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Cultural Variations in the Placebo Effect: Ulcers, Anxiety, and Blood Pressure

An analysis of the control groups in double-blind trials of medicines demonstrates broad variation—from 0 to 100 percent—in placebo effectiveness rates for the same treatment for the same condition. In two cases considered here, drug healing rates covary with placebo healing rates; placebo healing is the ultimate and inescapable "complementary medicine." Several factors can account for the dramatic variation in placebo healing rates, including cultural ones. But because variation differs by illness, large placebo effects for one condition do not necessarily anticipate large placebo effects for other conditions as well. Deeper understanding of the intimate relationship between cultural and biological processes will require close ethnographic scrutiny of the meaningfulness of medical treatment in different societies. [placebo effect, ulcer disease, anxiety, hypertension, cross-cultural variation]

> Nocebo and placebo effects are integral to *all* sickness and healing, for they are concepts that refer in an incomplete and oblique way to the interactions between mind and body and among the three bodies: individual, social and politic.
>
> Scheper-Hughes and Lock, 1987

Some years ago in this journal I reported on an analysis of 31 double-blind controlled trials of the anti-ulcer drug cimetidine (Moerman 1982). I recently reviewed those data, added to them, and repeated the process for several other conditions and drugs. The analysis of these new data materially expands and complicates the original conclusions.

The Placebo Effect

The placebo effect is an important part of the human healing process that has been considered several times in the anthropological literature (Moerman 1979,

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1997; van der Geest and Whyte 1989); I will, therefore, only briefly indicate some of the dimensions of the placebo effect here.

I define placebo effects as the desirable[1] psychological and physiological effects of meaning in the treatment of illness.[2] Participating in a healing process, regardless of its content, can lead to healing. While this is clearly true, it is much easier to assert than to demonstrate to a skeptic.[3] One of the clearest demonstrations comes from what is known as a "three-arm trial" of medical treatment. In such a trial, after a diagnosis, patients are randomly allocated to one of three groups. The first group typically receives some sort of (presumably) active medication. The second receives placebo treatment, (presumably) indistinguishable from the active one but lacking the item being tested. The third, untreated, "natural history" group serves to represent what happens to patients who receive no treatment. If the group receiving placebos (inert pills, perhaps) does substantially better than the untreated group, one can attribute the difference to the placebo effect. Trials of this sort show just how difficult it is to create, or even conceptualize, an "untreated group." Every part of an intervention—taking a history, stating a diagnosis, making repeated blood pressure readings or multiple endoscopic observations of the gut, having patients keep symptom diaries—may well have therapeutic value.[4]

Few three-arm trials have been carried out, but the ones that have are very interesting. One well-designed study compared ultrasound therapy to sham ultrasound therapy (the machine is applied but not turned on) for swelling following third molar extraction; the study included a third group that received ordinary dental care (as did the patients in the two study groups), but neither real nor sham ultrasound treatment. "The placebo [ultrasound] treatment . . . reduced [swelling] in all conditions in which the dentist applied the equipment to the patient's face" compared with the results in the untreated group (Ho et al. 1988:203; see also Hashish et al. 1986). In another study, placebo treatment was shown to improve both exercise duration and functional class in patients with congestive heart failure compared with patients receiving no treatment (Archer and Leier 1992). In trials of this sort, it is not uncommon that the untreated group improves, too. Things often do heal by themselves; these are often called "natural history effects."[5] It is also often the case that people seek treatment (and are enrolled in trials) when their (fluctuating) symptoms are at their worst; improvement in such patients is (awkwardly) called "regression to the mean" (McDonald and McCabe 1989).

In any event, the placebo effect is most unambiguously evident when a group receiving sham treatment heals significantly faster than an untreated group. A number of additional three-arm studies have recently been reviewed (Ernst and Resch 1995). It is also possible to infer the existence of a placebo effect in many controlled trials where placebo groups but no "natural history" groups are utilized. A number of controlled trials are considered in this article.

Controlled trials are of many types. The simplest trial treats two groups of patients using two different drugs and compares the outcome. If there is a difference in improvement between the two groups, it may indicate that the drug taken by one group is somehow better than the other drug. Other factors, however, may intrude. The conclusion of superior effectiveness can only be true if the patients in both groups are "the same." Typically, achieving equivalence is attempted by randomization—people are randomly assigned to one group or another, and, subsequently, an analysis is done to see if indeed they are the same on relevant measures like sex,

age, degree of illness, and so on.[6] This comparability ensures that the "only difference" between the two groups is the drug they receive. The second major factor in such a study is "blinding." Studies are occasionally "single blind"—the patients are not told what medication they are receiving. Since physician bias is a strong element in many such situations, a "double-blind" trial—where neither the patients nor the physicians treating the patients know who is receiving what drug—is usually required to demonstrate drug efficacy. Minimally, double-blinding prevents physicians from evaluating the improvement of those taking the new drug more favorably than others. The third important element of controlled trials is the use of a control. While one can compare two active drugs (cimetidine vs. ranitidine, for example), such tests are often inconclusive, especially if both drugs work reasonably well. Many trials, especially in the absence of widely recognized effective treatments, compare treatment groups with placebo control groups; one of the groups is given drugs that appear and taste the same as the drug being tested, but lack the active ingredient under study. Putting all these elements together, one then would have a "randomized, double-blind, placebo-controlled trial," which is often referred to as the "gold standard" of modern medicine. Such trials are understood to demonstrate how the drug under study differs from "no treatment." I have already noted that the control group in such a trial has had far more than "no treatment," and, not surprisingly, perhaps, many control group patients get better, too.

There is another interesting situation where one can detect placebo effects. The randomized controlled trial (RCT) has only become common in conventional medical practice since the early 1970s. Before then, there was much serious scientific investigation of drugs which did not control for the bias and enthusiasm of the clinicians. This led to the widespread use of treatments that were only later put to the test of the RCT. In a number of such cases, drugs with high levels of effectiveness in actual practice could not be shown to be more effective than inert treatment in subsequent trials. There are two major reviews of cases of this sort. The first examined a number of "subsequently discredited" treatments for angina pectoris. "The pattern is consistent: the initial 70 to 90 per cent effectiveness in the [early] enthusiasts' reports decreases to 30 to 40 per cent 'base-line' placebo in the [later] skeptics' reports" (Benson and McCallie 1979:1424). The second such study considered five medical procedures once considered efficacious (mostly for treating viral infections) but subsequently abandoned when they could not outperform a placebo in trials. For these five treatments combined, "40 percent excellent, 30 percent good, and 30 percent poor results were reported by proponents" (Roberts et al. 1993:375). There is remarkable agreement in these two studies. Both report good to excellent effects of apparently inert substances which are much higher—70 percent or more—than those usually attributed to such treatment—about 30 to 35 percent. A primary ingredient in the effectiveness of the earlier experience is probably physician enthusiasm. Several studies have manipulated clinician enthusiasm and shown significant effect on patient response (Gryll and Katahn 1978; Uhlenhuth et al. 1966). There is good reason to believe that placebo effects are generally lower in RCTs than in the ordinary practice of medicine. In an RCT, everyone knows that half the patients are not going to receive the "exciting new drug." This may dim the overall enthusiasm of the investigators in that clinical context. In addition, the process of eliciting informed consent may diminish patient expectations. The

"naive enthusiasm" of both doctor and patient in these cases from the 1950s and 1960s was a compelling factor in the improvement of serious sickness.

In July 1999, the BBC reported in the business section of its World Wide Web site that the share price of a biotech company had dropped 33 percent on news that its new food allergy drug, which had been successful in 75 percent of patients trying it, had been shown to be no more effective than a placebo treatment for the same allergies (BBC 1999). Three-quarters of placebo-treated patients were able to eat foods that previously had made them ill. The company announced that it would drop development of the drug. There is no indication that anyone is going to follow up this quite remarkable result.

In addition to such effects, which seem to follow from the relationship between clinician and patient,[7] there are other sorts of mechanisms that also may play a role. A group of American medical students was asked to participate in a study of two new drugs, one a tranquilizer and the other a stimulant (Blackwell et al. 1972). Each student was given a packet containing either one or two blue or red tablets; the tablets were inert. Hours later, the students' responses to a questionnaire indicated that the red tablets tended to act as stimulants, while the blue ones acted as depressants, and two tablets had more effect than one. The response of these students was not to the inertness of the tablets and cannot be easily accounted for by natural history or by clinician enthusiasm. While the *fact* of their experience may have had something to do with the authority of their professors, the *directions* of their experience and its intensity can be accounted for by the "meanings" in the experiment: red means "up," "hot," "danger," while blue means "down," "cool," "quiet," and two means "more than one." A recent Dutch study has shown that stimulant medications tend to be marketed in "hot" colors—red, yellow, or orange tablets—while depressants tend to be marketed in "cool" colors—blue, green, or purple tablets (de Craen et al. 1996). One can consider "one-a-day" vitamins to be among the most neutral of medications; they are not imagined to have immediate or dramatic effects at all. Observations suggest that vitamins are marketed in tablets with pale pastel tones.[8]

An elaborate British study demonstrated that aspirin tablets labeled with a widely advertised brand name are more effective against headache than generically labeled aspirin tablets; similarly, inert tablets with the same brand name are more effective against headache than generically labeled inert tablets (Branthwaite and Cooper 1981). Aspirin is more effective than a placebo, and advertised pills are more effective than generic ones. Aspirin relieves headaches, but so does the knowledge and/or belief that surrounds medication; people know from watching the television that brand X is better, and, as a result, it may well be.

More direct kinds of discourse can also affect the healing process. Several studies have shown that short conversations can have substantial effects on the healing course of surgical procedures.[9] In one study, short pre-operative conversations with an anesthetist, which described frankly the typical postoperative course, led to substantially reduced analgesic use and shortened hospital stays for abdominal surgery patients (Egbert et al. 1964). In another study, equally short, frank conversation between mothers and nurses substantially reduced objective and subjective discomfort for children having tonsillectomy (Skipper and Leonard 1968). More recently, 200 British patients who presented in a general practice with symptoms but with no abnormal signs, and for whom, therefore, no firm diagnosis could

be made, were randomly given a positive or negative consultation. "In the positive consultation, the patient was given a firm diagnosis and told confidently that he would be better in a few days." In the negative consultation, the doctor said, "I cannot be certain what is the matter with you." "A total of 64 (64 percent) of those receiving a positive consultation [reported two weeks later that they] got better compared with only 39 (39 percent) of those who received a negative consultation" (Thomas 1987:1201).

Similar, but more significant, variations have been shown on a cultural level. A large study examined the deaths of 28,169 adult Chinese Americans and nearly half a million randomly selected matched "white" controls. It was found that "Chinese Americans, but not whites, die significantly earlier than normal (1.3–4.9 yr) if they have a combination of disease and birthyear which Chinese astrology and medicine consider ill fated" (Phillips et al. 1993:1142). For example, among the Chinese Americans whose deaths were attributed to lymphatic cancer (n = 3,041), those who were born in "Earth years"—and consequently were deemed especially susceptible to diseases involving lumps, nodules, or tumors—had an average age at death (AAD) of 59.7 years; among those born in other years, AAD was 63.6 years, nearly four years longer. Similar differences were found for other sorts of cancers, for heart attack, and for a series of other diseases. No such differences were evident in a large series of "whites" who died of similar causes in the same period. The intensity of the effect was shown to be correlated with "the strength of commitment to traditional Chinese culture." This study is phrased negatively, but the terms might be reversed, with certain astrological characteristics being associated with AAD longer than "normal."

Finally, there is evidence that shows, at least in some circumstances, that the adherence (or "compliance") of patients to their drug or placebo regime can substantially influence the outcome of treatment. For example, in a very large study of beta blockers to prevent heart attack after myocardial infarction, it was found that "good adherers"—patients who took more than 80 percent of their prescribed medication—had a five-year mortality rate of 15 percent compared to "poor adherers"—patients who took less than 80 percent of their medication—who had a five-year mortality rate of 25 percent. The more startling result was that "virtually identical findings were noted for patients who received a placebo (15 percent mortality for good adherers and 28 percent for poor adherers)" (Horwitz et al. 1990:542).[10] "Taking your medicine" may be construed as a sort of autodiscourse, a confession of faith that can affect the body.

These effects are not, as some would have it, only "psychological." In the previous two cases, the outcome variable is not some sort of patient preference or other psychological measure; it is mortality. In addition, placebo analgesia, induced by injection of sterile saline, can be reversed by a subsequent injection of the opiate antagonist naloxone (Levine et al. 1978), thus indicating that the symbolic act has led the patient to produce endorphins, endogenous opiates. There are many other similar examples.

In sum, many things shape the placebo response (more than have been considered here). Placebo effects follow from and are shaped by factors that influence the meanings patients attribute to their illnesses and to the treatments they receive. These include clinical factors such as physician enthusiasm and provider-patient interaction and cultural factors such as patients' understandings of colors, forms,

and names of medications, as well as their understandings of fate and faith. Reflexively, these can in turn influence additional clinical factors such as the patients' adherence, mood, and attitude. The placebo effect is of particular interest to anthropologists because it is a clear case of symbolic and meaningful events—involving relationship, discourse, form, belief, knowledge, commitment, history—having an apparently direct effect on human biology. From an anthropological perspective, these processes may best be labeled the "meaning response." There is no better single demonstration of the force (Rosaldo 1993) of the mindful body (Scheper-Hughes and Lock 1987) than the placebo effect. In what follows, I will examine in more detail how cultural factors may be at play in these engagements.

Measuring Placebo Effects

Regardless of how omnipotent the placebo effect is (or perhaps because of that omnipotence), it is not a simple or straightforward process to recognize and isolate it for analysis. In part, the difficulty of measuring placebo effects is a consequence of the complexity of the human healing process and the complexity of *measuring* the various elements of this process. Generally speaking, there are three sorts of healing processes: *autonomous ones* based on the immunological and homoeostatic processes of the body, *specific ones* based on the pharmacological or physical dimensions of the healing process, and *meaningful ones,* based on knowledge and interaction (Kleijnen et al. 1994; Moerman 1979). It is often difficult to differentiate these processes.

Consider an elaborate Australian study of the treatment of moderate hypertension: tens of thousands of Australians were screened for high blood pressure. Only those with systolic pressure (SBP) greater than 200 or diastolic pressure (DBP) greater than 90 millimeters of mercury (mm Hg) were entered in the study. Various drugs or placebos were provided in a double-blind manner, and blood pressure in the participants generally dropped, as shown in measurements made every four months. The study wisely included a relatively small group of 237 untreated people with moderate hypertension whose blood pressure was also measured every four months. Their blood pressure dropped, too. The mean DBP in this group dropped from 101.5 mm Hg (mildly elevated) to about 80 mm Hg (normal) in 32 months, and then stabilized at that level (plus or minus 1 mm Hg) for the next two years (MCATT 1982). This may be evidence of "regression to the mean" in this group of people, who were selected for study because one of their vital signs was extreme; the vital sign may simply have returned to "normal" as the result of human homoeostatic processes. There are other explanations. It may be that these individuals were, when first enrolled into the study, responding nervously to having their blood pressure taken, which gave them higher blood pressure; "doctor's office hypertension" is a common phenomenon. Subsequent (tri-annual) blood pressure readings may have gradually desensitized them to this event, and their blood pressure then no longer increased with the approach of the cuff. This would be a case of a distinct "measurement effect," where the measurement created the object of study (at least for a while). There is another possibility: this may be an example of the placebo effect. There is ample evidence to indicate that the use of various medical instruments and machines can have significant healing effects. It has been suggested that this is particularly true of any instrument with the word *laser* in

its name (Johnson 1994).[11] Repeated blood pressure readings may have a similar effect, lowering pressure to normal levels.

These matters are necessarily complex, and every case requires careful analysis. Measurement—which can act as treatment—is an important element in the entire situation.

The Case of Ulcer Disease

Ulcer disease has, since the development of gastroenterology, been recognized as a classic disease of unknown origin; despite recent enthusiasm for new and simpler explanations, they have their own problems, which are addressed below. Ulcers are generally characterized as one of two main types: gastric (or stomach) ulcers or duodenal ulcers, which together constitute the class "peptic ulcers." Duodenal ulcers are generally understood to be relatively easier to treat than gastric ulcers, which are often associated with carcinoma of some sort and can be more dangerous. Pain often varies independently of ulcer disease (pain relief from treatment has a varying association with actual ulcer healing); another painful condition known as duodenitis may account for some of this variation, but that remains unclear.

Popular explanations for ulcer disease are usually of two sorts and are based on commonsense notions of "stress" and "acid." There is little evidence to support either factor; both vary independently of the incidence of ulcer disease. It is widely recognized that cigarette smoking inhibits ulcer healing under almost any treatment scheme, but the great majority of smokers do not develop ulcers. Although ulcers seem to heal more quickly in an acid-reduced or acid-neutralized environment, acid seems not to cause the ulcers in the first place. In the past decade or so, peptic ulcer disease has come to be seen as caused by infection from a bacteria, *Helicobacter pylori* (Hp). Most, but not all, ulcer patients are infected with this bacteria: infection rates for duodenal ulcer patients range from 80 to 100 percent; gastric ulcer infection rates are somewhat lower. However, only 15 or 20 percent of people with Hp infections will ever have an ulcer in their lifetime (Walsh and Peterson 1995). Ulcer disease remains a serious matter: in 1994, 6,088 deaths from ulcer of stomach and duodenum occurred in the United States (Singh et al. 1996).

For many years, the primary treatment option for ulcers was antacids. The effectiveness of antacids is unclear; some studies have shown some effectiveness (Lublin et al. 1985), and others have not (Butler and Gersh 1975), but this treatment was all that was available, and, at least for some patients, antacids reduced pain. Refractory cases (then as now) were treated surgically. In the mid 1970s, a new approach to ulcer treatment appeared with a class of drugs called "histamine H_2 receptor antagonists." These drugs, commonly called hydrogen blockers, reduce the ability of the gut to produce hydrogen ions, hence limiting the amount of acid that can be produced. The first widely used drug of this type was cimetidine, sold under the trade name Tagamet® in the United States by the manufacturer Smith Kline & French. After a number of trials demonstrated its effectiveness, Tagamet became, for some years, the leading drug in world sales. Subsequently, several additional drugs of this class and related ones were developed. The most significant was ranitidine, another hydrogen blocker sold in the United States as

Zantac® by the manufacturer Glaxo Pharmaceuticals. There were many trials of this new drug as well. It is these two sets of drug trials that I describe here.

Variability in Randomized, Double-Blind, Placebo-Controlled Trials in Ulcer Disease

In the earlier article on this topic, I gathered 31 trials of cimetidine treatment of ulcer. Using more powerful search techniques that are now available, I have found a total of 72 such trials from 28 different countries. In all these trials, ulcers were diagnosed and ulcer healing was confirmed by endoscopic examination;[12] patients were randomly assigned, under double-blind conditions, to either cimetidine or placebo treatment. In most cases, the drug (or placebo) was taken four times a day. Usually, tablets contained 200 mg of cimetidine, and patients were to take one at each meal[13] and two at bedtime, for a total daily dose of 1,000 mg. Some trials called for four 300-mg tablets; a few others used somewhat different dosing regimens. The outcome was clearly defined as "endoscopically observed healed ulcer craters." In all cases where it was possible, sample size was the number of patients enrolled in the trial ("intention to treat" analysis) rather than the number who completed it ("per protocol" analysis). Although this more conservative measure of drug (and placebo) effectiveness is more or less standard today, it was not in the 1970s and 1980s when most of these studies were done.[14] In many cases, it was possible to determine sample size reasonably easily; in some it was not, for example when investigators reported a total number of patients that dropped out, but did not report how many dropped out from each group. I have also gathered results from an additional 45 trials of ranitidine from 16 countries. In most of these trials, the same considerations as those of the cimetidine trials applied, except that medication was usually taken twice a day, usually 300 mg per day. A total of 32 countries are represented in the 117 trials. I eliminated from consideration other trials because they did not meet the criteria of randomization, blinding, endoscopic diagnosis, or the like.

Figure 1 displays the enormous variation in the placebo healing rate in these trials. The mean placebo healing rate in the 117 trials is 35.3 percent; but the rates vary enormously, from zero to 100 percent.

Figure 2 shows the relationship between the placebo healing rates and the drug healing rates in duodenal and gastric ulcer using cinetidine and ranitidine (the four measurements are indicated with different markers). Overall, it is clear that the effectiveness of the drug treatment and placebo treatment are related—as placebo effects increase, overall drug effects increase, too; the correlation between the rates is .40 ($p = .0000$).

This finding is highly counterintuitive for medical researchers who usually consider placebo effects to be constant—sort of like "noise" in the system—and orthogonal, unrelated, to medical effects. Both of these notions are clearly incorrect. Even those whose only interest in therapy is the use of drugs ought to be interested in the placebo effect.

These two figures stimulate several interesting questions. First, what might account for the enormous variation in placebo effect (note that the effect of placebo treatment is far more variable than is drug treatment)? Second, how can so many ulcers be healed with "nothing?"

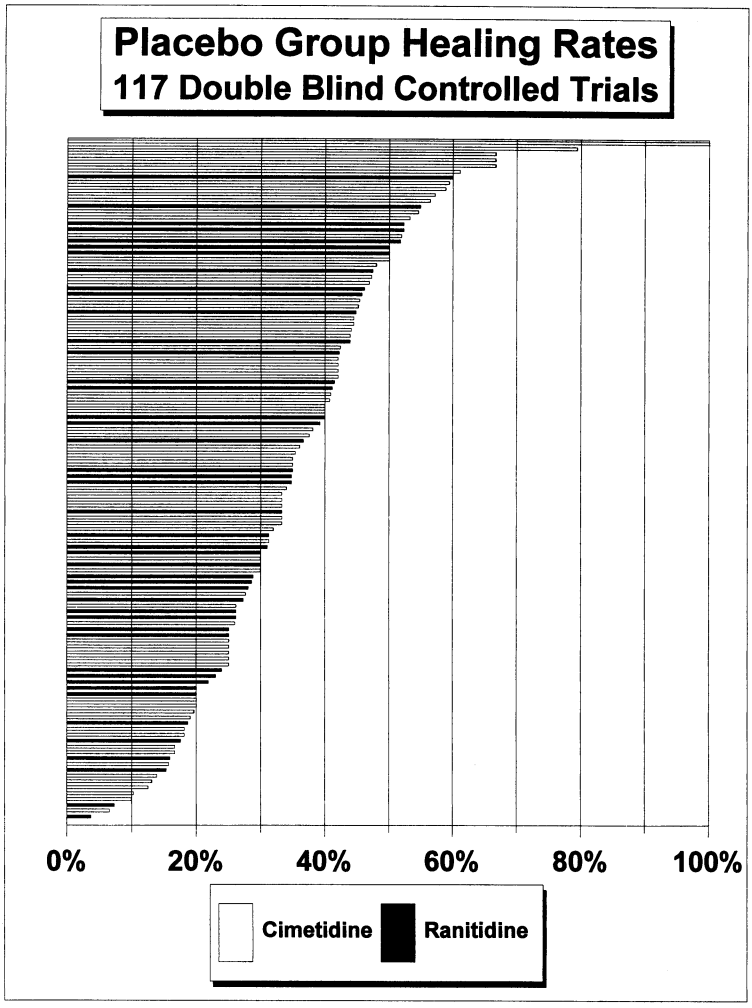

FIGURE 1.

Accounting for Variability in Placebo Healing Rates

To what can we attribute the healing of placebo-treated patients in these studies? Many factors are probably involved, but just exactly what those factors might be is a difficult question.

Autonomous Healing

Ulcers just might "go away all by themselves." Perhaps there is a medical version of the Heisenberg principle at work here, where the observation of a phenomenon changes the phenomenon itself. The presenting symptom of ulcers is usually very sharp pain, the source of which, at least for first-time sufferers, is probably

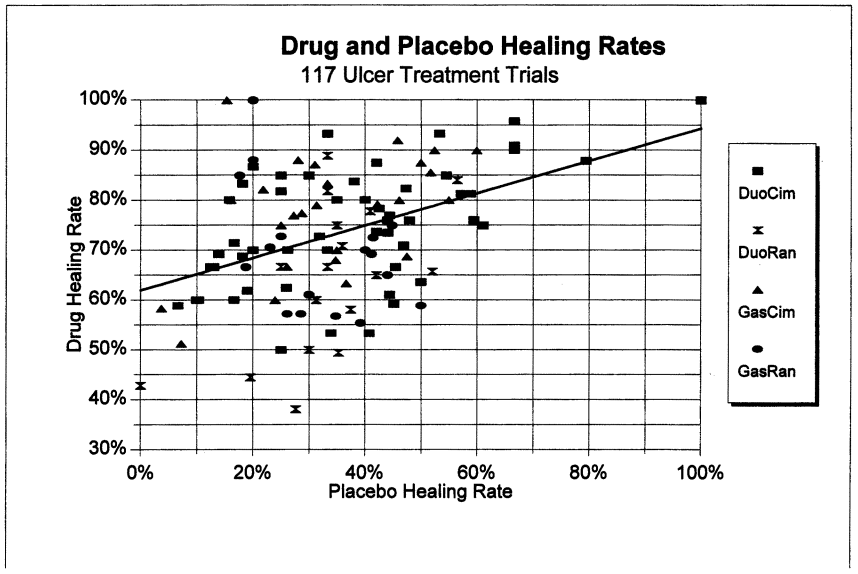

FIGURE 2.

quite terrifying, raising images of potentially catastrophic disease. The diagnosis of "ulcers," rather than, say, heart disease or cancer, is likely a calming, perhaps even therapeutic or analgesic event, reminding us of Howard Brody's classic argument that "Diagnosis is Therapy" (Brody and Waters 1980). By labeling the condition, we necessarily change it.

Another explanation is that ulcer disease is often said to be cyclical, and that ulcers often may "heal by themselves." But not always or even often; recall that over 6,000 Americans died of ulcer disease in 1994. It is often the case that gastroenterologists speak of treating ulcer patients to "hasten ulcer healing." And it is clear that medication may facilitate this process.

One study that addresses the issue is a fascinating one. A Danish group diagnosed duodenal ulcers endoscopically in 91 patients who were then subjected to "passive observation for 2 weeks," whereupon they were endoscoped again. Twenty-nine patients (32 percent) had healed ulcers in two weeks. Unhealed patients were checked again at two-week intervals two more times. By six weeks, 52 (75 percent) had healed. (Four-week healing rates, like those in most of the studies shown in Figure 1, were not reported). Can we say that these patients were "untreated?" Patients gave informed consent, although of what they were informed the report does not indicate. They received a substantial physical examination and two or more endoscopies and were asked not to consume aspirin or other nonsteroidal anti-inflammatory drugs; they were given antacids (which may have appeared to them little different than the placebos in normal double-blind trials) and were required to keep diaries noting presence of pain and antacid consumption. The authors conclude that "less than half of the ulcer patients need active treatment," although they note that they are unable to predict which half it is (Fredriksen et al.

1984). It is clear enough that these patients did not experience "nothing," and the attention they received is not well described by the phrase "passive observation."

Antacid Treatment

One assertion made occasionally is that uncontrolled medical treatment in trials like this—particularly with antacids—could account for placebo healing in ulcer disease (Keinle and Kiene 1996). Indeed, in many of the studies shown in Figure 1, patients were allowed unlimited access to antacid tablets for pain relief. The situation is somewhat different regarding ulcer pain and ulcer healing.

Antacid Treatment for Ulcer Pain. Ulcer pain is relatively easy to treat. Several gastroenterologists have argued that "it is likely that any white medicine sold as an 'antacid' will give relief of ulcer pain" (Butler and Gersh 1975:805; see also Baume and Hunt 1969).[15] Moreover, in what may have been a more daring past, researchers demonstrated that they could relieve ulcer pain with injections of sterile saline solution (Flood and Mullins 1936). Pain relief may also facilitate ulcer healing, although I am aware of no data that demonstrate this proposition. Unfortunately, there is only a modest relationship between the presence of ulcers and pain in ulcer patients; one study, for example, notes that "the severity of 'ulcer' symptoms after four weeks' antacid/placebo treatment was a poor indicator of whether the ulcer was healed or not" (Berstad et al. 1982:958, see also Peterson et al. 1977).

Antacid Treatment for Ulcer Healing. The effect of antacids on ulcer healing is much less clear than on pain relief. The standard treatment for acute ulcers from about 1920 until the 1970s was the "Sippy regimen," which consisted of hourly feeding of milk and antacids (Sippy 1915). The effectiveness of this treatment was always controversial. For example, as recently as the 1970s, a popular handbook for physicians on gastroenterology listed 16 reasons why "acid-pepsin cannot be responsible" for ulcer disease, which the author calls a "whole-body disease. The patient has trouble with people (ulcer is caused by people)" (Palmer 1975:62). In addition, a number of double-blind trials of antacid for ulcer disease have had highly variable outcomes, and outcomes in the control groups were nearly as high as those reported for the treatment groups (Gudjonsson and Spiro 1978).

In some studies, no supplementary antacids were allowed to patients in the placebo group. In one, endoscopically diagnosed ulcer patients were randomly assigned to antacid or placebo treatment; no supplementary antacids were allowed. In addition, patients were told to avoid caffeine, alcohol, and milk, but were otherwise advised to continue life normally. Twenty-four of 27 patients (89 percent) taking antacids were healed after four weeks, but so were 17 of 23 patients (74 percent) taking placebos; this is not a statistically significant difference, with $\chi 2 = 1.89$, $p = .17$ (Hollander and Harlan 1973).[16] At least six of the 117 acid blocker studies reviewed here did not allow any supplementary antacids (Collen et al. 1980; Frank et al. 1989; Mach and Bogdal 1992; Moshal et al. 1977; Salgado et al. 1981). Placebo healing rates in these studies ranged from 10 percent to 74 percent and averaged 39 percent; it seems unlikely that antacid medication can account for much of the placebo effectiveness seen in these trials.

Finally, antacids are easily available over the counter in most of the world; by one estimate for Great Britain, £30,000,000 were spent annually on antacids in the

early 1980s (Faizallah et al. 1984). Recognizing that these drugs may effectively relieve pain, one imagines that if they were all that effective for healing ulcer disease, few people would show up at the gastroenterologist's office to enter those controlled trials.

Generally, it seems that while antacid medication may reduce some of the pain of ulcer patients, it is unlikely that systematic differences in antacid consumption can account for the substantial variations in ulcer healing seen in these trials.

Other Factors

Age, Gender, and Length of Study. A few additional factors also do *not* account for differences in any substantial way. Placebo healing rates (PHR) are not related to length of study time; studies lasting four weeks have the same outcome (mean PHR = 36 percent, 86 studies) as those lasting six weeks (PHR = 33 percent, 25 studies). Age of the participants in the studies also does not affect the outcome: the correlation between average age of participants and drug healing rate is .02, and between age and placebo healing rate is .03 (neither figure is statistically significant with data available for 90 studies). Gender, likewise, has no relationship to the outcome: correlation between male/female gender ratio and drug healing rate is .05, and between gender ratio and placebo healing rate is –.21 (neither is statistically significant with data available from 82 studies).

Dosing Regimen. It is possible to show a small difference in outcome depending on the number of times per day that individuals take their placebos: 201 of 618 patients (32.5 percent) who took placebos twice a day were healed after four weeks, while 405 of 1,058 patients (38.2 percent) who took placebos four times a day were healed after four weeks; this difference is statistically significant ($\chi^2 = 5.6$, $p = .018$).

This finding is an important one in that it is the only one that I know of outside a psychological experiment,[17] and within a real medical setting, where one can see this meaning affecting outcome: "More pills, more healing." The difference, however, is obviously a modest one.[18]

National Differences. By contrast, it is possible to show a number of substantial and significant variations in outcome when studies from different countries are compared. Three studies from Brazil demonstrate that placebo healing rates there are much lower than in other countries. The placebo healing rate is 7 percent in Brazil versus 36 percent in the rest of the world ($t = 3.13$, $p = .0016$).

Similarly, the placebo healing rate in six studies in Germany averages 59 percent, twice as high as in the rest of the world ($t = 3.88$, $p = .00018$) and three times that of two of its neighboring countries, Denmark and the Netherlands, where, in five studies, it averages 22 percent ($t = 3.21$, $p = .011$).

In summary, the placebo rate is very low in Brazil and in northern Europe (Denmark, Netherlands). The German placebo rate is extremely high.

Some Other Conditions and Treatments

Are cultural variations in placebo effectiveness constants? Are the rates of placebo healing in Germany always high, and in Brazil always low? To address

this, I will briefly describe data for two other medical conditions, the treatment of hypertension and generalized anxiety disorder.[19]

Hypertension

I examined more than 400 studies of drugs for the treatment of moderate hypertension; 32 studies provided comparable data.[20] Overall, active drug treatment reduced diastolic blood pressure (DBP) by an average of 10.9 mm Hg (range 7 to 21) while placebo treatment reduced DBP by 3.5 mm Hg (range −5 to 9; in two studies, placebo-treated patients had an increase in mean DBP). Active drug treatment reduced systolic blood pressure (SBP) by 15.9 mm Hg (range 7 to 28), while placebo treatment reduced SBP by 3.9 mm Hg (range −6 to 15). The correlations between drug- and placebo-induced changes in blood pressure are modest: .20 for SBP and .10 for DBP; neither is statistically significant.

The clearest international variation in these data is opposite the findings in the ulcer data. The mean placebo group change in DBP in four German trials is .25 mm Hg, while in the remaining 29 trials it is 3.9 ($t = 2.6$, $p = .013$); one study that showed an *increase* of 5 mm Hg in DBP with placebo treatment was done in Germany. The drug group change in the German studies is the same as in the remaining trials. Hence, Germany, with the highest placebo healing rates in ulcer disease, shows the least improvement in placebo treatment of hypertension. High rates of placebo effect seem to vary by medical condition within cultures. (I was unable to find any usable trials for hypertension from Brazil.)

Generalized Anxiety Disorder

I examined over 400 studies of a broad range of treatments for Generalized Anxiety Disorder (GAD) and extracted 37 more or less comparable trials. In all of them, individuals had some approximation of GAD as defined in DSM-III or DSM-IV[21] (see section 300.02) plus an elevated score on the Hamilton Anxiety Scale (HAS), usually above 17 to 20 (of a maximum of 56).[22]

The outcome measure was the decrease in the Hamilton score. The correlation of change in HAS by placebo treatment with change by drug treatment is .39 ($p = .017$), the same as the ulcer trials; this can be interpreted to mean that the placebo effect contributes to the improvement of those patients treated with active drugs.

The mean drop in HAS in the placebo-treated groups in four Italian studies is 4.3, while the mean drop for the remaining 33 studies is 7.1 ($t = 2.06$, $p = .046$). Italians seem more resistant to placebo treatment for anxiety than others. The German studies are in the middle of the list, and the American ones are found all along the scale (two of the bottom five, five of the top seven). While there are some national variations in these data, they seem unrelated to the ones noted for ulcer treatment and for hypertension.

The Germans, with their extraordinarily high placebo rates for ulcer, have middling rates for treatment of anxiety and are among the lowest for treatment of hypertension. Just because placebo effects are high for one condition in some setting they need not be high for other conditions in that setting. Placebo effects vary between national cultures, they vary within them, and sometimes they seem to be

unaffected by national culture. Placebo effects seem to be highly variable regardless of the axis on which you examine them.

The Placebo Effect in Germany and Brazil

Among the strangest findings in this study are the very low placebo effects in Brazil and high placebo effects in Germany for ulcer disease. Why do these occur? I do not know. Colleagues and students, when apprised of the German data, often break into their best "Hogan's Heroes" accent and assert that German doctors must tell their patients that "You vill get better!" The notion that medicine is somehow more authoritarian in Germany than elsewhere is not, however, borne out by others who know more about the situation. German medicine is probably the most holistic of any western European country and shows a strong concern with emotional balance; regular spa treatment is still routinely covered by the national health care system (Maretzki 1987; Payer 1996). Germany is well known for widespread use of herbal medicines and a broad range of constitutional cures.

And the data reported here for hypertension suggest that, at least for Germany, the high or low placebo effect is not a generalized phenomenon, but specific to different diseases. For example, German medicine and culture have an unusually strong concern with the "heart" and its workings; I put the word in quotation marks to indicate that I am describing an emic category. Payer (1996) notes that Germans, but not French, British, or Americans, regularly diagnose and treat low blood pressure; in the United States, such treatment in otherwise normal individuals would probably be considered malpractice. This uncommon German view of blood pressure may be related to the low placebo effect in the treatment of *high* blood pressure there; concern about their blood pressure getting too low may inhibit their response to antihypertensive treatment.

Regarding ulcer disease, Payer (personal communication, 1999) has suggested that a variable which may account for some of these cultural variations is adherence. As noted earlier, there is evidence to show that patients who take all their placebos do better than those who do not. It is possible that there may be systematic differences in adherence among patients in different Western nations (perhaps different for different medical conditions) which might account for some of the variation in healing seen here. Or there may be persistent differences in the doctor-patient relationship or in patients' understanding of various illnesses, which can influence these different healing rates. These different factors may all be at play, and they may vary independently. For the moment, without sustained field research, there is simply no way to tell.

When I have described these findings to Brazilian colleagues, they have, essentially, denied them. "It can't be true," they have said. Further research is clearly needed to answer these fascinating questions.

Conclusions

I have shown

- that in three different conditions—ulcer disease, anxiety disorder, and hypertension—placebo effects are highly variable.

- that, in two of these cases, there is a functional relationship between placebo effects and drug effects; as placebo effects are higher, drug effects are higher.
- that at least some portion of this variation is due to factors involving what medical treatments "mean" (for example, "4 is more than 2").
- that variations in national culture can account for some of this variation.
- that more research will be required to account for these variations.

Medicine's symbolic reality is the first principle of medical anthropology (Kleinman 1973). Meaning is the inescapable complementary medical treatment, accompanying all specific treatments—pharmacological, herbal, surgical, or manipulative. Symbolic, meaningful acts in a medical context can have a substantial effect on the sick person's experience of illness; they can have a substantial effect on actual physical lesions and, indeed, on mortality. The intervening processes (in any such case) are not at all clear and likely vary in different circumstances, probably from individual to individual, from illness to illness, and probably also from society to society. To specify these processes in more detail will require a very thick description indeed, one as sensitive to immune processes and gastric secretions as it is to metaphor and symbol.

NOTES

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1. The negative effects of meaning are called "nocebo effects." I do not deal with these effects in this article, except in passing. Anthropologist Robert Hahn (1997) has written extensively about the nocebo effect.

2. The definition of *placebos* and the *placebo effect* is an extremely vexing and difficult matter. Since the essential problem (and promise) of the placebo effect appears to be getting something (healing) from nothing (inert pills), the matter seems inherently paradoxical. For a demonstration (unwitting?) of these paradoxes, see Gøtzsche 1994. The definition adopted here differs from many others in that it differentiates placebo effects from other non-drug elements of the medical process that may account for healing (some things go away by themselves, for example). It posits a cause (meaning). It is not said to be nonspecific, or, as I have said in the past, "general." Note that, if placebo effects are said to be nonspecific, and if, subsequently, the mechanisms are identified so that the effects became "specific," they would no longer be placebo effects. To specify that something (meaning, mass) has an effect (healing, gravitational attraction) is not to specify exactly what that effect is or how it happens to be.

3. It may be worth noting that many are, indeed, intensely skeptical; while the placebo effect is commonplace, it also poses a serious challenge to much of the ideology of biomedicine, in particular, the reductionist notion that disease is a mechanical phenomenon. Much of the literature about the placebo effect is, in effect, an effort to debunk, confuse, or minimize it (Gøtzsche 1994). Even much of the more positive work usually simply suggests that the

placebo effect exists, and that physicians should try to enhance its workings in their patients (Chaput de Saintonge and Herxheimer 1994, for example). Efforts to try to actually move forward our understanding of this fundamental human phenomenon are very rare.

4. This is illustrated in a rather complex study of the effect of biofeedback training on migraine headaches (Kewman and Roberts 1980). Several different training groups were established along with a group that received no training; all groups kept diaries of their headaches for six weeks. All groups, regardless of the presence or absence or effectiveness of training, had fewer headaches at the end of the study than at baseline. Diary-keeping was quite elaborate and included symptom checklists, impairment ratings, and so on; subjects were reminded with phone calls every ten days or so to continue their diaries. The one thing always associated with improvement in migraines was diary-keeping. A similar three-arm trial of treatment of nausea and vomiting during pregnancy showed that patients wearing acupressure bands, those wearing acupressure bands improperly placed, and an "untreated group" all improved over the study period; all participants kept diaries and were telephoned daily by a research assistant who recorded symptoms (O'Brien et al. 1996). Keeping a record of symptoms in a diary may be the minimal form of psychotherapy.

5. In an article that accompanied my earlier paper on this subject, Howard Brody persuasively argued that human diseases do not have "natural histories," but only meaningful and symbolic ones (1983).

6. Note that in an extended treatment of this argument, the phrase "were the same on relevant measures" would have to be unpacked; it would be shown to be a shorthand for "were the same on measures agreed upon to be construed as relevant." For a review, see Romanucci-Ross and Moerman 1997.

7. There is some evidence to indicate that the gender of clinician and patient, which may condition their relationship, may affect the outcome of treatment (von Kerekjarto 1967).

8. Thanks to my student Edward Gould for this observation. Color and form are not invariably this clear: Viagra, for example, is marketed in a blue tablet.

9. Surgery itself can have significant placebo effects that will not be reviewed here. This was first clearly pointed out by Beecher (1961). For a more recent review, see Moerman 1997. Placebo-controlled trials of surgical procedures are rare; for a recent one, see Moseley et al. 1996.

10. Similar observations of higher success in patients taking all their placebos have been made in studies of treatments for excessive cholesterol, schizophrenia, and alcoholism, and for antibiotic treatment in cancer patients. For a review, see Horwitz and Horwitz 1993.

11. A newly developed treatment for serious and otherwise untreatable angina pectoris is called "transmyocardial laser revascularization." With this technique, the surgeon uses a carbon dioxide or holmium laser to create 20 to 50 small channels on the epicardial surface of the left ventricle, small holes in the heart. Two studies in the *New England Journal of Medicine* have reported significant and sustained improvement in up to 75 percent of patients. However, in an editorial accompanying the articles, Hillis argues that there is no acceptable mechanism for how this treatment might work except a "marked placebo effect" and observes that "For laypersons and physicians alike, the word 'laser' is synonymous with state-of-the-art, successful therapy" (1999:1075).

12. An endoscope is an instrument constructed essentially of a fiber-optic tube that allows visual examination of the gut. Endoscopy is a complex procedure usually requiring anesthesia, which may have placebo effects of its own.

13. The world around, medical researchers seem to assume that people eat three meals a day.

14. Suppose 40 patients are entered in a trial of a new drug for ulcers. Half get the drug, half get a placebo. In each group, ten patients have healed ulcers after four weeks. But suppose five patients in the drug treatment group drop out of the study because the drug causes

serious headaches. On a "per protocol basis," ten of 20 (half) of placebo-treated patients are cured, while ten of 15 (two-thirds) of drug-treated patients are cured. On an "intent to treat basis," the healing rates are the same in both groups (ten of 20).

15. This may not be simply a placebo effect. It is often the case that antacid medications are flavored with mint. Mint has long been used as medication for the treatment of dyspepsia, and may have some influence on gastric pain. Various species of the genus *Mentha* and their constituents (menthol, thymol) have been listed as useful carminatives, antinausea, antivomiting, and antispasmodic agents in the United States Pharmacopoeia since the first edition of that work in 1820.

16. This study had another interesting twist. "Seven patients were switched to a [randomly selected] second batch of medications because of continuing peptic discomfort of high intensity after three days of therapy. Due to lack of pain relief after the first switch, one patient was switched twice. The sequence of switching was from placebo to placebo to placebo again. On the third batch of placebos, the patient obtained pain relief and his ulceration healed after four weeks of therapy" (Hollander and Harlan 1973:1183).

17. The (experimental) case of two red or blue pills being more effective than one has already been described (Blackwell et al. 1972).

18. Ton de Craen of the University of Amsterdam has done a similar analysis using more sophisticated statistical methods. He included studies with drugs (proton pump inhibitors, synthetic prostaglandins) in addition to ranitidine and cimetidine, but he considered only duodenal ulcers. In 80 eligible trials, 805 of 1,821 ulcer patients taking placebos four times a day (44.2 percent) were healed after four weeks, while 564 of 1,554 (36.5 percent) of patients taking placebos twice a day were healed ($\chi^2 = 20.41$, $p = .0000$) (de Craen et al., in press).

19. Data used in this section are available from the author.

20. The patients are more variable in these than in the ulcer studies: mean initial systolic blood pressure (SBP) on entry to the trial, for example, varied from 140 millimeters of mercury (mm Hg) to 200 mm Hg. Mean diastolic blood pressure (DBP) ranged from 76 to 107. Most of these studies began with some sort of "placebo washout" or "run-in" stage; in these cases, patients were given inert medication for a week or two before the study actually began. During this period, individuals whose blood pressure fell below the low-level cutoff point for entry into the study were then usually dropped. Such studies have a bias against individuals responsive to meaningful treatment. These "washout/run-in" rates can be substantial. In one study from Hong Kong, 16 of 52 patients (31 percent) originally recruited were excluded because the blood pressure dropped below entry requirements for the study after four weeks of placebo treatment (Chan et al. 1992). In a study in the United States, 125 of 507 recruited patients (25 percent) were dropped during the four-to-six week placebo lead-in phase, "most often because their diastolic blood pressure fell below 92 mm Hg" (Schoenberger and Wilson 1986:381). Note that these run-ins are "single blind," that is, the physicians, but not the patients, are aware that the patients are receiving inert treatment. The run-in phase is usually understood as a period during which other drugs the patients may have been taking are being cleared from their systems. Since physician bias inevitably leans toward some sort of treatment, even if not the ones the patient may have been taking, these substantial effects seem all the more remarkable and indicate how physiologically effective it can be for people to be entered into a trial. A rigorous study of the effects of placebo washout phases would be very interesting to do; it would be difficult, however, as the reports of washout effects in the literature are almost always incomplete and hard to interpret. Nonetheless, in all of these studies, patients were treated for hypertension with drugs generally deemed to be effective, or with inert placebos, and both groups usually responded with blood pressure declines.

21. DSM-III and DSM-IV are the third and fourth editions of the *Diagnostic and Statistical Manual of Mental Disorders*, published by the American Psychiatric Association.

They are standardized listings of characteristics of a broad range of mental disorders (American Psychiatric Association 1987, 1994).

22. The Hamilton Anxiety Scale has a number of minor variants, and sometimes investigators modify it for their particular interests, usually by deleting a question or two. Generally, as used, the scale has 14 items (Anxious mood; Fears; Insomnia; etc.), which are each rated from 0 to 4 points in terms of a series of fairly explicit definitions (Bech et al. 1986). Most of these studies of GAD have a short placebo run-in phase after which patients who have dropped below the entry boundary are eliminated from the trial; usually this is 5 or 10 percent of patients, although sometimes it is more than that. As in the case of hypertension, this biases the studies against placebo effects. After the test period, the HAS is determined again, often along with a battery of other measures of mood. A number of the trials examined included two active drugs and placebo; the active drug considered here in those cases was the more effective of the two in that trial.

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