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Once, doctors prescribed crocodile dung, fly specks, and eunuch fat: patients came back for more, because they wound up feeling better.

I'm the doctor and you're the patient: I tell you I'm giving you something to make you feel better. You take it and, sure enough, you do feel better. Yet there's nothing in what I gave you to account for it. Maybe it's an injection of salt solution, which can relieve severe surgical pain by no physiological mechanism known to medical science. Or a sugar pill, which logically, pharmacologically, or any other way can have no effect, for good or ill, on the common cold. But it does anyhow: That's the placebo effect.

In his famous 1955 review of 15 placebo studies, which involved 1,082 patients suffering from conditions that ranged from headache and seasickness to wound pain and the common cold, pioneer placebo researcher Henry K. Beecher found that placebos worked about one third of the time, or to use the precise figure cited frequently since, "35.2 plus or minus 2.2 percent."

Consider this: A research team at the University of California at San Francisco (Jon D. Levine, Howard L. Fields, and two others) in 1980 reported that, on average, a placebo packed the pharmacological punch of a four to six milligram dose of morphine in treating the pain of tooth extractions.

Or this: In a clinical trial during the early 1960s, surgeons tied off certain arteries of patients suffering from anginal pain. The idea was to improve circulation to the heart. It worked, or seemed to; patients reported at least 60 percent relief from pain. But this pleasing result was tainted when mock "operations" in which the skin of patients was cut, leaving a scar, while internal organs were left untouched—an experimental control involving a form of placebo surgery not apt to be condoned today—achieved almost identical results.

A placebo's effects needn't be beneficial: Placebos have been found to elicit side effects ranging from headache and drowsiness to nausea and a "warm glow," just like pharmacologically active drugs. And they can be addictive: In one famous case, colored pills—a "new major tranquilizer," she was told—were given to a 44-year-old schizophrenic woman. They did help relieve her headache, insomnia, and anxiety. But after a while, she started doubling and redoubling her dosage. Pretty soon she was taking 25 tablets a day and couldn't stop without psychiatric help.

But by and large, placebos do leave patients suffering less. In one 1965 study conducted at Johns Hopkins Hospital by Lino Covi and Lee C. Park, both now associate professors of psychiatry, 14 out of 15 patients declared that the inert pink pills they'd been given to treat their neurotic symptoms had helped. In fact, four of the 15 rated them "the most effective ever prescribed for them"—although they'd been *told* they were receiving sugar pills. In at least one instance, a placebo effect has even reversed the effects of an active drug: When, in the early 1950s, a pregnant woman in a New York hospital complained of nausea, her physician, Stewart Wolf, gave her a drug he assured her would cure it. Sure enough, the nausea disappeared. The medicine he'd given her? Ipecac, normally given to *induce* vomiting.

Like other medicines, a placebo may or may not work; the "placebo effect" is what happens when it does. It may be prescribed to actually help the patient. Or it may be used as a control in the clinical trial of some drug or treatment. It may be a small green pill, or a big impressive red capsule; size, shape, and color don't seem to matter. It may be an injection. It may be superficial surgery whose only effect is to leave a scar. It may succeed in lowering the pulse, or causing gastric juices to secrete, or easing depression, or reducing pain. It is, in short, the form of treatment without its substance; yet it can achieve substantive results.

Placebos work on some of the people some of the time, but not on all the people all the time. Is there one kind of person who responds to placebos and another who doesn't? Is there, in short, such a thing as a "placebo reactor"?

Though students of the subject disagree, the more widespread view these days is that there is not. The fact is, some studies find that females respond to placebos more than do men, others the reverse. Some studies find correlations with IQ, while others do not. And many people respond to placebos at one time but not another.

There are, however, certain paradoxical consistencies about the *situations* in which placebos tend to work. First, placebos are clearly more effective in easing clinical pain than experimentally induced pain—by one crude measure about twice as effective, according to Michael Jospe in *The Placebo Effect in Healing*.

Magic Medicine

"The doctor gave me something. Now I feel better."

Second, placebos work better on severe pain than they do on mild pain: In one study by Beecher, a placebo was only 29 percent as effective as a standard dose of morphine on patients with "mild" pain, but 77 percent as effective on patients with "very severe pain."

Finally, there is "the Anzio effect": Soldiers badly wounded on the beachhead at Anzio, one of World War II's bloodiest battles, and removed to rear positions for care, complained far less often of pain than do typical hospital patients recovering from surgery. Placebo pioneer Beecher, who first took note of the discrepancy, found that less than a third of the wounded soldiers complained of enough pain to require morphine. But morphine was needed by four out of five civilians recovering from analogous wounds incurred in surgery.

What to make of it all? The interpretation fashioned by Beecher, and now widely accepted, is that pain has two distinct components. One is associated with the original source of the pain. The other factor superimposes on the sensation itself the patient's fears, anxieties, and ignorance about his situation. GIs pulled to safety at Anzio were relieved at having survived the battle and now perhaps being on their way home, thus easing their pain. Surgery patients on the other hand, plucked from home and family and subjected to a hospital ordeal, generally feel a heightened anxiety. The anxiety compounds their pain.

Likewise, the kinds of experimental pain inflicted on willing subjects, through electrical shock and other controlled means, mostly lack that secondary component of pain that intensifies suffering: They carry no ambiguity and fear. That holds for mild pain of any sort, like that from a scratched thumb. Its victim is apt to be aware of the pain, yet not concerned.

It's this second component of pain, then, that the placebo is thought to reduce. Acting not upon the wound itself, but rather easing the patient's emotions about it, it lessens its perceived intensity. This "cognitive" dimension is what NIH researcher Ronald Dubner also comes back to in trying to explain the placebo's salutary effects—not just on pain but on all manner of physiological and psychological conditions. "The meaning of the pain changes because you get a placebo," he says. "What you're altering is not the intensity of the sensation but the relative unpleasantness of the situation as a whole.

"Since it doesn't do anything, it won't be easy to get people to take it every day. There's just no demand for a preventative placebo."

The Placebo

by Robert Kanigel

"Find out who set up this experiment. It seems that half of the patients were given a placebo, and the other half were given a different placebo."

The placebo alters the meaning of the experience: 'The doc gave me something; now I feel better.'"

Once, of course, placebos were virtually the only treatment physicians prescribed. Once, before CAT scans and penicillin, doctors prescribed crocodile dung, teeth of swine, fly specks, oil of ants, fur, feathers, and eunuch fat. They purged their patients, punctured them, blistered them, bled them, froze them, and shocked them. Remarkably, patients kept coming back for more. Came back because they wound up feeling better. Came back for something in those few moments with witch doctor, faith healer, or physician, something in his healing touch, that left them better off—freer of symptoms, further from death—than they'd been before.

"Today we know," writes veteran placebo researcher Arthur K. Shapiro of Mount Sinai Hospital in New York, "that the effectiveness of those procedures and medications was due to psychological factors often referred to as the placebo effect. Since almost all medicines were until recently placebos, the history of medical treatment can be characterized largely as the history of the placebo effect."

But then along came modern medicine: Antibiotics do not depend for their potency on the personality of the physician administering them, or the kindness he shows, or the ritual setting in which he renders treatment. The old remedies, meanwhile, which worked only some of the time and in mysterious ways, were by and large discarded. And the placebo effect itself, whose potency had masked their ineffectiveness? As if guilty by association with crocodile dung and bleeding cups, it came to be "considered merely as a variable to be controlled," as one revisionist commentary in the *Journal of the American Medical Association* noted in 1975, and so "ignored."

Coming from Latin, the word placebo translates as "I shall please." After the Middle Ages it came to mean a servile flatterer, sycophant, or toady. By 1811—it appeared that year in *Hooper's Medical Dictionary*—it was being used about as it is today, complete with faintly unsavory aroma, as an "epithet given to any medicine adapted more to please than benefit the patient."

Contempt dogged the subject, and in some quarters still does. Around the turn of the century, the eminent Harvard medical ethicist and physician Richard C. Cabot observed that "No patient whose language you can speak, whose mind you can approach, needs a placebo. I give placebos now and then . . . to Armenians and others with whom I cannot communicate." A more recent commentator lamented that "some patients are so unintelligent, neurotic, and inadequate as to be incurable, and life is made easier for them by a placebo."

In keeping with these attitudes, it is only in the last 35 years or so that the placebo effect has been studied as a phenomenon all its own. As Hopkins pharmacologist Paul Talalay observes, "The major textbooks of medicine don't even mention the subject"—although, as he says, the placebo "confounds every transaction between the physician and patient."

"Most physicians tend to disbelieve the magnitude of it," says Talalay, and are uncomfortable with the subject. "It undermines a doctor's confidence in the effectiveness of his treatment. We're not comfortable with the idea that much of the time what we're doing has no therapeutic basis . . . . It makes us edgy. I suppose it's because the placebo is the meeting ground between the physician and the charlatan."

Psychiatrist Jerome Frank of Hopkins likes to speak to "the faith that heals." That was the title of an address he gave a group of medical school graduates in 1975 in which he outlined how Christian Scientists, acupuncturists, yoga masters, and the like view illness and health. All such non-medical healers, he observed, see health "as a state of harmonious integration of the person with himself, and with his society, nature, and the cosmos." Illness represents a disruption of this harmony, and "the task of the healer is to restore the disrupted harmony," mobilizing the patient's faith

And mobilizing the patient's faith, argued Frank, is part of what happens every day in every hospital, right alongside the

I give placebos . . ." *said medical ethicist Richard C. Cabot,* "*to Armenians and others with whom I cannot communicate.*"

surgery and the drugs. "One need only substitute Science for the supernatural healing powers invoked at faith-healing shrines to discover striking similarities," Frank told his Commencement Day listeners. At a hospital, which enjoys "an immense reputation as a site of amazing cures," physicians "perform arcane rituals." Their labs and operating rooms and intensive care units are places to "which they alone have access." They employ "spectacular machines that beep and gurgle and flash lights or emit immensely powerful but invisible rays." From time to time they perform "a dramatic, expensive, and impressive operation in which the surgeon stops the patient's heart, repairs it and starts it up again. The surgeon literally kills the patient and then resurrects him. Few faith healers can make an equally impressive demonstration of healing power."

A patient typically comes to every encounter with his physician, says Frank, with an attitude of " 'Oh, he must have very powerful medicine,' which is the equivalent of 'Oh, he has powerful magic.' " This "magic," and the patient's belief in its power, are the basis of the placebo effect.

Frank concludes, "History has shown that faith healing works, and the placebo is an attenuated form of it . . . Faith healing conjures up witchcraft and all sorts of quackery," he admits. but what the modern physician does, through the placebo effect, is simply "smuggle it in through the back door."

"As the doctor-patient relationship is rediscovered as a worthy focus for medical research and medical education," writes Howard Brody of Michigan State University in a recent issue of the *Annals of Internal Medicine*, "the placebo effect assumes center stage as one approach to a more sophisticated understanding of this relationship." It is not the medical expertise the doctor can bring to bear that counts most heavily here, but the *doctor in person*, and the kindness, caring, and warmth that are offered—or not offered.

Consider this study from the mid-1960s: Two matched groups of patients facing abdominal surgery got differing styles of care. One had the anesthesiologist in to tell them about the coming operation but heard nothing about any postoperative pain they might face. The other group got special treatment: The anesthesiologist spent much more time with them, discussed the nature and severity of the pain they were likely to experience, and reassured them that backup medication was available from the nursing staff. As it turned out, those in the more sympathetically treated group needed only half the pain medication, and were discharged from the hospital an average of two days earlier, than members of the other group. "A placebo effect without the placebo," was how the investigators put it (L. D. Egbert, G. E. Battit, C. E. Welch, and M. K. Bartlett, *New England Journal of Medicine*). What it amounted to, though, was caring and respect for the patients as people.

This and other studies yielding similar results moved Herbert Benson and Mark D. Epstein to lament, in a commentary in the *Journal of the American Medical Association* entitled "The Placebo Effect: A Neglected Asset in the Care of Patients," "the growing trend toward decreasing doctor-patient contact, for example through the use of computer facilities to obtain histories." Benson has elsewhere been quoted as saying that "the most important thing a doctor can do in terms of dispensing care is simply to *care* about the patient. And establishing rap-

"Well, I went to medical school overseas, and for your type of low-back pain, we sprinkle dried roots on the ground, then chant for ten minutes."

"It makes us edgy," says pharmacologist Paul Talalay. "I suppose because the placebo is the meeting ground between physician and charlatan."

port is the real basis for the placebo effect."

To what can be traced the physician's healing influence? Until 40 years ago, of course, very often all a physician could do was diagnose, laying out the likely course of an illness and informing the patient what he would face. *And this actually helped.* In an insight Jerome Frank credits to a Hopkins colleague, Paul R. McHugh, those early physicians were at least addressing the awful ambiguity a sick patient feels about his condition, and ambiguity is, as Frank notes, "one of the greatest sources of anxiety." Anxiety, in turn—as Henry K. Beecher, with his two-level pain model 30 years ago surmised—tends to aggravate the pain the patient actually perceives. Thus a doctor who "offers clear, concise, unambiguous treatment immediately reduces anxiety," says Frank, and so, in many cases, the patient's suffering as well.

But the physician's healing influence is hardly cut and dried. "Between the doctor and the patient's getting better there may be 50 complicated variables that affect one another," says medical psychologist Michael Jospe; medicine is an art as well as a science and, like any art, some practitioners may be better at it than others. Whether physicians differ innately in their ability to heal is, as Jerome Frank says, an "awkward question." But Michael Jospe plainly thinks so. "Some doctors are better healers than others," he says, and the differences lie in their personalities, in the intuition, the calming influence they bring to their dealings with patients.

Is this, then, what faith healers and other "primitive" practitioners offer? "Oh, yes," Jospe replies. "We only say it's 'primitive' because it's so complex we don't know how to deal with it."

As to the placebo itself, though, there is one intriguing lead on a possible physiological mechanism, discovered in California a few years ago. Jon Levine's research team at the University of California at San Francisco gave first placebos, then intravenous naloxone, to patients recovering from surgery for tooth extraction: the naloxone cancelled any placebo effects they'd experienced. The article was published in *Nature*, Britain's pre-eminent journal, and created international excitement among researchers in the life sciences.

Naloxone is an "opiate antagonist": Often used in helping addicts detoxify, it locks onto the same receptor sites in the brain at which endorphins hook up (the brain's natural opiates), thus blocking their pain-killing action. Therefore, if an injection of naloxone blocks the placebo's analgesic effect in patients who had been relieved by it, perhaps the placebo effect works through the endorphin system.

Years before, in 1965, Louis Lasagna had commented on the "curious hyperalgesic [pain-heightening] effect" of naloxone on patients with post-operative pain, but couldn't explain it. Now here, maybe, lay the explanation: The placebo marshals the body's natural pain-killing system—which the naloxone disrupted, thus exacerbating pain.

Maybe. Recent studies at the National Institutes of Health seem to lend another interpretation to the California results. Just as in Levine's work, says Ronald Dubner (chief of neurobiology and anesthesiology at the National Institute of Dental Research), dental patients in his studies reported greater pain when they got naloxone. But so did patients who got *no* placebo.

In their still-unpublished experiment, the results of which were presented to the annual meeting of the Society for Neuroscience last November, Dubner, research psychologist Richard Gracely, and their colleagues, established a "no-treatment" group that got neither pain-killer nor naloxone. Yet the pain level in this group shot up the same amount when it got naloxone as did the placebo group's pain. In other words, the results can be explained without the placebo. Perhaps, says Dubner, it was simply "the stress of surgery" that activated the endorphin system, not the placebo at all.

But the endorphin placebo hypothesis is by no means a closed book. "The placebo is not the only thing in the world that turns on the endorphin system," says Levine. Why should the pain increase in the NIH no-treatment group be surprising? His group is repeating the experiment—with a no-treatment group—but with different pain levels. He hopes to resolve the discrepancies between his group's results and those at NIH.

But even if endorphins or related mechanisms should come to explain certain aspects of placebo action, that leaves wide open the intriguing fundamental question of how symbolic input—a thought or an emotion—can release endorphins, or for that matter other neurotransmitters. Then, too, the endorphin hypothesis would seem to apply only to the placebo's pain-killing powers, not to its capability to bring relief in other ways. So, despite the promise of the endorphin work, a neat physiological explanation for the placebo effect is still a long way off. "Most likely," as Paul Talalay says, "the placebo effect is like cancer—a whole series of different things that operate through a variety of different mechanisms."

Afterword: A few years ago, the *Journal of the American Medical Association* reprinted an old piece from its June 23, 1900 issue in which one W. W. Keen, MD, LLD, outlined what he saw as the characteristics of "The Ideal Physician." At times of "sickness and weariness and woe," Keen wrote in the overwrought prose of that era, the physician is a welcome visitor indeed: "Then can his gentle touch give assurance; then can his sympathetic voice bring hope; then can the thousand and one acts of thoughtful kindness bind to him for life the anxious hearts looking to him as the messenger of life. Even in the daily routine of a hospital clinic," he wrote in the first year of the twentieth century, "a kind word is often better than any medicine."