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FEATURE

What if the Placebo Effect Isn't a Trick?

New research is zeroing in on a biochemical basis for the placebo effect — possibly opening a Pandora's box for Western medicine.

By Gary Greenberg

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The Chain of Office of the Dutch city of Leiden is a broad and colorful ceremonial necklace that, draped around the shoulders of Mayor Henri Lenferink, lends a magisterial air to official proceedings in this ancient university town. But whatever gravitas it provided Lenferink as he welcomed a group of researchers to his city, he was quick to undercut it. "I am just a humble historian," he told the 300 members of the Society for Interdisciplinary Placebo Studies who had gathered in Leiden's ornate municipal concert hall, "so I don't know anything about your topic." He was being a little disingenuous. He knew enough about the topic that these psychologists and neuroscientists and physicians and anthropologists and philosophers had come to his city to talk about — the placebo effect, the phenomenon whereby suffering people get better from treatments that have no discernible reason to work — to call it "fake medicine," and to add that it probably works because "people like to be cheated." He took a beat. "But in the end, I believe that honesty will prevail."

Lenferink might not have been so glib had he attended the previous day's meeting on the other side of town, at which two dozen of the leading lights of placebo science spent a preconference day agonizing over their reputation — as purveyors of sham medicine who prey on the desperate and, if they are lucky, fool people into feeling better — and strategizing about how to improve it. It's an urgent subject for them, and only in part because, like all apostate professionals, they crave mainstream acceptance. More important, they are motivated by a conviction that the placebo is a powerful medical treatment that is ignored by doctors only at their patients' expense.

And after a quarter-century of hard work, they have abundant evidence to prove it. Give people a sugar pill, they have shown, and those patients — especially if they have one of the chronic, stress-related conditions that register the strongest placebo effects and if the treatment is delivered by someone in whom they have confidence — will improve. Tell someone a normal milkshake is a diet beverage, and his gut will respond as if the drink were low fat. Take athletes to the top of the Alps, put them on exercise machines and hook them to an oxygen tank, and they will perform better than when they are breathing room air — even if

room air is all that's in the tank. Wake a patient from surgery and tell him you've done an arthroscopic repair, and his knee gets better even if all you did was knock him out and put a couple of incisions in his skin. Give a drug a fancy name, and it works better than if you don't.

You don't even have to deceive the patients. You can hand a patient with irritable bowel syndrome a sugar pill, identify it as such and tell her that sugar pills are known to be effective when used as placebos, and she will get better, especially if you take the time to deliver that message with warmth and close attention. Depression, back pain, chemotherapy-related malaise, migraine, post-traumatic stress disorder: The list of conditions that respond to placebos — as well as they do to drugs, with some patients — is long and growing.

But as ubiquitous as the phenomenon is, and as plentiful the studies that demonstrate it, the placebo effect has yet to become part of the doctor's standard armamentarium — and not only because it has a reputation as "fake medicine" doled out by the unscrupulous to the credulous. It also has, so far, resisted a full understanding, its mechanisms shrouded in mystery. Without a clear knowledge of how it works, doctors can't know when to deploy it, or how.

Not that the researchers are without explanations. But most of these have traditionally been psychological in nature, focusing on mechanisms like expectancy — the set of beliefs that a person brings into treatment — and the kind of conditioning that Ivan Pavlov first described more than a century ago. These theories, which posit that the mind acts upon the body to bring about physical responses, tend to strike doctors and researchers steeped in the scientific tradition as insufficiently scientific to lend credibility to the placebo effect. "What makes our research believable to doctors?" asks Ted Kaptchuk, head of Harvard Medical School's Program in Placebo Studies and the Therapeutic Encounter. "It's the molecules. They love that stuff." As of now, there are no molecules for conditioning or expectancy — or, indeed, for Kaptchuk's own pet theory, which holds that the placebo effect is a result of the complex conscious and nonconscious processes embedded in the practitioner-patient relationship — and without them, placebo researchers are hard-pressed to gain purchase in mainstream medicine.

But as many of the talks at the conference indicated, this might be about to change. Aided by functional magnetic resonance imaging (f.M.R.I.) and other precise surveillance techniques, Kaptchuk and his colleagues have begun to elucidate an ensemble of biochemical processes that may finally account for how placebos work and why they are more effective for some people, and some disorders, than others. The molecules, in other words, appear to be emerging. And their emergence may reveal fundamental flaws in the way we understand the body's healing mechanisms, and the way we evaluate whether more standard medical interventions in those processes work, or don't. Long a useful foil for medical science, the placebo effect might soon represent a more fundamental challenge to it.

In a way, the placebo effect owes its poor reputation to the same man who cast aspersions on going to bed late and sleeping in. Benjamin Franklin was, in 1784, the ambassador of the fledgling United States to King Louis XVI's court. Also in Paris at the time was a Viennese physician named Franz Anton Mesmer. Mesmer fled Vienna a few years earlier when the local medical establishment determined that his claim to have cured a young woman's blindness by putting her into a trance was false, and that, even worse, there was something unseemly about his relationship with her. By the time he arrived in Paris and hung out his shingle, Mesmer had acquired what he lacked in Vienna: a theory to account for his ability to use trance states to heal people. There was, he claimed, a force pervading the universe called animal magnetism that could cause illness when perturbed. Conveniently enough for Mesmer, the magnetism could be perceived and de-perturbed only by him and people he had trained.

Mesmer's method was strange, even in a day when doctors routinely prescribed bloodletting and poison to cure the common cold. A group of people complaining of maladies like fatigue, numbness, paralysis and chronic pain would gather in his office, take seats around an oak cask filled with water and grab on to metal rods immersed in the water. Mesmer would alternately chant, play a glass harmonium and wave his hands at the afflicted patients, who would twitch and cry out and sometimes even lose consciousness, whereupon they would be carried to a recovery room. Enough people reported good results that patients were continually lined up at Mesmer's door waiting for the next session.

It was the kind of success likely to arouse envy among doctors, but more was at stake than professional turf. Mesmer's claim that a force existed that could only be perceived and manipulated by the elect few was a direct challenge to an idea central to the Enlightenment: that the truth could be determined by anyone with senses informed by skepticism, that Scripture could be supplanted by facts and priests by a democracy of people who possessed them. So, when the complaints about Mesmer came to Louis, it was to the scientists that the king — at pains to show himself an enlightened man — turned. He appointed, among others, Lavoisier the chemist, Bailly the astronomer and Guillotin the physician to investigate Mesmer's claims, and he installed Franklin at the head of their commission.

To the Franklin commission, the question wasn't whether Mesmer was a fraud and his patients were dupes. Everyone could be acting in good faith, but belief alone did not prove that the magnetism was at work. To settle this question, they designed a series of trials that ruled out possible causes of the observed effects other than animal magnetism. The most likely confounding variable, they thought, was some faculty of mind that made people behave as they did under Mesmer's ministrations. To rule this out, the panel settled upon a simple method: a blindfold. Over a period of a few months, they ran a series of experiments that tested whether people experienced the effects of animal magnetism even when they couldn't see.

One of Mesmer's disciples, Charles d'Eslon, conducted the tests. The panel instructed him to wave his hands at a part of a patient's body, and then asked the patient where the effect was felt. They took him to a copse to magnetize a tree — Mesmer claimed that a patient could be treated by touching one — and then asked the patient to find it. They told patients d'Eslon was

in the room when he was not, and vice versa, or that he was doing something that he was not. In trial after trial, the patients responded as if the doctor were doing what they thought he was doing, not what he was actually doing.

It was possibly the first-ever blinded experiment, and it soundly proved what scientists today call the null hypothesis: There was no causal connection between the behavior of the doctor and the response of the patients, which meant, as Franklin's panel put it in their report, that "this agent, this fluid, has no existence." That didn't imply that people were *pretending* to twitch or cry out, or lying when they said they felt better; only that their behavior wasn't a result of this nonexistent force. Rather, the panel wrote, "the imagination singly produces all the effects attributed to the magnetism."

When the panel gave d'Eslon a preview of its findings, he took it with equanimity. Given the results of the treatment (as opposed to the experiment), he opined, the imagination, "directed to the relief of suffering humanity, would be a most valuable means in the hands of the medical profession" — a subject to which these august scientists might wish to apply their methods. But events intervened. Franklin was called back to America in 1785; Louis XVI had bigger trouble on his hands and, along with Lavoisier and Bailly, eventually met with the short, sharp shock of the device named for Guillotin.

The panel's report was soon translated into English by William Godwin, the father of Mary Shelley. The story spread fast — not because of the healing potential that d'Eslon had suggested, but because of the implications for science as a whole. The panel had demonstrated that by putting imagination out of play, science could find the truth about our suffering bodies, in the same way it had found the truth about heavenly bodies. Hiving off subjectivity from the rest of medical practice, the Franklin commission had laid the conceptual foundation for the brilliant discoveries of modern medicine, the antibiotics and vaccines and other drugs that can be dispensed by whoever happens to possess the prescription pad, and to whoever happens to have the disease. Without meaning to, they had created an epistemology for the healing arts — and, in the process, inadvertently conjured the placebo effect, and established it as that to which doctors must remain blind.

Photo illustration by Paul Sahre

It wouldn't be the last time science would turn its focus to the placebo effect only to quarantine it. At a 1955 meeting of the American Medical Association, the Harvard surgeon Henry Beecher pointed out to his colleagues that while they might have thought that placebos were fake medicine — even the name, which means "I shall please" in Latin, carries more than a hint of contempt — they couldn't deny that the results were real. Beecher had been looking at the subject systematically, and he determined that placebos could relieve anxiety and postoperative pain, change the blood chemistry of patients in a way similar to drugs and even cause side effects. In general, he told them, more than one-third of patients would get better when given a treatment that was, pharmacologically speaking, inert.

If the placebo was as powerful as Beecher said, and if doctors wanted to know whether their drugs actually worked, it was not sufficient simply to give patients the drugs and see whether they did better than patients who didn't interact with the doctor at all. Instead, researchers needed to assume that the placebo effect was part of every drug effect, and that drugs could be said to work only to the extent that they worked better than placebos. An accurate measure of drug efficacy would require comparing the response of patients taking it with that of patients taking placebos; the drug effect could then be calculated by subtracting the placebo response from the overall response, much as a deli-counter worker subtracts the weight of the container to determine how much lobster salad you're getting.

In the last half of the 1950s, this calculus gave rise to a new way to evaluate drugs: the double-blind, placebo-controlled clinical trial, in which neither patient nor clinician knew who was getting the active drug and who the placebo. In 1962, when the Food and Drug Administration began to require pharmaceutical companies to prove their new drugs were effective before they came to market, they increasingly turned to the new method; today, virtually every prospective new drug has to outperform placebos on two independent studies in order to gain F.D.A. approval.

Like Franklin's commission, the F.D.A. had determined that the only way to sort out the real from the fake in medicine was to isolate the imagination. It also echoed the royal panel by taking note of the placebo effect only long enough to dismiss it, giving it a strange dual nature: It's included in clinical trials because it is recognized as an important part of every treatment, but it is treated as if it were not important in itself. As a result, although virtually every clinical trial is a study of the placebo effect, it remains underexplored — an outcome that reflects the fact that there is no money in sugar pills and thus no industry interest in the topic as anything other than a hurdle it needs to overcome.

When Ted Kaptchuk was asked to give the opening keynote address at the conference in Leiden, he contemplated committing the gravest heresy imaginable: kicking off the inaugural gathering of the Society for Interdisciplinary Placebo Studies by declaring that there was no such thing as the placebo effect. When he broached this provocation in conversation with me not long before the conference, it became clear that his point harked directly back to Franklin: that the topic he and his colleagues studied was created by the scientific establishment, and only in order to exclude it — which means that they are always playing on hostile terrain. Science is "designed to get rid of the husks and find the kernels," he told me. Much can be lost in the threshing — in particular, Kaptchuk sometimes worries, the rituals embedded in the doctor-patient encounter that he thinks are fundamental to the placebo effect, and that he believes embody an aspect of medicine that has disappeared as scientists and doctors pursue the course laid by Franklin's commission. "Medical care is a moral act," he says, in which a suffering person puts his or her fate in the hands of a trusted healer.

"I don't love science," Kaptchuk told me. "I want to know what heals people." Science may not be the only way to understand illness and healing, but it is the established way. "That's where the power is," Kaptchuk says. That instinct is why he left his position as director of a pain clinic in 1990 to join Harvard — and it's why he was delighted when, in 2010, he was contacted by

Kathryn Hall, a molecular biologist. Here was someone with an interest in his topic who was also an expert in molecules, and who might serve as an emissary to help usher the placebo into the medical establishment.

Hall's own journey into placebo studies began 15 years before her meeting with Kaptchuk, when she developed a bad case of carpal tunnel syndrome. Wearing a wrist brace didn't help, and neither did over-the-counter drugs or the codeine her doctor prescribed. When a friend suggested she visit an acupuncturist, Hall balked at the idea of such an unscientific approach. But faced with the alternative, surgery, she decided to make an appointment. "I was there for maybe 10 minutes," she recalls, "when she stuck a needle here" — Hall points to a spot on her forearm — "and this awful pain just shot through my arm." But then the pain receded and her symptoms disappeared, as if they had been carried away on the tide. She received a few more treatments, during which the acupuncturist taught her how to manipulate a spot near her elbow if the pain recurred. Hall needed the fix from time to time, but the problem mostly just went away.

"I couldn't believe it," she told me. "Two years of gross drugs, and then just one treatment." All these years later, she's still wonder-struck. "What was that?" she asks. "Rub the spot, and the pain just goes away?"

Hall was working for a drug company at the time, but she soon left to get a master's degree in visual arts, after which she started a documentary-production company. She was telling her carpal-tunnel story to a friend one day and recounted how the acupuncturist had climbed up on the table with her. ("I was like, 'Oh, my God, what is this woman doing?' " she told me. "It was very dramatic.") She'd never been able to understand how the treatment worked, and this memory led her to wonder out loud if maybe the drama itself had something to do with the outcome.

Her friend suggested she might find some answers in Ted Kaptchuk's work. She picked up his book about Chinese medicine, "The Web that Has No Weaver," in which he mentioned the possibility that placebo effects figure strongly in acupuncture, and then she read a study he had conducted that put that question to the test.

Kaptchuk had divided people with irritable bowel syndrome into three groups. In one, acupuncturists went through all the motions of treatment, but used a device that only appeared to insert a needle. Subjects in a second group also got sham acupuncture, but delivered with more elaborate doctor-patient interaction than the first group received. A third group was given no treatment at all. At the end of the trial, both treatment groups improved more than the no-treatment group, and the "high interaction" group did best of all.

Kaptchuk, who before joining Harvard had been an acupuncturist in private practice, wasn't particularly disturbed by the finding that his own profession worked even when needles were not actually inserted; he'd never thought that placebo treatments were fake medicine. He was more interested in how the strength of the treatment varied with the quality and quantity of interaction between the healer and the patient — the drama, in other words. Hall reached out to him shortly after she read the paper.

The findings of the I.B.S. study were in keeping with a hypothesis Kaptchuk had formed over the years: that the placebo effect is a biological response to an act of caring; that somehow the encounter itself calls forth healing and that the more intense and focused it is, the more healing it evokes. He elaborated on this idea in a comparative study of conventional medicine, acupuncture and Navajo "chantway rituals," in which healers lead storytelling ceremonies for the sick. He argued that all three approaches unfold in a space set aside for the purpose and proceed as if according to a script, with prescribed roles for every participant. Each modality, in other words, is its own kind of ritual, and Kaptchuk suggested that the ritual itself is part of what makes the procedure effective, as if the combined experiences of the healer and the patient, reinforced by the special-but-familiar surroundings, evoke a healing response that operates independently of the treatment's specifics. "Rituals trigger specific neurobiological pathways that specifically modulate bodily sensations, symptoms and emotions," he wrote. "It seems that if the mind can be persuaded, the body can sometimes act accordingly." He ended that paper with a call for further scientific study of the nexus between ritual and healing.

When Hall contacted him, she seemed like a perfect addition to the team he was assembling to do just that. He even had an idea of exactly how she could help. In the course of conducting the study, Kaptchuk had taken DNA samples from subjects in hopes of finding some molecular pattern among the responses. This was an investigation tailor-made to Hall's expertise, and she agreed to take it on. Of course, the genome is vast, and it was hard to know where to begin — until, she says, she and Kaptchuk attended a talk in which a colleague presented evidence that an enzyme called COMT affected people's response to pain and painkillers. Levels of that enzyme, Hall already knew, were also correlated with Parkinson's disease, depression and schizophrenia, and in clinical trials people with those conditions had shown a strong placebo response. When they heard that COMT was also correlated with pain response — another area with significant placebo effects — Hall recalls, "Ted and I looked at each other and were like: 'That's it! That's it!' "

It is not possible to assay levels of COMT directly in a living brain, but there is a snippet of the genome called rs4680 that governs the production of the enzyme, and that varies from one person to another: One variant predicts low levels of COMT, while another predicts high levels. When Hall analyzed the I.B.S. patients' DNA, she found a distinct trend. Those with the high-COMT variant had the weakest placebo responses, and those with the opposite variant had the strongest. These effects were compounded by the amount of interaction each patient got: For instance, low-COMT, high-interaction patients fared best of all, but the low-COMT subjects who were placed in the no-treatment group did *worse* than the other genotypes in that group. They were, in other words, more sensitive to the impact of the relationship with the healer.

The discovery of this genetic correlation to placebo response set Hall off on a continuing effort to identify the biochemical ensemble she calls the placebome — the term reflecting her belief that it will one day take its place among the other important "-omes" of medical science, from the genome to the microbiome. The rs4680 gene snippet is one of a group that governs the production of COMT, and COMT is one of a number of enzymes that determine levels of

catecholamines, a group of brain chemicals that includes dopamine and epinephrine. (Low COMT tends to mean higher levels of dopamine, and vice versa.) Hall points out that the catecholamines are associated with stress, as well as with reward and good feeling, which bolsters the possibility that the placebome plays an important role in illness and health, especially in the chronic, stress-related conditions that are most susceptible to placebo effects.

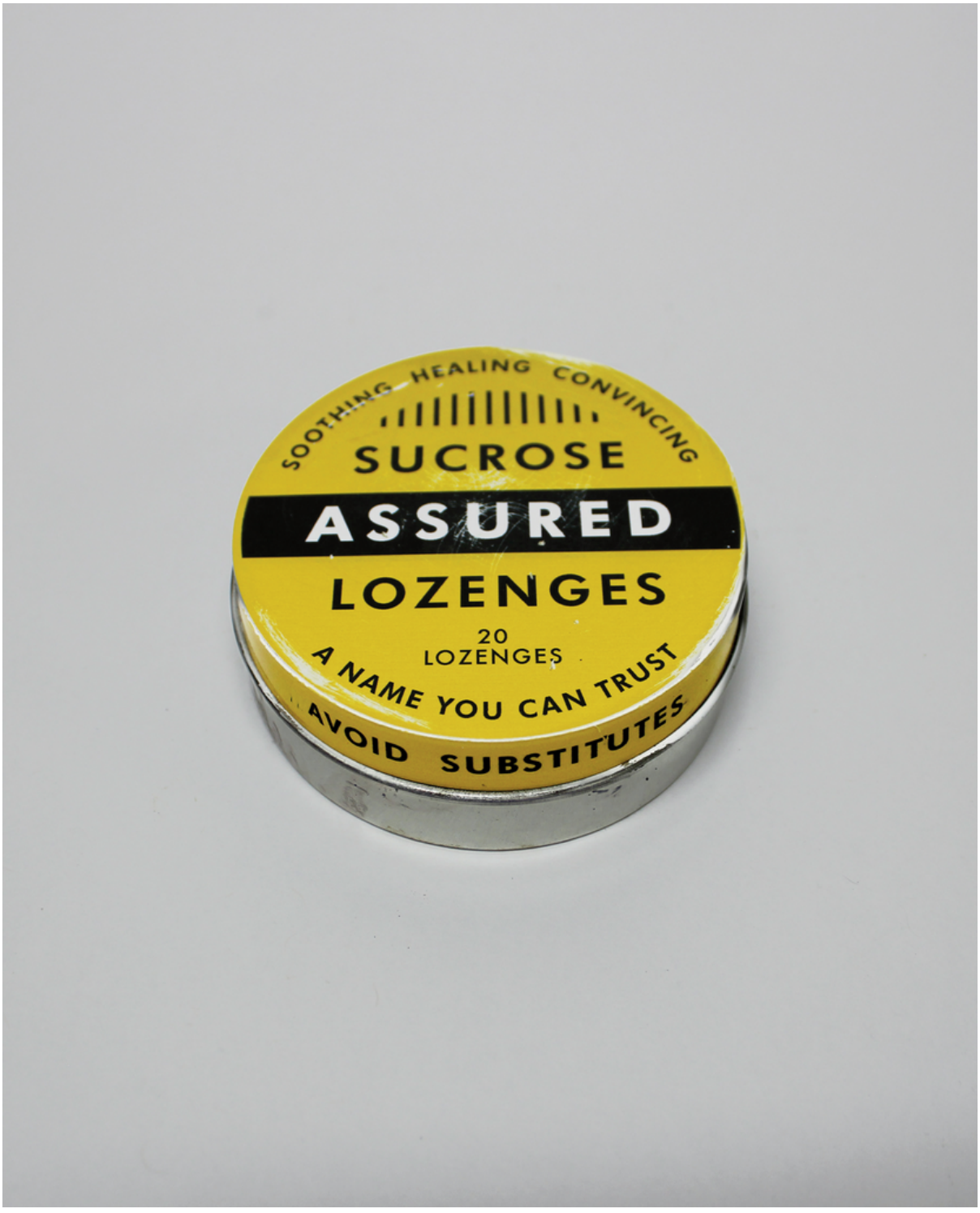

Photo illustration by Paul Sahre

Her findings take their place among other results from neuroscientists that strengthen the placebo's claim to a place at the medical table, in particular studies using f.M.R.I. machines that have found consistent patterns of brain activation in placebo responders. "For years, we

thought of the placebo effect as the work of imagination," Hall says. "Now through imaging you can literally see the brain lighting up when you give someone a sugar pill."

One group with a particularly keen interest in those brain images, as Hall well knows, is her former employers in the pharmaceutical industry. The placebo effect has been plaguing their business for more than a half-century — since the placebo-controlled study became the clinical-trial gold standard, requiring a new drug to demonstrate a significant therapeutic benefit over placebo to gain F.D.A. approval.

That's a bar that is becoming ever more difficult to surmount, because the placebo effect seems to be becoming stronger as time goes on. A 2015 study published in the journal Pain analyzed 84 clinical trials of pain medication conducted between 1990 and 2013 and found that in some cases the efficacy of placebo had grown sharply, narrowing the gap with the drugs' effect from 27 percent on average to just 9 percent. The only studies in which this increase was detected were conducted in the United States, which has spawned a variety of theories to explain the phenomenon: that patients in the United States, one of only two countries where medications are allowed to be marketed directly to consumers, have been conditioned to expect greater benefit from drugs; or that the larger and longer-duration trials more common in America have led to their often being farmed out to contract organizations whose nurses' only job is to conduct the trial, perhaps fostering a more placebo-triggering therapeutic interaction.

Whatever the reason, a result is that drugs that pass the first couple of stages of the F.D.A. approval process founder more and more frequently in the larger late-stage trials; more than 90 percent of pain medications now fail at this stage. The industry would be delighted if it were able to identify placebo responders — say, by their genome — and exclude them from clinical trials.

That may seem like putting a thumb on the scale for drugs, but under the logic of the drug-approval regime, to eliminate placebo effects is not to cheat; it merely reduces the noise in order for the drug's signal to be heard more clearly. That simple logic, however, may not hold up as Hall continues her research into the genetic basis of the placebo. Indeed, that research may have deeper implications for clinical drug trials, and for the drugs themselves, than pharma companies might expect.

Since 2013, Hall has been involved with the Women's Health Study, which has tracked the cardiovascular health of nearly 40,000 women over more than 20 years. The subjects were randomly divided into four groups, following standard clinical-trial protocol, and received a daily dose of either vitamin E, aspirin, vitamin E with aspirin or a placebo. A subset also had their DNA sampled — which, Hall realized, offered her a vastly larger genetic database to plumb for markers correlated to placebo response. Analyzing the data amassed during the first 10 years of the study, Hall found that the women with the low-COMT gene variant had significantly higher rates of heart disease than women with the high-COMT variant, and that the risk was reduced for those low-COMT women who received the active treatments but not

in those given placebos. Among high-COMT people, the results were the inverse: Women taking placebos had the lowest rates of disease; people in the treatment arms had an increased risk.

These findings in some ways seem to confound the results of the I.B.S. study, in which it was the low-COMT patients who benefited most from the placebo. But, Hall argues, what's important isn't the direction of the effect, but rather that there *is* an effect, one that varies depending on genotype — and that the same gene variant also seems to determine the relative effectiveness of the drug. This outcome contradicts the logic underlying clinical trials. It suggests that placebo and drug do not involve separate processes, one psychological and the other physical, that add up to the overall effectiveness of the treatment; rather, they may both operate on the same biochemical pathway — the one governed in part by the COMT gene.

Hall has begun to think that the placebome will wind up essentially being a chemical pathway along which healing signals travel — and not only to the mind, as an experience of feeling better, but also to the body. This pathway may be where the brain translates the act of caring into physical healing, turning on the biological processes that relieve pain, reduce inflammation and promote health, especially in chronic and stress-related illnesses — like irritable bowel syndrome and some heart diseases. If the brain employs this same pathway in response to drugs and placebos, then of course it is possible that they might work together, like convoys of drafting trucks, to traverse the territory. But it is also possible that they will encroach on one another, that there will be traffic jams in the pathway.

What if, Hall wonders, a treatment fails to work not because the drug and the individual are biochemically incompatible, but rather because in some people the drug interferes with the placebo response, which if properly used might reduce disease? Or conversely, what if the placebo response is, in people with a different variant, working against drug treatments, which would mean that a change in the psychosocial context could make the drug more effective? Everyone may respond to the clinical setting, but there is no reason to think that the response is always positive. According to Hall's new way of thinking, the placebo effect is not just some constant to be subtracted from the drug effect but an intrinsic part of a complex interaction among genes, drugs and mind. And if she's right, then one of the cornerstones of modern medicine — the placebo-controlled clinical trial — is deeply flawed.

When Kathryn Hall told Ted Kaptchuk what she was finding as she explored the relationship of COMT to the placebo response, he was galvanized. "Get this molecule on the map!" he urged her. It's not hard to understand his excitement. More than two centuries after d'Eslon suggested that scientists turn their attention directly to the placebo effect, she did exactly that and came up with a finding that might have persuaded even Ben Franklin.

But Kaptchuk also has a deeper unease about Hall's discovery. The placebo effect can't be totally reduced to its molecules, he feels certain — and while research like Hall's will surely enhance its credibility, he also sees a risk in playing his game on scientific turf. "Once you start measuring the placebo effect in a quantitative way," he says, "you're transforming it to be

something other than what it is. You suck out what was previously there and turn it into science." Reduced to its molecules, he fears, the placebo effect may become "yet another thing on the conveyor belt of routinized care."

"We're dancing with the devil here," Kaptchuk once told me, by way of demonstrating that he was aware of the risks he's taking in using science to investigate a phenomenon it defined only to exclude. Kaptchuk, an observant Jew who is a student of both the Torah and the Talmud, later modified his comment. It's more like Jacob wrestling with the angel, he said — a battle that Jacob won, but only at the expense of a hip injury that left him lame for the rest of his life.

Indeed, Kaptchuk seems wounded when he complains about the pervasiveness of research that uses healthy volunteers in academic settings, as if the response to mild pain inflicted on an undergraduate participating in an on-campus experiment is somehow comparable to the despair often suffered by people with chronic, intractable pain. He becomes annoyed when he talks about how quickly some of his colleagues want to move from these studies to clinical recommendations. And he can even be disparaging of his own work, wondering, for instance, whether the study in which placebos were openly given to irritable bowel syndrome patients succeeded only because it convinced the subjects that the sugar was really a drug. But it's the prospect of what will become of his findings, and of the placebo, as they make their way into clinical practice, that really seems to torment him.

Kaptchuk may wish "to help reconfigure biomedicine by rejecting the idea that healing is only the application of mechanical tools." He may believe that healing is a moral act in which "caring in the context of hope qualitatively changes clinical outcomes." He may be convinced that the relationship kindled by the encounter between a suffering person and a healer is a central, and almost entirely overlooked, component of medical treatment. And he may have dedicated the last 20 years of his life to persuading the medical establishment to listen to him. But he may also come to regret the outcome.

After all, if Hall is right that clinician warmth is especially effective with a certain genotype, then, as she wrote in the paper presenting her findings from the I.B.S./sham-acupuncture study, it is also true that a different group will "derive minimum benefit" from "empathic attentions." Should medical rituals be doled out according to genotype, with warmth and caring withheld in order to clear the way for the drugs? And if she is correct that a certain ensemble of neurochemical events underlies the placebo effect, then what is to stop a drug company from manufacturing a drug — a real drug, that is — that activates the same process pharmacologically? Welcomed back into the medical fold, the placebo effect may raise enough mischief to make Kaptchuk rue its return, and bewilder patients when they discover that their doctor's bedside manner is tailored to their genes.

For the most part, most days, Kaptchuk manages to keep his qualms to himself, to carry on as if he were fully confident that scientific inquiry can restore the moral dimension to medicine. But the precariousness of his endeavors is never far from his mind. "Will this work destroy the stuff that actually has to do with wisdom, preciousness, imagination, the things that are

actually critical to who we are as human beings?" he asks. His answer: "I don't know, but I have to believe there is an infinite reserve of wisdom and imagination that will resist being reduced to simple materialistic explanations."

The ability to hold two contradictory thoughts in mind at the same time seems to come naturally to Kaptchuk, but he may overestimate its prevalence in the rest of us. Even if his optimism is well placed, however, there's nothing like being sick to make a person toss that kind of intelligence aside in favor of the certainties offered by modern medicine. Indeed, it's exactly that yearning that sickness seems to awaken and that our healers, imbued with the power of science, purport to provide, no imagination required. Armed with our confidence in them, we're pleased to give ourselves over to their ministrations, and pleased to believe that it's the molecules, and the molecules alone, that are healing us. People do like to be cheated, after all.

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