

# Placebo, Meaning & Health

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## Abstract

Placebos are boon and bane to medical theory and clinical practice. On the one hand, randomized controlled trials employ concealed allocation of placebo to control for effects not due to specific pharmacological mechanisms. As a result, nearly all of evidence-based medicine derives from principles and practices based on placebo. On the other hand, medical researchers and physicians have tended to ignore, minimize, or deride placebos and placebo effects, perhaps due to values emphasizing scientific understanding of mechanistic pathways. This essay reviews the placebo literature, arguing that intention, expectation, culture, and meaning are: 1) central to placebo effect phenomena, and 2) substantive determinants of health. We introduce three dualities that are integral to placebo/meaning phenomena: a) body-mind, b) subconscious-conscious, and c) passive-active. These placebo-related dualities should be acknowledged, explored with research, and incorporated in theory. While we view consideration of placebo and meaning effects as essential to any adequate understanding of human health, we also feel that lessons from this area of inquiry may already provide practical tools for astute clinicians. Toward this end, we list eight specific clinical actions: i) speak positively about treatments, ii) provide encouragement, iii) develop trust, iv) provide reassurance, v) support relationships, vi) respect uniqueness, vii) explore values, and viii) create ceremony. These clinical actions can empower patients to seek greater health, and may provide a healthful sense of being cared for.

## Introduction

Hundreds of randomized controlled trials (RCTs) have reported psychological and physiological effects attributable to placebo pills,<sup>1-7</sup> and dozens have reported effects from placebo procedures, such as surgery faked by a skin incision only, or sham acupuncture.<sup>8-11</sup> A few controlled trials have reported health affects attributable to the style or content of doctor-patient interaction.<sup>12-15</sup> Many hundreds of studies have linked health outcomes with belief state, psychological outlook, or culture. This essay will explore the idea that phenomena conventionally called placebo effects are better understood as health-related responses to meaning, with expectation, intention, understanding, and personal and societal values all playing significant roles. We will place placebo in historical context, expose the limitations of conventional interpretations, and summarize some of the most relevant literature. While Moerman's meaning response<sup>16</sup> conceptual framework is most consistent with existing data, there is room for both expansion and refinement. To this end, we will explore evidence suggesting that feeling cared for (receiving treatment, being helped) and empowerment (taking care of one's self, achieving health, developing insight) are integral to the placebo effect / meaning response. We will show that the eight actions listed in the Table are broadly supported by the literature, relatively easy to enact, and are likely to contribute to better health outcomes. We will also highlight three dualities that are key to understanding placebo phenomena: a) body-mind, b) subconscious-conscious, and c) passive-active. With such understanding, we will be better able to design and interpret research, and perhaps positively impact human health.

## Definitions of placebo

The *Concise Oxford Dictionary* (1990) defines *placebo* as "a pill, medicine etc prescribed for psychological reasons but having no physiological effect."<sup>17</sup> *Webster's Encyclopedic Dictionary* (1997) defines "placebo" as "a substance having no pharmacological effect but given to placate a patient who supposes it to be a medicine."<sup>18</sup> Stewart Wolf, writing in the 1950s, defined the placebo effect as "any effect attributable to a pill, potion, or procedure, but not to its pharmacodynamic or specific properties."<sup>19;20</sup>

While these definitions may appear sensible, thoughtful consideration of the evidence exposes their limitations and raises serious questions about associated conceptual frameworks. We will describe several studies and refer to dozens more that report specific biological as well as psychological effects attributable to placebo treatments. Yet placebo therapies have been defined as inert, devoid of specific pharmacological effects. This gives rise to an obvious paradox. If placebos are inert, they can't cause effects; if placebo effects occur, then

placebos cannot be inert. Both cannot be true. And they are not. The conventional definition of placebo is not based on a rational assessment of empiric data. Rather, it reflects an outdated understanding of the relationship between the mind and body, and an over-reliance on experimentally verifiable causal mechanisms.

### **Intellectual framework of placebo**

Conventional definitions of placebo come from conceptual frameworks in which mind and body are considered separate. The psychology of the mind was assumed to be unconnected to the physiology of the body, and efforts to investigate biology and physiology were largely conducted independently of studies of cognition, emotion and psychology. Sometimes referred to as Cartesian dualism, this intellectual tradition also assumes that “specific properties” (ie. real, true findings) can be found only in the biology of the body, usually through the hypothesis-testing methods of experimental science.<sup>21</sup> Cartesian dualism is a particularly inappropriate framework for the study of placebo effects, where mind/body interactions are paramount, and where causal mechanisms have not been - and perhaps cannot be - fully elucidated.

It's easy to illustrate mind/body interactions. Consider the following scenarios. You are in a movie-theater, where the action sequence is thrilling. Your heart rate and blood pressure increase, and your pupils dilate. In another situation, you are held up at gunpoint in a dark alley. You experience intense fear, sweating and nausea, perhaps leading to emesis or incontinence. Finally, imagine biting into a raw lemon wedge. Your mouth puckers and the saliva starts to flow. These and countless other experiences and experiments suggest that thoughts and emotions trigger biological processes, which in turn influence and interact with perceptions, thoughts and feelings. An emerging body of research, fueled by technologies such as positron emission tomography (PET scans) and functional magnetic resonance imagery (fMRI), has demonstrated that psychological states can be visualized and mapped in the brain.<sup>22-25</sup>

Conventional understandings of placebo have also implied a subtle but important fallacy: that cause can be fully separated from effect. Briefly, the conventional biomedical model separates cause from effect by assuming that medical interventions are external, prior, and causal to the subsequent psychophysiological state of recipients. For example, a patient with diagnosis X takes the pill Y and is observed to have effect Z. We hypothesize that the pill causes the effect. Blinded randomized trials then test whether the observed effects may be due to chance or bias. If not, we conclude that the ingredients in the pill indeed caused the observed effects. While this model is internally consistent and often useful, it misses important aspects of clinical medicine, where the locus of healing lies not in the treatment but instead within the mind-body of the patient. In real life, people are acutely aware of their treatments, and may have strong feelings about them. These thoughts and feelings may in turn influence the response, both psychologically and physiologically.

The ‘meaning response’ has been suggested as a conceptual framework more consistent with available evidence.<sup>16;26;27</sup> Moerman has defined the meaning response as “the physiological or psychological effects of meaning in the treatment of illness”<sup>4</sup> and has noted that “much of what is called the placebo effect is a special case of the meaning response.” He has also asserted that “meaning responses accompany *any* effective medical treatment.” Similar conclusions about the need to reconcile mental and social health with biological health were reached by George Engel and other proponents of the biopsychosocial paradigm,<sup>28-30</sup> although they did not consider placebo/meaning effects specifically. In the following sections, we will review a broad array of evidence suggesting that awareness, belief, and perceived meaning significantly impact health-related responses to treatment.

### **Origins and trajectory of placebo research**

Translated from the Latin as “I shall please,” *placebo* has been used for hundreds of years in Western medicine to denote treatments chosen to please patients rather than cure their diseases.<sup>31;32</sup> During the development of the modern RCT in the 1940s and 1950s, dummy pills without active ingredients were used as controls, and were called placebos.<sup>33;34</sup> Medical scientists argued that: 1) comparison groups were needed to control for natural variability, spontaneous remission, and regression to the mean; and 2) both patients and doctors could be biased in the reporting of disease states, hence needed to be blinded.<sup>35-37</sup> Randomization and blinding appeared to address both concerns. Investigators implicitly or explicitly maintained that differences observed

between those in placebo and active treatment groups: A) were due to pharmacological effects of active ingredients, and B) could be generalized to clinical practice.

Not long after the invention of the RCT, some researchers suggested that perceptions of pills could influence outcomes, regardless of whether they contained active or inactive ingredients. In 1950, for example, Wolf reported that the usual effects of pharmaceuticals could be attenuated, even reversed, by “suggestions and conditioning.”<sup>19</sup> Women with nausea and vomiting during pregnancy reported relief when given ipecac (an agent used to induce vomiting) when it was accompanied by the suggestion that it would relieve nausea.<sup>19</sup> A pressure-measuring balloon in the stomach confirmed that muscular contractions normalized with suggestion, despite the ipecac. Thus, the meaning of the treatment – what the doctor said the pill would do – in some instances appeared more powerful than the pharmacological mechanisms.

In 1955, the *Journal of the American Medical Association* published H.K. Beecher’s “The Powerful Placebo,” a paper reviewing 15 controlled trials involving 1,082 patients.<sup>38</sup> Defining positive outcomes as “percent satisfactorily relieved by placebo,” Beecher reported effect sizes ranging from 26% to 58%, with an average of 35%. The notion that about a third of patients respond to placebo has since permeated medical texts and teachings. Beecher noted “However inert a placebo may be in the usual sense, it is not inert in its effect. It is a powerful agent whose primary site of action is the cerebral cortex. There is a great deal of evidence that the significance of a stimulus determines whether or not it will evoke a sensation.”<sup>9</sup>

Also in the 1950s, it was suspected that surgical procedures might also lead to placebo effects. At the time, mammary artery ligation was provided for patients with anginal chest pain. It was thought to be effective, with patients reporting decreased chest pain and increased exercise tolerance following surgery.<sup>39</sup> Nevertheless, double blind methods were employed by Cobb et al. to test the procedure.<sup>40</sup> Surgeons were shown a randomization card after the skin incision, telling them whether to proceed with surgery or close the wound. Patients and outcome assessors were blinded to full procedure vs. skin incision only. Patients in both groups improved dramatically, with trends favoring the skin incision group.<sup>40</sup> A year later, using similar methods, Dimond et al. reported very similar results.<sup>41</sup> Mammary artery ligation was subsequently discontinued. In 1961, Beecher published “Surgery as placebo: a quantitative study of bias,” concluding that “a placebo effect has been demonstrated for surgery.”<sup>9</sup>

Evidence accumulated that placebo interventions influenced both psychological and physiological outcomes.<sup>42;43</sup> For instance, a study of placebo effects in hypertension reported that changes in blood pressure could be attributed to placebo, and that placebo injections led to larger effects than placebo pills.<sup>44</sup> Several researchers reported that sedative responses could be observed among subjects given stimulant pills along with sedative suggestions, and vice versa.<sup>20;42;43</sup> The pharmacological effects of the bronchial relaxant drug isoproterenol and the bronchial constrictor carbachol were reported to be reduced - and even reversed - by suggestion.<sup>45</sup> In Japan, high school students known to be allergic to the lacquer tree were blindfolded, then falsely told which arm would be rubbed with a leaf of the lacquer tree, versus a leaf from the innocuous chestnut tree.<sup>46</sup> Reportedly, distinct red itchy rashes formed on arms in response to suggestion, regardless of the actual leaf used.

Placebo research later branched in number of directions, but few were fully explored. For example, evidence was advanced that different physicians or different styles of clinical interaction might influence health.<sup>47-51</sup> But definitive RCTs were never carried out. The idea that placebos could lead to harmful as well as beneficial effects was advanced, and the term “nocebo” was introduced.<sup>52;53</sup> Nevertheless, neither exhaustive description nor careful quantification of negative effects was accomplished. And while several studies sought to identify and classify “placebo responders,”<sup>54-57</sup> the search for a reproducible typology of placebo susceptibility largely failed, or, perhaps more accurately, failed to be fully investigated. A recent study has reported that suggestibility and tendency toward placebo response may be linked.<sup>58</sup> Throughout several decades, relevant evidence from a variety of fields has emerged, confirming the placebo/meaning effect, and pointing towards the need for an expanded placebo paradigm.

A thorough review of research relevant to placebo, health and meaning would span much of the epidemiological, biomedical, and social science literature. Indeed, the potential links between health and meaning are innumerable. Nevertheless, we will briefly review a few studies that we consider most pertinent, keeping in

mind the three dualities we identified as guides to furthering understanding of these phenomena: a) body-mind, b) subconscious-conscious, and c) passive-active.

### **Medicine and placebo are embedded in culture and meaning**

One factor that seems to be central to the strength of a placebo response is the extent to which a person adheres to a set of shared meanings or follows culturally approved behaviors. Several large studies have reported that subjects who follow medication protocols do better than those who do not, regardless of whether they were given placebo or active drugs. In 1981 it was reported that five year mortality in a 3,000 person RCT was 15.0% among people who took their pills at least 80% of the time, versus 24.6% among those who did not ( $p=0.0001$ ).<sup>59</sup> Mortality did not differ among those assigned to placebo (20.9%) compared to the study drug, clofibrate (20.0%)( $p=0.55$ ). In the Beta Blocker Heart Attack Trial ( $N=2,175$ ), those who took less than 75% of their pills were 2.6 times more likely to die in the next year (OR=2.6; 95% CI 1.2, 5.6). This was true both for those taking the effective medicine propranolol (OR=3.1), and for those taking placebo (OR=2.5).<sup>60</sup> In the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial ( $N=1,141$ ), relative risk of sudden death was twice as high among those who were not adherent to placebo, compared to those who were (RR = 2.1; 95% CI 1.03, 4.56).<sup>61</sup> To explain these results, we suggest that the meaning of “taking your pills” incorporates both active (taking care of one’s self) and passive (being taken care of) elements of the shared biomedical belief system. People who take part in biomedical research often share values with the biomedical “taking-your-pills-is-good-for-you” belief system, and tend to carry positive associations, both conscious and unconscious, between treatment adherence and good health.

Medical trainees are an example of a population with demonstrated interest in the biomedical paradigm. In a classic study, investigators randomized 56 medical students to either one or two placebo pills, colored either blue or pink.<sup>62</sup> The students were falsely told that they were receiving either sedative or stimulant medication. Afterwards they were asked to rate themselves regarding the following mental states: alert, calm, cheerful, drowsy, easy-going, irritable, jittery, relaxed, sluggish, talkative, tense, tired. Both color and number of pill were significantly associated with these reported mental states. Those assigned blue pills reported more sedation and less agitation than those receiving pink pills. Taking two rather than one pill exaggerated these results. Interestingly, and supportive of the emerging “nocebo” concept, 32% reported side effects, including headache, dizziness, stomach pain, etc.<sup>62</sup> Medical students are likely quite aware of possible side effects, and hence may tend to notice, interpret, and perhaps magnify their internal states in response to belief that they had been given active medication. Several other studies have taken similar tracks, randomizing subjects to different numbers and colors of capsules and tablets.<sup>63-65</sup> The findings were similar: people taking red or pink placebo pills tend to feel stimulated, and those taking blue pills tend to feel more sedated, regardless of active ingredients. More pills tend to have greater effect than fewer. Together, these findings support the meaning response framework, and suggest that the linear “active-ingredients-cause-physiological-effects” paradigm is inadequate.

One final example comes from a well-designed trial in England which tested the effects of aspirin, placebo, and brand names on headache.<sup>66</sup> Some 835 participants were recruited by door-to-door survey, then randomized to branded aspirin, unbranded aspirin, branded placebo, or unbranded placebo. Participants were instructed to take 2 pills at the first sign of a headache, then to rate its severity 30 and 60 minutes later. Pills were dispensed in either a plain bottle or a bottle with a prominent brand name on the label. Results clearly showed inter-group differences, with branded aspirin the most effective, followed by unbranded aspirin, then by branded placebo, and finally by unbranded placebo. The difference between those assigned branded and unbranded pills was of approximately the same magnitude as the difference between those assigned aspirin and placebo.<sup>66</sup> Whatever the brand name meant to these participants, it appeared to influence headache severity as much as did the pharmacological effects of aspirin.

For these studies, some have argued that specific methodological limitations may reduce confidence in interpretation.<sup>67-73</sup> However, evidence from a broad base of well-designed RCTs supports the notion that placebo/meaning effects are real, and provides estimates of the magnitude of these effects. To this end, we will summarize the best systematic reviews of the most sound RCT-based evidence available. We will then proceed to explore and expand existing theoretical structures, using a wider array of research findings.

## Systematic reviews

A number of book-length treatments<sup>1-5</sup> and systematic reviews of placebo-related evidence<sup>6;7;10;72;74-84</sup> have been published. While some take a theoretical or descriptive approach, others employ the principles of evidence-based medicine<sup>85-87</sup> with varying degrees of methodological rigor. For example, a meta-analysis by Hrobjartsson and Gotzsche has been widely cited.<sup>7</sup> Including several categories of intervention (pills, surgery, counseling), these authors identified 130 trials that included both a placebo and a no-treatment group. Sorting these into those with binary (32 trials, 3795 participants) and continuous (82 trials, 4730 participants) outcomes, they reported: 1) a non-significant trend toward placebo benefit for binary outcomes, and 2) a modest benefit for trials with continuous outcomes (0.28 relative risk reduction; 95% CI 0.19 to 0.38). While criticized for missing several relevant trials, for “lumping apples and oranges,”<sup>88</sup> and for including inappropriate trials (eg. ones in which the patients were unconscious when the placebo was given), this was the most rigorous meta-analysis to date. The authors responded to some of these concerns with an updated meta-analysis published in 2004, which included an additional 42 trials (3,212 participants), and yielded a pooled standardized mean difference of 0.24 for placebo-versus-no treatment trials with continuous outcomes.<sup>89</sup> Interestingly, the overall effect sizes implicated in these studies are consistent with the 35% relieved-by-placebo figure provided by Beecher 50 years earlier, and with condition-specific meta-analyses, such as those for pain,<sup>90-93</sup> and depression.<sup>75-77;83;84;94</sup>

## Pain

Physiological mechanisms involved in the placebo effect (meaning response) are perhaps best understood in the area of pain. In the 1950s, Beecher and others reported evidence that the administration of a placebo could lead to lower levels of reported pain.<sup>54;95;96</sup> Other studies followed. In 1964, Egbert et al. published “The reduction of post-operative pain by encouragement and instruction of patients.”<sup>51</sup> In 1978, only a few years after Hughes et al. discovered endogenous opioids,<sup>97</sup> Levine et al. published “The mechanism of placebo analgesia,” demonstrating that the opioid-blocking drug naloxone could block the “non-specific” effects of placebo analgesia.<sup>98</sup> Further studies using blinded infusions of placebo or naloxone, controlled by concealed pumps and timing devices, confirmed that the pain-relieving properties of placebo operated through mechanisms involving opioid receptors.<sup>92;99;100</sup> More recently, Benedetti and colleagues have confirmed and extended these findings, demonstrating beyond reasonable doubt that awareness of actual or potential treatment can reduce pain, and that opioid-related mechanisms are indeed involved in the causal pathway.<sup>101-105</sup> Various reviews have estimated the magnitude for various forms of placebo analgesia, with estimates of effect size ranging from 10% to 75%.<sup>106-111</sup> Combining data from 44 pain trials (2,833 participants), Hrobjartsson and Gotzsche reported the pooled standardized mean difference for placebo compared to no treatment at 0.25 (95% CI 0.16 to 0.35).<sup>89</sup> Most recently, Hoffman et al. have reviewed the research on placebo pain response, concluding that evidence is strong, and that biological pathways are beginning to be known in some detail.<sup>112</sup>

## Depression

RCTs testing antidepressant treatments provide some of the best evidence regarding placebo effects and meaning responses. A recent meta-analysis including data from 75 trials representing more than 6,000 patients found that “the mean proportion of patients in the placebo group who responded was 29.7%.”<sup>84</sup> This study also found that placebo response was greater in studies published in more recent years, and concluded that “the response to placebo in published trials of antidepressant medication for [major depression] is highly variable and often substantial and has increased significantly in recent years.”<sup>84</sup> As the mean proportion of responding patients in the active medication groups was 50.1%, it may be concluded that the majority of apparent response to antidepressant medications comes from placebo effect rather than from specific pharmacological mechanisms (0.297/0.501 = 59.3%). A meta-analysis including only those trials with both no treatment and placebo groups concluded that “23 percent of the response to antidepressant medication is due to spontaneous remission, 27% is due to the drug, and 50% is due to expectancy.”<sup>83</sup> A more recent and comprehensive meta-analysis of all antidepressant drug studies submitted to the FDA (published and unpublished) suggests that as much as 80% of effects from antidepressants can be attributed to the placebo effect.<sup>77;113</sup> Other systematic reviews of placebo effect in depression have provided similar findings and interpretations.<sup>74;75;79;114</sup>

## Clinical interactions

In 1987, Thomas<sup>15</sup> reported the results of a trial in which he randomized 200 consecutive patients “in whom no definite diagnosis could be made” in two directions: 1) to a prescription for a placebo (3mg thiamine) or no prescription, and 2) to either a “positive” or “negative” consultation. The positive visit was defined as one in which “the patient was given a firm diagnosis and told confidently that he would be better in a few days.” The negative visit included the phrase “I cannot be certain what is the matter with you,” and for those assigned to placebo, “I am not sure that the treatment I am going to give you will have an effect.” Follow-up monitoring at 2 weeks assessed resolution of illness. Of those treated with placebo, 53% were better, compared with 50% in the no-treatment group ( $p=0.5$ ). Of those in the positive consultation group, 64% reported recovery, compared with 39% in the negative consultation group ( $p<0.01$ ). This 25% absolute effect size (number needed to treat = 4) is larger than that attributable to many or most proven pharmaceutical or surgical interventions, where effect sizes are often in the 5% to 15% range (NNT 7 to 20). While in this case the placebo pill made little if any difference, the naming of a disease and the provision of a positive prognosis appeared quite powerful indeed.

A large body of research points towards the importance of positive clinical interaction.<sup>115-137</sup> While much of the literature focuses on subjective outcomes such as patient satisfaction, there are a number of controlled studies that point toward more objective benefit.<sup>138-142</sup> In 1995 Stewart reported the results of a systematic review of studies assessing health outcomes of physician-patient communication.<sup>134</sup> Of 21 studies meeting criteria, 16 reported positive health outcomes. Reported benefits ranged from decreased anxiety, distress, and pain to improvements in blood pressure, mobility, and general health-related quality of life. Effect sizes ranged from 20% to 40% improvement for anxiety scores, to a three-fold difference in resolution of headache.<sup>134</sup> In 1998 Roter et al. published a meta-analysis of 153 studies “that evaluated the effectiveness of interventions to improve patient compliance with medical regimens.”<sup>143</sup> They found significant benefit, ranging from improved pill counts and more consistent follow-up visits to improved laboratory and general health measures. Standardized effect sizes ranged from 0.17 to 0.60, with most in the 20% to 30% range.<sup>143</sup> In 2001, Di Blasi et al. published a systematic review of “influence of context effects on health outcomes.”<sup>6</sup> They reviewed 25 randomized trials, reporting generally positive results, noting that “one relatively consistent finding is that physicians who adopt a warm, friendly, and reassuring manner are more effective than those who keep consultations formal and do not offer reassurance.” These reviews and the constituent studies are the basis for the clinical recommendations that we outline in the Table. While none of these clinical actions is proven beyond the shadow of a doubt, all are reasonable, tentatively supported by the literature, and unlikely to harm.

## Placebo, culture and health

There are many factors known to predict health outcomes. Smoking, diet, exercise, age, gender, race, education, employment, marital status, poverty, income discrepancy and exposure to toxins are all known to associate with - and to predict - morbidity and mortality.<sup>144-149</sup> Most of these can be explained by causal pathways that fit within the dominant biomedical paradigm. Some observations, however, are more problematic. For instance, a study published in *The Lancet* in 1993 compared mortality data of 28,169 Chinese Americans with 412,632 randomly selected matched controls.<sup>150</sup> For Chinese Americans, but not for controls, average age of death was predicted by being born in years considered unlucky in traditional Chinese belief systems. This association was most pronounced for those born in China, and for those with diseases traditionally associated with specific birth years. On average, 1.3 to 4.9 years of life lost were attributable to unlucky birth year.<sup>150</sup>

Perhaps we should not be surprised by such apparent anomalies. There are many others. The death of a spouse or another family member can influence morbidity and even mortality.<sup>151-154</sup> Psychological traits (eg. cynicism,<sup>155</sup> optimism,<sup>156-158</sup> sense of coherence,<sup>159-161</sup> self-esteem,<sup>162</sup> suspiciousness,<sup>163</sup> and type A personality<sup>164-166</sup>) and states (eg. anger,<sup>167-169</sup> depression<sup>170-174</sup>) are associated with important health outcomes, including mortality. Acute and especially chronic stress are linked to important health outcomes.<sup>175-184</sup> Gender and ethnicity may mediate health effects of stress. Inequality and racism are especially unhealthy stressors.<sup>185-189</sup> The number and quality of social relations is an especially strong predictor of important outcomes, including death.<sup>190-198</sup> Specific attributes of interpersonal relations, such as hostility,<sup>199-205</sup> emotional relationships,<sup>206-208</sup> job control,<sup>209-211</sup> religious observance,<sup>212-214</sup> and social dominance<sup>215</sup> have been linked with major health outcomes. While none of these psychosocial attributes or conditions can be easily studied in prospective randomized trials, the

associations appear real, and cannot be readily explained by accepted biomedical risk factors. What is needed is an explanatory model that takes account of psychosocial attributes and social conditions as well as conventional risk factors, such as hypertension, cholesterol, tobacco use and family medical history. Before outlining the elements needed for such a framework, we will briefly review the two main theories put forth regarding placebo effects: expectancy and conditioning.

### **Conditioning and expectancy**

Classical (Pavlovian) conditioning is based on the pairing of a “neutral” conditional stimulus with an “active” unconditional stimulus. In the case of Pavlov’s dogs, the sound of a bell ringing was paired with feeding. Over time, this led to the conditioned response of profuse salivation at the sound of the bell, regardless of the presence of food.<sup>216</sup> Following this line of thought, the November 1962 issue of *Science* included an article entitled “The placebo effect in the rat,” in which R.J. Herrnstein reported that “inert” saline injections could induce physiological and developmental changes, if the saline injections were first coupled with injections of active pharmacologic agents.<sup>217</sup> This fueled the argument that placebo effects were simply a type of classical Pavlovian conditioning. Reports that previous administration of an active drug led to enhanced placebo response in humans supported this notion.<sup>218</sup> Subsequent experiments reported that classical conditioning can indeed be demonstrated in humans, as well as other animals.<sup>219</sup> Biological outcomes such as heart rate, blood pressure, and white cell count have been reported to respond to “neutral” conditional stimuli, as well as numerous “subjective” self-reported outcomes.<sup>220-223</sup>

Also in 1962, the theory of “expectancy” was developed in order to explain placebo effects.<sup>224</sup> In this model, conscious expectation of benefit can influence the course of illness. Several studies reported that manipulation of expectancies could lead to reduction in pain or nausea, and perhaps more convincingly, to changes in heart rate, blood pressures and other physiological measurements.<sup>42-44</sup> This line of research continued for decades, with numerous studies reporting the influences of suggestions and expectancies.<sup>3;62;66;225-229</sup> A few more sophisticated experiments, designed to test whether placebo effects are due to expectancies versus conditioning, have in general concluded that both are involved, and cannot easily be disentangled.<sup>90;223;230</sup>

### **Coffee: Expectancy or conditioning?**

Reflecting on the common experience of coffee drinking may be helpful in showing how expectancy and conditioning are neither mutually exclusive nor comprehensive explanations of placebo phenomena. Observational studies have reported that people show heightened alertness and physiological stimulation when given decaffeinated coffee, especially when told it is regular coffee. Experimental studies have shown that manipulation of expectancies can influence outcomes, and that paired conditional and unconditional stimuli can modulate these effects.<sup>231-235</sup> Similar mixed expectancy and conditioning effects have been reported for alcoholic beverages.<sup>69;236-238</sup> So, what exactly is going on here? In one view, experience with coffee drinking may shape conscious expectancies, which may in turn influence response patterns. In another, coffee drinking serves as natural experiment in classical conditioning, where the “neutral” stimuli of taste and smell are paired with the “unconditioned” stimulus of caffeine. In our view, these are both useful but insufficient explanatory frameworks. In coffee drinking, and perhaps in most health-related behaviors, there exists a subtle and complex interplay of conscious and subconscious processes. People hear about, observe, and experience coffee drinking in specific contexts, embedded within sociocultural networks of meaning. Conscious and subconscious “meanings” combine with personal experiences - physiological and psychological - to form mind-body response patterns. These patterns have central tendency (stimulation) as well as variability (drinking coffee can also lead to agitation, distraction, or even sleepiness), both within and between individuals. While the reductionist hypothetico-deductive scientific method may be able to test a few individual strands of this complex fabric, it cannot adequately describe the sum total. For that, we need a more encompassing conceptual framework.<sup>239-242</sup>

### **An expanded explanatory framework**

Human health is among the most complex, subtle, and emotionally charged areas of scientific inquiry. Dictionary definitions of health invariably include reference to psychological as well as biological health, and often invoke social and even spiritual health. One widely cited definition comes from the World Health



Organization's 1978 Alma Ata conference: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease."<sup>243</sup> Perception of - and response to - bodily sensations is dependent on functional integrity at many levels, from molecules to cells to organs to organ systems, all of which are exceedingly complex and highly inter-related. The nervous system, centered in the brain, interacts with both biological and sociological systems, and has been postulated to contain inherent "functional salutogenic mechanisms."<sup>244;245</sup>

With capacities of memory, learning, judgment, and conscious choice, it is clear that our brains are capable of independent thought and action. It is also clear that we are capable of habitual and conditioned responses. Habits and choices are not merely responses to simplistic stimuli, but are instead embedded in and influenced by a tremendous array of personal and cultural factors. Mental health is a product of innumerable personal and social experiences, and is expressed through many subtle, complex, and inter-related conscious and unconscious processes. None of these factors exist in isolation, and none are truly stable over time. Instead, all are interdependent, and most are constantly changing. Given the multidimensional and unstable nature of biopsychosocial health, it is perhaps not too surprising that health-related placebo/meaning effects are neither simple nor well understood.

While a placebo pill in isolation may be biologically inert, health-related responses to the process of placebo pill administration will vary, depending on contextual, cultural and psychological factors. Previous experiences and current context (words that are said, attitude and demeanor of people involved, physical surroundings) are likely more important than the color, shape or size of the pill. By focusing on the intervention (placebo pill, sham procedure) rather than on the person and the situation, investigators have unknowingly set the terms and the limits of the placebo debate. By instead focusing on the response process of the whole person in context, many of the inconsistencies, contradictions, and dead-ends of placebo research may be more satisfactorily resolved.

We suggest that at least two larger processes are involved in health-related placebo phenomena. The first we term "feeling cared for." This could also be classified as "being helped" or "receiving treatment." The second is "empowerment," which could also be termed "taking care of one's self," "achieving health," or even "self-actualization." These active and passive processes may influence human health when subconscious signals trigger thoughts leading to healthy behaviors. Doctors and other clinicians can help facilitate healthful thoughts and behaviors in a number of ways. The Table highlights eight simple actions that may be useful: i) speak positively about treatments, ii) provide encouragement, iii) develop trust, iv) provide reassurance, v) support relationships, vi) respect uniqueness, vii) explore values, and viii) create ceremony. Further research into these processes might be guided by the dualities of body-mind, conscious-subconscious, and passive-active.

### **Body-mind, conscious-subconscious, passive-active**

The Cartesian separation of mind and body is slowly being replaced by a more holistic, integrated, and comprehensive conceptual framework.<sup>21</sup> Within science and medicine, conceptual and disciplinary separation of thought and emotion from physical biology is giving way to an integrated multidisciplinary approach. Terms such as "psychoneuroimmunology," "neuropsychopharmacology," and "psychoneuroendocrinology" have come into general scientific parlance.<sup>246-248</sup> Increasing numbers of scientists are concluding that human health should be considered within a body-mind framework allowing for complexity, change, and wholeness. It is also increasingly common to consider each individual as integrated within a larger society, with individual behavior and biology inextricably linked to internal and external stimuli, including cultural values.

Separation of thought into conscious and subconscious may be useful in thinking about the placebo/meaning effect. While conditioned responses are usually considered subconscious, expectancies can appear as explicit conscious thoughts, or as vague, primarily subconscious feelings. In some instances, awareness of subconscious processes may enhance mental or physical health. For example, a person who becomes aware of self-destructive thoughts arising from experiences with an abusive parent may subsequently be less likely to be influenced by that critical voice than someone who is unable to make that cognitive connection. While some individuals spontaneously develop these levels of cognitive and emotional intelligence, others may become more adept using introspection, meditation, or psychotherapy.

Placebo/meaning effects attributable to “feeling cared for” or “caring for one’s self” may be conscious or subconscious, depending on the individual and the context. While “feeling cared for” tends to be passive rather than active, associated interpersonal interactions invariably involve back-and-forth processes, where the health-seeker is both active giver and passive recipient. Similarly, the primarily active process of taking care of one’s self sometimes involves passive components. Experiments designed to test these notions have shown that substantive influences arise from the external presence of the investigators and the experimental context. While these “Hawthorne effects”<sup>249-252</sup> may work through subconscious or passive processes, conscious recognition and active response to experimental context may also be involved. Placebo/meaning effects arising from “empowerment,” “understanding,” or “self-actualization” may reflect subconscious as well as conscious processes, may involve both active and passive processes, and may or may not be substantively influenced by context.

On a practical level, recognition of the dualities of mind-body, conscious-subconscious, and passive-active may be useful in harnessing the placebo/meaning effect in clinical practice.<sup>253</sup> The clinical actions that we think are supported by the literature and are likely to have positive impact are listed in the Table. The salutary effects of doctor patient interaction, cognitive behavioral therapy, group therapy, and various types of counseling and health-coaching may arise in part from similar actions. Such actions may assist patients towards understanding of the external and internal forces shaping thoughts, emotions, and physiological processes. Or they may simply provide positive and negative reinforcement towards more healthful behaviors. As scientists, we realize that we are only beginning to map the relations of thought, emotion, and health.<sup>254-256</sup> As healers, we may be in our infancy in terms of using mind-body techniques to enhance health.<sup>257-259</sup> New levels of understanding powered by better research may very well change the way that medicine is practiced.

### **Doctors, patients and medical science**

Why do people experience less pain and depression when they are given pills that contain only inert ingredients? Perhaps taking a pill symbolizes and evokes personal action toward better health. Why do colors of pills and brand names seem to make a difference? Perhaps because color and brand names have associated health-related meanings. Why do people experiencing sham surgery or sham acupuncture respond favorably? Perhaps because they have faith in the surgeon or acupuncturist, and expect to be helped by these symbolically powerful healers. Why do people drinking decaffeinated coffee feel stimulated? Perhaps because the smell, taste, and warmth evoke memories, learned responses, and expectations of stimulation. Why do people of Chinese heritage die younger if they are born in unlucky years? Perhaps because unlucky years are symbolically powerful, capable of influencing health-related beliefs and behaviors. If we accept that body, mind, and culture are inextricably linked, and that causality is a complex network with multiple feedback loops, we will be more careful interpreting reductionist science testing only individual strands.

There is little doubt that conscious understanding and active choice may affect health-related behaviors. Nevertheless, many important influences are below the conscious level, and not subject to active intention. Some of the predisposing factors are linked to beliefs regarding medicine and science. Many arise from the system of shared meaning that we call culture. Within culture, medicine has tremendous symbolic power. Belief in the pills and procedures of physicians and in the knowledge of researchers is widespread and deeply rooted. Simply being in a clinical or research setting supervised by physicians and scientists may trigger conscious and subconscious processes that influence health. Being cared for by an authority figure may relieve anxiety, leading to more confidence and higher expectations. Having a surgery may be an even more profoundly important experience, and may elicit a variety of powerful healing responses. When clinicians are aware of these possibilities, actions such as those listed in the Table might usefully contribute toward health.

People come into clinics and research settings with a variety of prior experiences, predispositions and expectations, and with innate, learned, or not-yet-determined healing response patterns. Participants in health-related research are human beings first, and research subjects second. They respond to many factors, just as they do in other arenas of life. They listen, watch facial expressions, and sometimes pay attention to written words. They interact with research personnel, exchange pleasantries, and ask questions. Some take the study personnel at their word regarding the purpose of the study. Others suspect ulterior motives, and ask themselves “what are *they*

(doctors/scientists) *really* trying to study?” Often, participants try to respond “in the right way,” and to provide the sort of responses they believe the researcher would want to hear. Almost inevitably, they tend to pay more attention to both the intervention and to their response than they would in a non-study context. They may or may not be aware of their personal attitudes and beliefs regarding the interventions being studied, and may or may not try to compensate or take into account possible prejudices and preconceptions. Some may even consciously choose to provide incorrect information. While self-reported outcomes are more likely to be influenced by these factors, observer-recorded or even laboratory-measured outcomes may also be affected.

Balint focused attention on “the possibilities of patient-centered medicine.”<sup>115</sup> Engel introduced “biopsychosocial” medicine.<sup>28</sup> Benson encouraged physicians to “harness the power of the placebo effect,” which he has suggested would be better named “remembered wellness.”<sup>253;260;261</sup> Brody has similarly put forth the idea that a doctor, through “sustained partnership,” can foster “emotional resilience,” which in turn can “enhance placebo effects,” hopefully leading to better health.<sup>117;262-264</sup> We agree, and suggest that the creative use of placebo in the broad sense is central to the art of medicine. The meanings and processes that underlie placebo phenomena are the same as those that a skillful physician employs during a therapeutic encounter. Words, symbols, facial expressions, and body language can be utilized as allies in a clinical encounter. Those burdened by disconcerting symptoms or subconscious fears may be relieved when the doctor names a disease, or provides reassurance. Those powerless under the weight of chronic malady can regain some control when a self-administered therapy is prescribed and incorporated into daily life.

In countless ways, symbols of health and healing can be artfully employed in an effort to allow a person to regain lost health, to remember wellness. At the same time, physicians should be aware that words can cause harm as well as good, and should take care when forecasting disease processes, or even when naming diseases or side effects. As a final point, we believe that all healers should remain both honest and humble. Even the more optimistic estimates of the power of placebo suggest limited effects. Empowerment, positive suggestion, and sustained partnership may help to ameliorate suffering, but are unlikely to reverse the course of established disease. From an ethical perspective, where individual autonomy is rightfully given high priority, it is wrong to use deception in the name of healing. Our goal, then, is to artfully enhance healing, while telling only the truth. We hope this essay helps others to reach in that direction.

**Table****Key points for clinicians**

Action	Result
Speak positively (yet truthfully) about the therapy being prescribed	Create positive expectations
Provide encouragement and education to empower the individual to take positive action	Enhance active health-seeking thoughts, emotions, and behaviors
Develop relationships of trust, compassion and empathy	Enhance passive feeling of being cared for
Provide reassurance	Relieve anxiety and fear
Reinforce the importance of interpersonal relations	Support the development of healthful social connection
Learn about the individual's unique outlook, values, past experiences and belief system	Allow a more efficient matching of individual needs with existing therapies and resources
Help the patient explore his or her own health-related value system	Facilitate appropriate, meaningful, and sustainable health-related choices
Create ceremony and ritual that facilitate meaning and expectancy for the patient	Help patient bridge conscious-subconscious divide, developing healthful mind-body responses and patterns

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