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Commentary on Benedetti et al. (2003)

Expecting That a Treatment Will Be Given When It Won't, and Knowing That a Treatment Is Being Given When It Is

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ABSTRACT
Research on psychosomatic interactions and placebo effects forms the background for a commentary on a comparison of "open" versus "hidden" medical treatments. While contemporary medicine appears to be striving for increasingly impersonal techniques for prevention and treatment, these studies show that patients' knowledge, beliefs, and expectations can make a difference to outcome.

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A couple of years ago, I served on a committee to review the training of researchers on health and health care, which ended up recommending increases in funding for physician researchers, and for work in

neuroscience and other multidisciplinary areas, but no new funds for the behavioral and social sciences (National Research Council, 2000). I thought this was a very bad idea and argued vigorously for the importance of psychosocial processes in both health and health care, and the need to redirect behavioral and social scientists into research on health and health care (see Appendix F of the committee's report). In 1990, for example, behavioral and social factors such as tobacco use, diet, and activity accounted for about five times as many premature deaths as did microbial and toxic agents (McGinnis & Foege, 1993). More than two decades after the identification of AIDS and the isolation of the HIV virus, there is still no cure and no vaccine, but psychosocial interventions have effectively reduced the incidence of HIV-related sexual risk behaviors, and "altering behavior" remains "the primary way to control the epidemic" (Coates & Collins, 1998, p. 96).

At one point in the discussion, I raised the issue of compliance: It was all very good to create new and more effective medications to treat various diseases, but then you had to get people to *take* the pills, and that proves not to be so easy (Gochman, 1997; Sackett & Snow, 1979). As many as 50% or more of patients take prescribed medicines improperly, if they take them at all, and the situation is likely to be even worse when it comes to the treatment of mental illnesses, or behavioral approaches to the prevention of illnesses of any kind. In response to this information, one committee member retorted, "We'll make a pill for that, too!"

It was a good joke, but it also revealed a fundamental disconnect between biomedical scientists and behavioral and social scientists in their approach to issues of health and health care. Throughout the scientific revolution in medicine, from the experimental medicine of Claude Bernard and the microbe-hunting of Louis Pasteur and Robert Koch in the 19th century (Magner, 1992; Porter, 1997) through successive phases of the pharmaceutical revolution of the 20th (Calfee, 2002), the emergence of laboratory diagnostics and the development of imaging techniques (Cunningham & Williams, 1992), the Human Genome Project (Murray, Rothstein, & Murray, 1996), and the advent of pharmacogenomics (Licinio & Wong, 2002), a major trend of biomedical research has been to develop diagnostic and therapeutic techniques that minimize human social interaction between physician and patient. The ideal seems to be to develop a *feinberger*, the hand scanner that Dr. McCoy used in *Star Trek* to diagnose and treat illnesses,[1] without any need to consult with the patient, make any judgment about symptoms and test readings, choose among therapeutic options, or take account of any psychosocial dimension of illness, prevention, or treatment.

Psychosomatics

A case in point is the sorry reputation of psychosomatic medicine, which is concerned with the role of emotional or other psychological factors in organic pathology. The psychophysiological disorders used to have their own special place in the diagnostic nosology, but they have been replaced by the somatoform disorders, which do not involve underlying organic pathology, and relegated, shorn of their glorious name, to the back of the *DSM–IV* ("316, Psychological Factor Affecting Medical Condition"; American Psychiatric Association, 1994). Commenting on the discovery of the role of *helicobacter pylori* in gastric ulcers, Steven Hyman, a molecular neuropsychiatrist who was then director of both psychiatric research at Massachusetts General Hospital and Harvard's Interfaculty Initiative on Mind, Brain, and Behavior,

and soon to become director of the National Institute of Mental Health (and now back at Harvard, as provost), wrote an article gleefully entitled “Another One Bites the Dust” (Hyman, 1994). In the brave new world of biomedicine, mind is to be replaced by brain, thoughts and emotions are to be replaced by genes and molecules, behavior is an effect, not a cause, and society and culture are out of the picture entirely.

One does not have to embrace the psychoanalytic proposition that, for example, rheumatoid arthritis was a symbolic manifestation of rebellion against restrictive parental influences (Alexander, 1950) to mourn the fact that the very idea that psychosocial factors might play a causative role in medical illness is so contemptuously dismissed (Ader, 1994). In fact, Hyman’s verdict appears to have been premature. Although one study found *h. pylori* in the guts of over 90% of patients with gastric or duodenal ulcers, it also found the bacterium in almost 80% of ulcer-free controls (Nomura, Stemmermann, Chyou, Perez-Perez, & Blaser, 1994). Even Barry Marshall, who originally discovered the link between *h. pylori* and ulcers, has expressed doubt that the former causes the latter (Marshall, 1995). Furthermore, carefully controlled experiments with an animal model of gastric ulcers show a clear causal role for experiences of unpredictability and uncontrollability (the psychological definition of stress; see Mineka & Kihlstrom, 1978) in their origin (Overmier & Murison, 1997, 2000). *H. pylori* is a risk factor for ulcers, but so is psychological stress. **Note change, for emphasis.**

Placebos

The reluctance to acknowledge the role of psychosocial factors in health care is also evidenced by recent literature on placebos (Harrington, 1997; Shapiro & Shapiro, 1997). The placebo effect has been called the jewel in the crown of psychosomatic medicine because it reveals the effect of physicians’ and patients’ attitudes, beliefs, and expectations—that is, that they are providing and receiving effective treatments—on medical outcomes. Since the seminal studies of Beecher (1955), the placebo effect has become so firmly institutionalized that the placebo control has become the gold standard of clinical trials (Zivin, 2000), and we have even begun to see a revival of interest in sham surgery (Moseley et al., 2002). In this journal, Kirsch and his colleagues have gone so far as to claim that 75%–80% of the effects of antidepressant medications are due to placebo (Kirsch & Sapirstein, 1998, 2002). A cover article in the *New York Times Magazine* reported “Astonishing Medical Fact: Placebos Work!” and went on to asked why the placebo effect should not be deliberately exploited in medicine (Talbot, 2000).

At the same time, it is clear that the placebo effect is treated by medical researchers as more of a nuisance than a worthy phenomenon in its own right. New drugs are approved for use if they prove to be better than placebos—on at least two trials, no matter how many trials it takes to reach statistically significant differences. But that is as far as most studies go, and there is a general reluctance to give placebos any credit at all. How else to explain the reaction to a paper by Hrobjartsson and Gotzsche, published as a “special article” in the *New England Journal of Medicine*, which claimed that the placebo effect in the studies they reviewed was barely distinguishable from the changes observed in no-treatment control groups—in other words, that placebos are powerless after all (Hrobjartsson & Gotzsche, 2001b, 2003)? Within a week, the *Wall Street Journal* published a commentary touting the article as a refutation of the

“Dale Carnegie school of medical thought” (Dalrymple, 2001). Other newspapers reassured their readers that the placebo effect is a myth or a mirage (Greene et al., 2001).[2]

Hrobjartsson and Gotzsche are certainly right that a proper evaluation of placebo effects requires comparison with a no-treatment control, in order to distinguish them from spontaneous recovery and regression to the mean. I think it is testimony to the lack of interest in the placebo effect, *as an effect*, that out of all the thousands of placebo-controlled randomized clinical trials that have been performed and published, these investigators were able to find 114 studies that included such a condition. But there are other ways to evaluate placebo effects, and these kinds of studies indicate that beliefs and expectations can, in fact, play a salient role in treatment. For example, placebo injections are more powerful than placebo pills (De Craen, Tijsse, de Gans, & Kleijnen, 2000); placebos taken four times a day are more powerful than placebos taken two times a day (De Craen et al., 1999); and red and yellow pills make better stimulants, while blue or green pills better tranquilizers (De Craen, Roos, de Vries, & Kleijnen, 1996). Studies employing the balanced placebo design (Rohsenow & Marlatt, 1981) indicate that beliefs and expectations can moderate the effects of drugs on both subjective experience and objective endpoints (Hull & Bond, 1986; Kleijnen, De Craen, van Everdingen, & Krol, 1994). Asthmatic subjects inhaling a saline mist show bronchoconstriction when told they are inhaling a bronchoconstrictor, and bronchodilation when told they are inhaling a bronchodilator (Luparello, Lyons, Bleecker, & McFadden, 1968; Pastorello et al., 1987a, 1987b). These sorts of studies show that not only is there a placebo effect but that the placebo effect can be manipulated to the patient’s advantage.

Some years ago, Evans reported that the magnitude of the placebo effect in pain reduction was a constant percentage (roughly 55%) of the effectiveness of the active agent with which placebo was being compared (Evans, 1974). A placebo believed to be aspirin is half as effective as real aspirin, but a placebo believed to be morphine is half as effective as morphine. McQuay and his colleagues misinterpreted this finding as suggesting that randomized clinical trials are not really blind (McQuay, Carroll, & Moore, 1995), but the point of Evans’s analysis is that physicians *always* know what drugs (they think) they are giving, and patients *always* know what drugs (they think) they are taking, and these beliefs have an effect on outcome. When these critics repeated Evans’s analysis, they confirmed his result almost to the decimal point. Kirsch and his colleagues have found a rather different constant (closer to 75%) for the placebo effect in the treatment of depression, but that only means that people have different expectations about the relief of pain than they do about the relief of placebo (Kirsch & Sapirstein, 1998, 2002). In any event, the fact that different placebos have different effects shows clearly that there is a placebo effect. If drugs are better than no treatment at all, so are placebos.

Open and Hidden Treatments

This literature formed the deep cognitive background for my reading of the study by Benedetti and his colleagues, who turned the balanced placebo design inside out—or, at least, rotated it 90 degrees (Benedetti et al., 2003). The result was clear evidence that patients’ response to a treatment was greater when they knew the treatment was being delivered than when they did not. This was the case for subjective endpoints, such as postoperative pain and anxiety, but it was also true for objective endpoints,

such as motor control in Parkinson's patients and cardiac activity in healthy volunteers given propranolol or atropine.

Benedetti et al. may be a little too hard on themselves when they list various "confounds" in their study: awareness of the treatment, the presence of the therapist (who is also aware of the treatment), and the expectation of the outcome. These are not confounds in the usual sense of variables that are mistakenly left uncontrolled in an experiment—such as, for example, the possibility that subjects got more drugs in the open conditions than in the hidden ones. While it might well be interesting to conduct further research in which, for example, the patient is aware that a treatment is being given but the therapist is not, as a practical matter of medical treatment these are all part of the package. I would be particularly interested in the role that prior experience (of morphine, subthalamic stimulation, propranolol, or atropine) has on mediating the differential response to open or hidden treatments. What happens when patients know they're being treated but have no detailed expectancies as to what will happen?

Potentially more serious is the possibility that some form of response bias might be involved in the effects on subjective outcomes. The fact that there are similar effects for objective outcomes is somewhat reassuring. Although it would be an easy matter for healthy subjects to deliberately speed up or slow down their heart rates, I suspect it is somewhat more difficult for Parkinson's patients to voluntarily control their hand movements. The question of whether psychosocial manipulations have effects on objective, biological endpoints as well as subjective, psychological endpoints is one that often crops up in the placebo literature as well—even Hrobjartsson and Gotzsche found greater placebo effects for subjective than for objective endpoints (Hrobjartsson & Gotzsche, 2001b)—and certainly further research on open versus hidden treatments is in order.

I am not so concerned about the apparent discrepancy between the present results, which show that open morphine is more effective as a painkiller, and the results of animal research, which show that signaled morphine is less effective in rats (Siegel & Ramos, 2002). It may be true that expectancies are more important to the behavior of humans than of nonhuman animals, but it's also true that conditioning in rats is mediated by expectancies (Kamin, 1969). It may well be that the physiological processes underlying tolerance can be conditioned to environmental cues, such as a signal that morphine is being delivered, but it is also true that the signaling conditions are very different in the two cases. For rats, who do not have the benefit of linguistic communication, the signal is learned relatively slowly, over a period of direct experience with the contingencies of the classical conditioning experiment. For humans, the signal is "learned" immediately, in the single "trial" in which the doctor tells the patient that the drug is coming. The two situations are so different that it's not clear that there is any sort of generalization gap.

Benedetti et al. (2003) are right to point out that their findings are not exactly placebo effects, in that no placebos were actually used in their experiments. Nevertheless, their findings effectively remind us that every treatment has a placebo component involving expectations and beliefs. The impact of these factors can be evaluated—for example, by means of placebo-controlled clinical trials—but they cannot be eliminated. This is true for medical treatment, whether it involves drugs or surgery, and it is true for psychotherapy, whether psychodynamic or cognitive–behavioral. As much as doctors might like to have a feinberger, they still have to interact with their patients, and their patients still bring to treatment a fund of beliefs, knowledge, and expectations—call them health cognitions—that affect the course of treatment.

Rather than viewing this as some sort of nuisance that can be minimized as more effective medical and surgical treatments are developed, perhaps physicians and therapists should deliberately and actively mobilize the psychosocial context, including patients' knowledge, expectations, and beliefs, to make these treatments even more effective than they would otherwise be.

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Footnotes

[1] I am grateful to "Trekkinguy," who maintains a website devoted to the original *Star Trek* series (http://www.geocities.com/Area51/Nebula/8690/), for providing this information (personal communication, April 12, 2003). In fact, *feinberger* was the generic name given to many of the devices used in the series, after Irving Feinberg, the prop master who designed them. The term *feinberger* appears frequently in summaries of individual episodes (just do a Google search), and apparently McCoy actually refers to his device as a feinberger on at least one occasion.

[2] Clearly recognizing what was at stake, *Advances in Mind–Body Medicine* published a symposium (Ader et al., 2001) in which the contributors picked at the study on every conceivable methodological ground—but also giving Hrobjartsson and Gotzsche an opportunity to reply to their critics (Hrobjartsson & Gotzsche, 2001a).