Thirteen: Can Placebos Survive Disclosure?

Chapter Thirteen

Can Placebos Survive Disclosure?

Open placebos would tap the placebo effect without violating the dictates of transparency.

Besides inducing the side effects of the drugs they stand in for, placebos raise concern on the grounds that they may distract doctors from the practice of sympathetic attention, relieve symptoms while leaving an underlying condition untouched, turn off the alarm function of symptoms themselves, breed dependence.[1] As I have argued, the placebo effect can also validate all manner of "story-work." All in all, however, placebos perform remarkably well—perhaps only too well—considering their composition. This surprising efficacy combined with their potentially broad application in medicine helps account for the surge of research interest in placebos in recent years.

A decade after his landmark paper on "The Powerful Placebo" Henry Beecher published another no less important, "Ethics and Clinical Research," which by documenting and deploring the practice of experimenting on patients without their knowledge helped inaugurate the era of informed consent.[2] Though much experimentation on the placebo effect employs deception under the guise of informed consent,[3] and though we still hear of placebo treatments it is difficult to imagine anyone knowingly consenting to, such as the implantation of a pacemaker switched to Off,[4] in the post-Beecher era most of us believe in transparency. A saline solution that acted like a drug even though it was known to the patient to be saline solution would be a triumph of transparency. If placebos could be administered openly, the wall separating research from clinical practice would come down and medicine could exploit the manifold power of placebos that has been shown in one study after another—a power perhaps even more far-reaching than Beecher supposed. The proposal that therapists inform patients of the placebo content of psychotherapy itself is but one marker of rising enthusiasm for the possibility of open placebos.

But the findings of placebo research may not translate into clinical prac-

tice. Although research has shown that the results of sham arthroscopic surgery on the knee may rival actual surgery, I can't see myself seeking out fake surgery for an arthritic knee. Suppose, however, despite everything, that a patient who learned that fake knee surgery seems to work, and is no more dangerous than an injection, did seek it. What ethical surgeon would accommodate? He or she would refuse because sham surgery was intended not as a medical procedure but as a test of the efficacy of performed surgery, and because its success depends on the deception of the study subject. A patient seeking out sham surgery wishes, in effect, to pretend to be deceived.[5]

However, it is sometimes said that subjects don't really need to be deceived in order for placebos to work their wonders. In a notable paper published some thirty years ago Howard Brody and David Waters claim that "Even when patients are informed of the inert nature of the placebo, they may respond positively,"[6] their authority for this contention being a small study conducted in 1965 that employed no control group and was never replicated.[7] More recently David Jopling, investigating the possibility of open placebos, offered the guarded conclusion that "While this has not been the subject of much research, there is some clinical evidence to suggest that patients who are informed that they are receiving saline injections, sugar pills or other placebos sometimes continue to experience measurable objective symptom relief."[8] The evidence referred to turns out to be the same unreplicated 1965 study faulted for "a small patient sample, questionable symptom matches and comorbidity profiles between patients, an overly short treatment course, no wash-out period for potentially confounding psychoactive medications taken by patients, and no control groups (e.g. a no-treatment group)" by Jopling himself.[9] It bears noting that the fifteen "neurotics" who constituted the population of the study in question were specifically told twice that the sugar capsules they were being given helped many others with similar conditions, and that this strong recommendation was "usually repeated again, especially if the patient asked questions concerning the treatment, conveying doubtful attitudes about its possible effectiveness."[10] The invitation to experience the same benefits as others seems to have been more emphatic than the disclosure of the medical nullity of the capsules. In that the others already helped by sugar pills took them in the belief that they were an active medication, the open placebos in this study turn out to be somewhat less than open; a degree of deception was grandfathered into the study protocol. (It is also noteworthy that the study concludes that treatment with sugar capsules "could be viewed as having some affinity to psychotherapy.") While

open placebos have received very little experimental validation, the principle that we tend to experience what we believe others do has been confirmed in studies and illustrated in life at large time and again.

Recently the foremost investigator of the neuroscience of the placebo effect reported a study in which athletes treated with morphine in training but placebo on the day of competition responded to the placebo as if to the drug, a carry-over that raises the possibility of achieving "drug-like effects without drugs" in real-world conditions. However, the experiment hinged on a deception. Far from receiving truthful information, placebo groups were told on the last day that they were getting morphine and should expect an increase in pain tolerance—a strong message indeed.[11] Even given our impressive capacity for self-deception, it does not seem credible that athletes in the real world, looking to circumvent doping regulations, would train with morphine the better to fool themselves into mistaking placebo for morphine at a later date. (Writes a medical commentator on the placebo effect, "I doubt that one could give oneself a placebo.")[12] Elsewhere the author cites a body of research showing that expectation strongly influences placebo analgesia, which is to say that placebos engender analgesic effects in good part because we expect them to behave like the active drugs we mistake them for.

Placebos score high in clinical trials of antidepressants. Of interest, therefore, is the postscript of a study of placebo antidepressant in which the subjects were eventually informed that they were in fact in the placebo group. According to the study director,

> At eight weeks . . . you couldn't tell [the treatment and placebo groups] apart in terms of mood ratings. What happened at eight weeks plus a day is a bit different. Some of the placebo responders, when told they were on a placebo, had a deterioration of their mood. In fact, most of them did. Within a month, most of the placebo responders had enough depressive symptoms that they actually ended up on medications.[13]

While this result will disappoint those who believe the placebo effect can survive unblinding, it seems consistent with the body of placebo research. (And with common experience. Now that the mineral waters of Bath are known to have no curative value, people no longer flock to Bath to enjoy their benefits.) If placebos didn't depend on concealment, it is hard to see why their use in research would be so bound up with concealment.[14] Similarly, while placebos in one guise or another are used in clinical practice, only rarely are

they prescribed openly. A recent survey of Canadian doctors found that while somewhere over half said that they used placebos now and then, only five percent reported "telling their patients that they were receiving a placebo."[15] Why would so many conceal the placebo, thereby putting themselves in violation of ethical principles written or unwritten,[16] unless its efficacy depended on concealment?

Unless and until it is refuted by robust evidence from replicated experiments, the presumption must be that placebo responses to medications, especially for pain, do hinge on deception. A challenge to this presumption is an unusual study of some 26 children with ADHD reported in 2008. To determine if part—not all—of their medication could be replaced with placebo, researchers offered the children, who were supervised by their parents, certain capsules along with a clear explanation that they contained no drug but might boost the effect of regular medication. Persuaded of the power of placebos but opposed to deception, the researchers explicitly assumed that revealing the placebo in this way would not destroy its efficacy. "We hypothesized that disclosure would not eliminate the placebo effect." Though the assumption was confirmed, the published study contains the following weighty disclaimer: "This pilot study has important limitations, including very short-term treatment outcomes and relatively few subjects. The outcome measures are inherently subjective and the open-label study design introduces the potential for bias. Teachers were the only blinded raters during the study, and the teacher data did not show significant differences in child behaviour among the [experimental] conditions."[17] As in this case, enthusiasm for open placebos tends to run well ahead of the evidence.

A similar ADHD study had the placebo disclosed to children as young as six.[18] Can a child of six understand something as paradoxical and bewildering as an inactive substance that happens to be active? For their part, children from ten to twelve in this study were told,

> This little capsule is a placebo. Placebos have been used a lot in treating people. It is called 'Dose Extender.' As you can see, it is different from Adderall. Dose Extender is something new. It has no drug in it. I can promise you that it won't hurt you at all. It has no real side effects. But it may help you to help yourself. It may work well with your Adderall, kind of like a booster to the dose of Adderall. That's why it's called a Dose Extender. I won't be surprised when I hear from you and your parents and your teachers that you're able to control your ADHD better.[19]

The open placebo turns out to be a highly leading rigmarole. Note too the suppression of the critical fact that the placebos "used a lot in treating people" are not known to them to be placebos.

In another defense of open placebos that comes up short, a group of researchers in 2007 conducted two studies designed to determine whether "learning that pain reduction is the consequence of a placebo treatment reduce[s] responses to subsequent placebo treatments." The second of these experiments "employed repeat sensory testing after participants were informed about their previous placebo response, allowing for assessment of the effects of such knowledge on subsequent placebo responding." At a certain point in this pain study, then, subjects in the placebo-informed group were notified that they had actually received a placebo cream. However, they were then told that they would now receive an active cream, while in truth they received the placebo for a second time. They continued to respond as before to the sham medication. "Interestingly," conclude the authors, "the placebo effect persisted when a second placebo cream was applied even after participants were told that the first cream used in the study was a placebo. Although the strength of that second placebo was slightly reduced, approximately 84% of the original placebo effect remained."[20] But surely this does not establish the efficacy of an open placebo. On the contrary, the subjects were specifically told the second time that they were being given an active medication. They were lied to. They fell for the lie presumably because the researchers made themselves appear honest by confessing that the first administration of the cream was a sham. The experiment in question was a study of the possibility of fooling someone twice.

As this case illustrates, placebo research sometimes converts the very disclosure of information into an act of equivocation.[21] Often, it seems, a placebo is craftily described to induce study subjects to mistake it for an active drug. Thus, for example, in a study investigating the effect, if any, of verbal suggestion on analgesia, a number of patients suffering from irritable bowel syndrome were told, "The agent you have just been given is known to significantly reduce pain in some patients"—the magic words—when in fact they had been given a placebo. This invitation to feel what others feel, which resembles in outline the sales pitch for the Perkins tractor used by experimenters two centuries ago and appeals powerfully to our social nature, was intended specifically to arouse an expectation of pain relief, in contrast to a similar study in which patients were truthfully informed that they "may receive an active pain-reducing mechanism or an inert placebo agent." Though

it is highly unlikely that the patients interpreted the pitch to mean they would receive a placebo—after all, it was phrased to create exactly the opposite impression—the authors contend that because the placebo did work in a previous study, their statement wasn't really a lie. On this lawyerly claim they ground the inference that verbal suggestions for pain relief in general "need not be deceptive and thereby ethically problematic."[22]

As in this instance, the principle that we tend to feel what others do, and expect the therapies that help them to help us, crops up in proposals for the ethical use of placebos. A proposal for the use of placebos in clinical practice suggests that doctors offer placebos to depressed patients with cover language like the following: "I do not know why you are depressed—modern medicine does not understand depression very well. It could be that you have a chemical imbalance or it could be due to stress in your life. Trials have found that 60% of patients feel significantly better when they take an antidepressant, so that is what I am prescribing for you."[23] This statement, which logically resembles a sort of private joke, conceals the cardinal fact that the antidepressant being prescribed contains no active ingredient at all: yet another careful equivocation. Also exploiting ambiguity, some doctors now recommend "probiotics" that certainly sound to the lay ear like medications, but for which there is little or no evidence of efficacy. Popular with consumers and believed to be harmless, these commodities fit the profile of a placebo and are probably discussed in doctors' offices with the same craftiness.

Some believe, however, that under certain conditions placebo-prescribers could dispense with disguise. According to a philosopher,

> Were the general efficacy of placebos well accepted, and, in particular, were it well recognized that successful treatment by placebo does not indicate that an illness is merely imaginary or that the patient is of a peculiarly gullible or dependent personality type, there would be no reason for deception in their administration. In those cases where placebos may reasonably be expected to be useful, and where pharmacologically active agents are ineffective or contraindicated, a physician could simply report to a patient that the prescribed agent appears to be pharmacologically inert with respect to his or her disorder, but that *in fact*, it has been shown to be therapeutically effective in other patients suffering from the condition.[24]

The suggested script—"the prescribed agent appears to be pharmacologically inert with respect to . . ."—still has a certain studied obscurity. But why is

it that the line that "others have benefited" suggests itself to the defender of open placebos? No doubt because it is the strongest recommendation of an inert treatment that could be given with technical veracity. Addressed to our social nature, it is a tribute to the principle that we model our experiences on the reported, imagined, or presumed experiences of others. Note that the philosopher's argument assumes not the efficacy of placebos per se but public acceptance and recognition of their efficacy, so that candidates for placebo treatment will "simply" be asked to believe the same things that others generally do. Placebo efficacy under these conditions might turn out to be a pyramid scheme, with people investing belief in inert treatments because others do the same, until the entire structure collapses.

Unlike studies in which supposedly open placebos turn out to be cloaked in artful language, a recent study of placebo treatment of irritable bowel patients saw the treatment group given pills described as being inactive "like sugar pills" and explicitly labeled as placebo. After three weeks, 59% of patients treated with the placebo reported adequate relief as compared to 35% of the untreated control group—a finding qualified by a number of limitations laid out in the report of the study itself. Like Natasha in *War and Peace* who takes solace in the ritual of regular dosing ("though she declared that no medicine would cure her and that it was all nonsense"), the study subjects may have responded to the medication ritual that was withheld from the untreated group. Unlike Natasha, though, the study subjects had reason to believe their pills were effective, whatever they were labeled as. Potential subjects were told that half the study population would receive inert pills "which had been shown to have self-healing properties" [sic] and those entering the study that "placebo pills . . . have been shown in rigorous clinical testing to produce significant mind-body self-healing processes," so that the group that proved so responsive to placebo received a double dose of the message that others are known to benefit from the placebo pills and they can expect to as well.[25] Not that placebos actually "heal"—that is, cure—IBS; at best they alleviate symptoms.

If open, rather than deceptive, placebos had already been shown in rigorous testing to be therapeutic, there would have been no need for the experiment; it would have been redundant. The experiment does not establish that pills frankly described as containing no medication can have beneficial results. At best, it opens the possibility that placebos revealed as such, but hyped as having some kind of "healing" power and extolled as being of proven benefit to others—who in all likelihood believed them to be active

medications—may have beneficial results. In effect, then, the study put into operation the principle that if only people generally accepted the efficacy of placebos and the legitimacy of using them, they would no longer require deception. Ideologically, it is in the tradition of More's Utopia, where medicine is all but unnecessary, people think alike, and everyone lives "in the full view of all,"[26] without the need or even possibility of concealment. Just as the Utopians honor medicine highly but are less in need of it than any other people (so More tells us), the use of open placebos will enable "healing" without the use of medicine.

Some seem to believe, similarly, that by making the patient's condition comprehensible and pointing to something to remedy it, the very act of diagnosis constitutes a treatment. Diagnosis

> is medicine's way of explaining symptoms. The extent to which the explanation will satisfy the patient will depend on the extent to which he shares the physician's presuppositions about what sorts of things cause and contribute to disease and healing. Secondly, the diagnosis is often a crucial factor in encouraging the expressions of caring and support from family and friends. Before the patient's changed behavior has been given the interpretive label of a diagnosis, others may be uncertain as to how to react to him or her; but once the physician as the authority figure has legitimized the behavior with a diagnosis, the patient has "a mantle of distress that society will accept." Thirdly, the ability to give something a name implies the ability to gain control over it. This is true both in magical belief systems, where words and names have special powers in and of themselves, and in scientific belief systems . . . [27]

What's in a name? A great deal, evidently. Note, however, that the authors do not concern themselves with the possibility of a mistaken diagnosis, evidently because the act of diagnosis per se is therapeutic, whether medically accurate or not. But surely something is wrong with a medical argument indifferent to the possibility of a diagnosis itself being wrong.

In view of the risks of offering diagnosis per se as a treatment, and the ethical traps of using placebos in ways that seem open but perhaps aren't, or of disguising them as active medications (as in the prescription of drugs at sub-operative doses), the best and least controversial way to exploit the placebo effect in medicine is surely the humane, attentive practice of medicine itself. By consensus, after all, the manner and behavior of doctors contribute

richly to the "power of context" that frames the placebo effect. A study of the differential components of the placebo effect among patients with irritable bowel syndrome found the most potent contributor to be the quality of the relation between physician and patient, as measured not only by time spent with the patient but the projection of both confidence and sympathetic concern.[28] Perhaps if doctors were less hurried and more attentive to care as well as cure, interest in placebos as short cuts to health would not be running so high. If it is really nothing but a "reaffirmation of man's essential tie with his sociocultural nexus" as some theorize,[29] then the placebo pill, the subminimal dose, the probiotic, is secondary to the actual bond between patient and doctor anyway. If the power of context activates the pill—and some now refer to the placebo effect as a context effect—perhaps in some cases we can forego the pill and make do with the context.

In the course of the second of the ADHD studies cited here, subjects formed "strong relationships" with the medical team, while parents became "more attentive" observers of their children.[30] Given these circumstances, it is entirely possible that social bonds are the really operative factors in the study—that the power of context is speaking through the Dose Extender. The cardinal health benefits to come to us through social channels actually go quite beyond the effects imputed to a pill. As noted, in a number of studies social connection—marriage, bonds with extended family, and other forms of affiliation—correlates inversely with the risk of mortality itself.

Belonging to a family is a more robust form of membership than participating in a trend or even movement, though "the negative or conflictive aspects of social relationships need also to be considered, since they may be detrimental to the maintenance of health,"[31] as both medical literature and the literature of the imagination well know. In any case, it is impossible to be married without knowing it. There can't be a clinical trial in which one group believes itself married but actually isn't, while another is actually married but is led to believe otherwise. The question of deception does not and cannot enter into the matter of social connection. In More's ideal commonwealth there is no need to resort to medical trickery because the social institutions of a closely integrated people serve as the guarantors of health.

In keeping with the principle that social bonds enhance health, and more specifically with the theory that "Positive emotions and ideas can help to heal

the body through the powerful placebo effect"[32] (a theory that may or may not be utopian itself), studies have investigated whether support groups improve survival for breast-cancer patients. At first it appeared they might—a result doubly to be welcomed, first of course for its own sake, secondly because this mobilization of the placebo effect was achieved without deception of any kind. The tested treatment consisted of a series of sessions "designed to build new bonds of social support, encourage expression of emotion, deal with fears of dying and death, help restructure life priorities, improve communication with family members and healthcare professionals, and enhance control of pain and anxiety."[33] Naturally this "supportive-expressive group therapy" was not advertised as something else; disguise was neither possible nor necessary. Later, however, it was found that the survival benefit associated with the therapy could not be replicated[34]—a reminder that the benefits of social bonds have their limits, that it is one thing to inhibit suicide, as Durkheim found, and another to arrest cancer, and that transparency, however desirable ethically, may have no particular therapeutic merit.[35]