that at the end of the trial period when the casts are removed, up to one quarter of the experimental group are much better, while there is very little improvement among the control group. Thus the gold standard test reveals that CLL is an effective treatment for UBL in about 25 percent of cases.

This victory for the randomized control trial shows us how little we know about the body once we move away from some gross assault such as a broken limb. Because we understand broken limbs, we can see just how clumsy the randomized control trial is, curing just a quarter of the population when better understanding would lead to a more carefully tailored treatment for 100 percent of victims. To be in a position to understand all ailments in the way we currently understand broken bones is what medical sci-
ence must aspire to. Such a complete understanding of the body (better, the mind and the body), would allow treatment to be tailored at the level of the individual cell (or individual thought, as it were), with as much certainty as it can now be tailored to the individual bone. When that happens the randomized control trial will disappear, just as it has in the case of bonesetting, and the main theme of this book will no longer be of interest, because medicine as science and medicine as succor—the long term and the short term, the interest of the collective and the interest of the individual—will have converged.

We do not know if such a state will ever come about—probably it won’t, since, as we argue in the introduction, it would mean that the social and psychological sciences as well as the physiological had been perfected. But we cannot give up the hope that we will one day get there, and that is why we must hold on to medical science even though it is fallible in so many ways. In the meantime we can see that the very description of the RCT as medicine’s gold standard means that the tensions that form our main theme remain and that each citizen will continue to have difficult choices to make. We hope the chapters, including this one, will reveal why maximizing short-term individual gain at the expense or in the face of science is not always the right, or even the best, choice.

2

Faking It for Real

Bogus Doctors

One way to understand the nature of a skill is to ask how hard it is to fake. We can learn a lot about faking and fraud from the newspapers, films, and television. The film *House of Games*, directed by David Mamet, took the viewer into a kaleidoscopic world where nothing turned out to be quite what it seemed. The techniques of confidence trickery portrayed in *The Sting*, with Paul Newman and Robert Shaw, were taken from journalist David Maurer’s brilliant sociological analysis published in 1949, *The Big Con*. More familiar nowadays is the television show *Faking It*, where hamburger cooks are trained to take the place of gourmet chefs, punk rockers conduct a symphony orchestra, classical musicians take the role of the disk jockey in a club, and so on. The showdown comes when the faker competes with real chefs, classical conductors, and DJs in front of a panel of judges. Usually the expert judges are unable to distinguish the fake performance from the real thing. Even assuming that what we see on the screen is not too distorted by the editing process, *Faking It* is still far from the world of confidence trickery as it is practiced, and we can learn less from it than from the older sources. For ex-