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Placebo Effect: A Cure in the Mind

Belief is powerful medicine, even if the treatment itself is a sham. New research shows placebos can also benefit patients who do not have faith in them

By Maj-Britt Niemi

A man whom his doctors referred to as “Mr. Wright” was dying from cancer of the lymph nodes. Orange-size tumors had invaded his neck, groin, chest and abdomen, and his doctors had exhausted all available treatments. Nevertheless, Mr. Wright was confident that a new anticancer drug called Krebiozen would cure him, according to a 1957 report by psychologist Bruno Klopfer of the University of California, Los Angeles, entitled “Psychological Variables in Human Cancer.”

Mr. Wright was bedridden and fighting for each breath when he received his first injection. But three days later he was cheerfully ambling around the unit, joking with the nurses. Mr. Wright’s tumors had shrunk by half, and after 10 more days of treatment he was discharged from the hospital. And yet the other patients in the hospital who had received Krebiozen showed no improvement.

Over the next two months, however, Mr. Wright became troubled by press reports questioning the efficacy of Krebiozen and suffered a relapse. His doctors decided to lie to him: an improved, doubly effective version of the drug was due to arrive the next day, they told him. Mr. Wright was ecstatic. The doctors then gave him an injection that contained not one molecule of the drug—and he improved even more than he had the last time. Soon he walked out of the hospital symptom-free. He remained healthy until two months later, when, after reading reports that exposed Krebiozen as worthless, he died within days.

As Mr. Wright’s experience illustrates, a patient’s expectations and beliefs can greatly affect the course of an illness. When psychological factors tied to an inactive substance such as Krebiozen lead to recovery, doctors call the improvement a placebo effect.

In recent decades reports have confirmed the efficacy of such sham treatments in nearly all areas of medicine. Placebos can help not only to alleviate illnesses with an obvious psychological component, such as pain, depression and anxiety, but also to lessen the symptoms of Parkinson’s disease and inflammatory disorders. Occasionally, as in Mr. Wright’s case, placebos have shrunk tumors.

The latest research has shown that the placebo effect does not always arise from a conscious belief in a drug. Alternatively, it may grow out of subconscious associations between recovery and the experience of being treated, from the pinch of a shot to a doctor’s white coat. Such subliminal conditioning can control bodily processes, including immune responses and the release of hormones. Meanwhile researchers have decoded some of the biology of placebo responses, demonstrating that they stem from active processes in the brain.

Subconscious Cues

The placebo effect is probably as old as the healing professions themselves. In the 18th century physicians deliberately used inert pills when they had no suitable drug in their armamentarium. They spoke of supporting the healing process. After the middle of the 19th century medical scientists began viewing disease in purely physical and chemical terms. And by 1900 placebos had lost much of their previous popularity as therapy.

Indeed, modern medical investigators have often regarded the placebo response as a nuisance. But a cadre of psychologists, biologists, and other behavioral and social scientists instead view placebos as a key to understanding how the brain can control bodily processes to promote healing.

In the classic placebo effect, a person consciously believes that a substance is therapeutic, and this faith has a physiological consequence that dampens the pain or ameliorates other symptoms. Inversely, in the so-called nocebo effect, a negative attitude or expectation leads to harm or another undesirable outcome.

For several decades, however, researchers have known that placebo effects can also arise from subconscious associations as opposed to overt beliefs. Stimuli that a patient links with feeling better or with physical improvement—say, a doctor's white lab coat, a stethoscope or the smell of an examining room—may induce physiological reactions even if a patient has no explicit faith in the treatment being given. That is, simply seeing a doctor holding a syringe can produce a placebo reaction if a patient has previously associated that scenario with feeling better. In such cases, the overall effect—improvement or even complete recovery—stems from a combination of the pharmacological action of the drug and the subconscious or conditioned response.

My colleague, psychologist Manfred Schedlow-ski, and our team at the University of Duisburg-Essen in Germany and the Swiss Federal Institute of Technology Zurich have demonstrated that such conditioning can have pharmacological effects that mimic those of the drug being given—in this case, altering immune system status. We conditioned rats by first injecting them with the immunosuppressive drug cyclosporine A, which is used to prevent the rejection of transplanted organs. At the same time, we fed the rats water sweetened with saccharin.

The rats apparently associated the cyclosporine with the sweet drink so that, later, feeding them the drink alone weakened their immune systems, presumably because their brain sent messages to the immune system that partially shut it down. Because the rats cannot consciously believe the drink is therapeutic the way a human might, unconscious, associative learning must have depressed their immunity. These findings suggest that a placebo effect does not require that a person hope for or believe in a positive outcome.

Immune Therapy

Subsequent transplantation experiments published in the 1990s showed that such conditioning has clinical significance. Rats that received a sweet drink that previously had been paired with cyclosporine A survived with the transplanted hearts of another rat species (which the rats' immune system would have otherwise rejected) considerably longer than did nonconditioned control animals. In some of the conditioned rodents, the transplanted hearts beat for more than 100 days, which suggests their bodies had accepted the transplants. Some of this work also hinted at a mechanism for this effect: in response to behavioral conditioning, the nervous system inhibits the spleen from releasing molecules called cytokines that immune cells use to

communicate with one another. Such dampened immunity thus enables the body to tolerate a foreign organ.

Immune conditioning with cyclosporine works in humans as well. In 2002 Schedlowski, psychologist Marion U. Goebel of the University of Duisburg-Essen and their colleagues reported giving 18 healthy men a cyclosporine A capsule four times over three days, along with a greenish strawberry milk shake that smelled of lavender. Not surprisingly, their immune systems showed signs of reduced function. Five days later, when the subjects took just a dummy capsule (but no active drug) with the strange drink, the beverage similarly weakened their immune system, though somewhat less than cyclosporine had. In contrast, no such effect was seen in 16 men who received a dummy pill throughout the experiment. “This study demonstrates for the first time in humans in a double-blind, placebo-controlled design that behavioral conditioning is able to mimic the immunological effects of an immunosuppressive drug,” the authors wrote.

Subconscious placebo responses can also dampen the overactive immune responses that give rise to allergies. In 2008 Goebel and her colleagues reported conditioning 30 people who were allergic to dust mites by giving them, on five consecutive days, an unusual drink followed by a tablet of the allergy treatment desloratadine. This drug blocks the action of histamines, which mediate allergic reactions. Later, 11 of the patients received the novel drink, along with a placebo pill that looked like desloratadine, whereas the others received plain water and either a placebo or the drug.

The subjects who later sipped the strange beverage, but not those who drank water, showed a reduction in their allergy symptoms, accompanied by lowered immunological reactivity comparable to that seen in those who took the desloratadine in the second phase of the experiment. Thus, the placebo treatment measurably attenuated the subjects’ immune response.

But what is the neurological basis for conditioned placebos? In a 2005 study Schedlowski and I, along with our colleagues, identified several areas of the brain that play a role in cyclosporine-saccharin conditioning in rats. We selectively damaged the brains of rats in each of three areas—the insular cortex, the amygdala and the ventromedial nucleus of the hypothalamus—before or after the rats underwent the first phase of conditioning in which they were exposed to cyclosporine paired with saccharin.

We found that the insular cortex—an area that modulates sensory experiences such as taste along with emotions and the physiological state of the body—is essential for conditioning at all times. Animals with a damaged insular cortex exhibited no conditioned immune response, no matter when the experimental lesion was made. Yet an intact amygdala, which is involved in emotional learning, was indispensable only for immune conditioning during the first, so-called acquisition phase of conditioning, suggesting that the amygdala governs the input of visceral information, including the status of the immune system, during learning. Lesions to the hypothalamus, in contrast, had an effect only if they were made after the initial acquisition phase of conditioning, indicating that this almond-size neural structure participates in relaying information from the brain to the immune system to evoke the conditioned response.

Expecting Relief

Given the power of conditioned placebo effects, scientists have wondered whether conditioning might account for most such phenomena, leaving only a minor role for expectation. Data

suggest, however, that expectation does often contribute but that its influence extends mainly to symptoms that humans can perceive, such as pain.

In 2003 neuroscientist Fabrizio Benedetti of the University of Turin Medical School in Italy and his team tested the relative influence of expectation and conditioning in 60 volunteers who underwent a procedure that caused severe arm pain. They gave some of the participants a saline injection and told them the shot would intensify their pain; other volunteers were also given the placebo pain promoter but in addition underwent conditioning to decrease pain in which the saline shot was preceded by injections of the nonsteroidal anti-inflammatory drug (NSAID) ketorolac. In both groups pain increased, demonstrating that negative expectation is a powerful nocebo in the case of pain. What is more, anticipating more pain led to increased agony despite conditioning to an analgesic, showing that expectation influences pain more than conditioning does.

On the other hand, suggestion is relatively impotent when it comes to involuntary bodily responses. In another experiment in the same study, Benedetti's team told participants that a saline shot would alter levels (either up or down, depending on the group) of growth hormone or the stress hormone cortisol. But the suggestions had no effect on either hormone. In contrast, a saline injection did alter hormone concentrations when the researchers conditioned subjects with sumatriptan, a drug that influences their secretion. These placebo-induced biological changes occurred even if the participants were told the saline injection would have an effect opposite to that of sumatriptan. Thus, conditioning can manipulate involuntary physiological processes more than conscious beliefs can.

Expectation and conditioning placebos also work through separate biological mechanisms. In an experiment conducted by Benedetti and Turin neuroscientist Martina Amanzio, volunteers who received a shot of saline touted to be a pain reliever could bear more pain in their arms than they could without the shot. No pain relief was evident, however, when the saline was replaced by naloxone, a substance that blocks the function of the body's natural painkillers, endogenous opioids. This result suggests that the expectation effect works through the release of these opioids.

Then researchers conditioned subjects by preceding a saline injection with doses of the NSAID ketorolac. But in this case, the resulting placebo effect was not blocked by naloxone. What is more, naloxone only abbreviated the placebo response from saline paired with ketorolac when the participants also believed that the saline was a pain-blocking agent. In other words, naloxone exclusively impinged on the conscious part of that pain-reducing response. The scientists conclude that the placebo effect can consist of two components: the expectation effect, which is mediated by opioids and abolished by naloxone, and the conditioned effect, which seems to work in the same manner as whatever analgesic is used in the conditioning—and is therefore not generally sensitive to naloxone.

Additional support for the notion that endogenous opioids are behind the expectation effect comes from psychiatrist Jon-Kar Zubieta and his co-workers at the University of Michigan at Ann Arbor. In 2005 the investigators reported using molecular imaging techniques to measure opioid-mediated neuronal activity in the brain while they induced sustained muscle pain in volunteers. During one of the scans, the investigators gave the volunteers a placebo infusion of plain saline that doctors described as a medication "thought to have analgesic effects." Compared with the trial in which no infusion was given, the saline produced increased activity precisely in those brain regions that inhibit pain and stress through endogenous opioid

neurotransmission, the researchers found. In addition, the volunteers reported lower ratings of pain intensity in the saline-injection trial, suggesting that a placebo with expected painkilling properties relieves pain by acting on the brain's endogenous opioid system.

Along with a flurry of activity from brain opioids, placebo analgesia is also accompanied by a quieting of brain regions responsible for processing painful sensations. In a 2007 study neuroscientist Donald Price of the University of Florida and his colleagues used magnetic resonance imaging to scan the brains of patients with irritable bowel syndrome while they underwent a painful procedure. Price's team showed that when patients believed they were receiving an analgesic, not only did their pain diminish but neuronal activity also declined significantly in five pain-sensing brain regions as compared with trials in which they were not given a fake painkiller.

Placebo Performance

Despite the proved power of suggestion, investigators have been unable to identify personality traits that increase susceptibility to placebos. Personality, after all, has little effect on subconscious conditioning. For such subliminal responses, presentation matters more than personality does. Giving a medication a popular brand name or prescribing more frequent doses can boost the efficacy of a placebo. Similarly, a physician can maximize a placebo effect by radiating confidence or spending more time with the patient. Such tactics may subconsciously build a patient's trust in a therapy.

A high price tag on the drug can apparently help, too. In one study, placebos reported to cost $0.10 worked considerably less well in relieving pain than did those priced at $2.50 per pill. Test subjects evidently distrusted the less expensive medication. Patients are also liable to benefit more from placebos that involve elaborate medical procedures than from those requiring simple measures. Thus, the most effective sham treatments may extend beyond dispensing inactive pills to a simulation of a multistep therapeutic regimen.

As evidence of this idea, counseling psychologist Cynthia McRae of the University of Denver and her colleagues reported in 2004 the surprising success of a sham brain surgery in improving the quality of life of patients with advanced Parkinson's disease. Surgeons performed the sham operation to compare its efficacy with that of implanting human embryonic dopamine neurons into the brains of Parkinson's patients, who suffer from a lack of dopamine. In McRae's follow-up study, which assessed the patients' quality of life up to a year later, the researchers found that the patients who received the sham surgery were doing just as well physically, socially and emotionally as were the patients who had received the new cells. What mattered was not the transplant itself but whether a patient thought he or she had received it.

In recent years extensive research revealing the many medical applications, types and mechanisms of placebo effects has given credence to this once orphaned phenomenon. Doctors are now considering placebo pills and procedures as a way of enhancing the effectiveness of drugs and surgery. Such uses may elicit new controversies and questions such as the use of placebos to boost athletic performance. In the meantime, sophisticated doctors might decide to manipulate the conscious and subconscious mind in ways that could cure—or at least, do no harm.

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