

In 2003 a paper in *Prevention and Treatment* reported that diazepam had no effect on anxiety when it was administered without the patient's knowledge. In an extraordinary experiment, researchers in Turin split a group of trial subjects into two. One half were given diazepam by a doctor who told them they were being given a powerful antianxiety drug. The other group were hooked up to an automatic infusion machine and given the same dose of diazepam—but with no one in the room and no way of telling they had received the drug. Two hours later, the people in the first group reported a significant reduction in their levels of anxiety. The second group reported no change. "Anxiety reduction after the open diazepam administration was a placebo effect," the researchers suggested.

A placebo is a medical procedure that has no medicine in it. A sugar pill, or a spoonful of sugar water, a saline drip—or anything, really. A parade of doctors in white coats coming to your bedside to offer reassurances can be enough to trigger the effect. The power of placebo comes from the deceptive message that comes with it. You are told (or you sense) this procedure or ritual will have an effect on your body or state of mind, and if you genuinely believe it, taking the pill or the drink, or in some cases just seeing the doctor, will produce exactly that effect. Witch doctors, shamans, and other purveyors of the magical arts are known to deal in placebos. When they carry out a sham ritual to cure a paying believer, that cure can work wonders. The same might be said of televangelists. And Western medical doctors, too; research has shown that white coats and stethoscopes can produce surprisingly effective placebo effects—as can a good bedside manner. Doctors know that if patients feel they are getting a suitable treatment, the treatment is enormously more effective.

In one sense there's an easy explanation for all this: the chemistry of the drug is being augmented by chemicals secreted in the brain—the effect of what Fabrizio Benedetti, the leader of the Turin group, calls "the molecules of hope." The difficult side of the new experimental evidence is that, where we once thought we had a handle on the placebo effect, it is now becoming clear that we don't.

In medicine, we have long been accustomed to accounting for placebo. Modern scientific medicine was constructed on the notion of the *randomized double-blind, placebo-controlled trial*, where drugs have to perform bet-

## THE PLACEBO EFFECT

Who's being deceived?

It has brought me great comfort to know that I could, in some way, help people feel better," said Leo Sternbach, inventor of the antianxiety drug diazepam. Sternbach certainly did that—in spades. What is only just starting to emerge is just how much Leo Sternbach's drug depends on people helping themselves to feel better.

From 1969 to 1982, diazepam, marketed as Valium, was the top-selling pharmaceutical in the United States. At the height of its powers, Sternbach's employer, the pharmaceutical giant Hoffman LaRoche, sold 2.3 billion of the little yellow pills marked with a V. That was in 1978, and the drug had already been part of popular culture for more than a decade; "Mother's Little Helper" by the Rolling Stones, released in 1966, is a satire on domestic abuse of Valium. In the same year that song was released, the drug gained a starring role in the cult novel *Valley of the Dolls*; diazepam "dolls" were the lead characters' means of getting through the strains of life in New York. Diazepam is now, according to the World Health Organization, a "core medicine," essential for any nation's pharmaceutical store. The strange thing is, it doesn't work unless you know you're taking it.

ter than a dummy pill or inert saline injection. Now, though, things aren't so clear. Some analyses of the data suggest that the placebo effect is largely a myth. What's more, the medical system was set up assuming not only the existence of placebo but also that its effects can be separated out from the chemistry of the drugs being tested. It seems that assumption was false, and the edifice of the pharmaceutical trial may have to be dismantled. No wonder a recent National Institutes of Health conference declared placebo research an "urgent priority."

Benjamin Franklin, the father of rational, "evidence-based" medicine, must be turning in his grave. In 1785 Franklin headed a commission to investigate the claims of "animal magnetism." The Austrian physician Franz Anton Mesmer had entranced (hence *mesmerized*) Paris with his claims that magnets and glasses of water could be used to healing effect. Louis XVI wanted to know whether these claims stood up, and some of the greatest scientists in Europe were commissioned to find out the truth. Their tests were the first scientific inquiries to use blindfolds that prevented the subjects from biasing the results—the original "blinded" trials really were just that. The commission's report came out in 1785. Any healing effect is "really due to the power of the imagination," it said.

Interestingly, 1785 was also the year the term *placebo* appeared for the first time in a medical dictionary. It was the expanded second edition of George Motherby's *New Medical Dictionary*, and the word, to Motherby, meant "a common place method or medicine." Though that is not particularly damning at first glance, it was most likely a negative label, meaning the medicine was trivial, or unimpressive, because the word already had a negative connotation. *Placebo*, which means "I will please," had come to signify insincerity, flattery, and profiteering since medieval times, when greedy churchmen would take mourners' money to sing Psalm 116 at funerals. The psalm begins, *Placebo Domino in regione vivorum* (I will please the Lord in the land of the living). By 1811, that negative connotation was well established; Robert Hooper published his *New Medical Dictionary* with an entry for *placebo* that read: "an epithet given to any medicine adapted more to please than benefit the patient." Little did the clinicians of Hooper's day know that a placebo might benefit patients just as much as it pleased them.

As often happens, that knowledge had been gained and lost before. It

was certainly known to the ancient Greeks. In 380 BCE Plato wrote *Charmides*, in which the Thracian king Zamolxis tells Socrates that the great error of the physicians of his day was the separation of the soul from the body. Despite doctors' best efforts, curing the body is impossible without flattering the mind, Zamolxis says.

If the head and body are to be well, you must begin by curing the soul; that is the first thing. And the cure, my dear youth, has to be effected by the use of certain charms, and these charms are fair words; and by them temperance is implanted in the soul, and where temperance is, there health is speedily imparted, not only to the head, but to the whole body.

Plato was right; words are powerful. If you communicate that you are doing something—if you utter what the French psychiatrist Patrick Lemoine calls the *incantation*—it can work wonders.

An example of an incantation, drawn from Lemoine's experience, might be, "I'm going to prescribe you some magnesium that will treat your anxiety." Magnesium isn't a licensed cure for anxiety, but magnesium deficiency produces symptoms similar to anxiety; in a bizarre nod to the principles of vaccination, European clinicians often prescribe magnesium for anxiety, Lemoine says. And not only are his patients satisfied; they get better—and relapse if the treatment is interrupted. Nearly 250 years into the era of evidence-based medicine, the incantation is still a powerful force.

A 1954 paper in the *Lancet* declared that the placebo effect is only useful in treating "some unintelligent or inadequate patients"; that seems almost laughable now. According to Ann Helm of the Oregon Health Sciences University, somewhere between 35 and 45 percent of all medical prescriptions are placebos. That estimate was made in 1985. In 2003 a survey of nearly eight hundred Danish clinicians, published in *Evaluation and the Health Professions*, found that almost half prescribed a placebo ten or more times per year. A 2004 study of Israeli doctors, published in the *British Medical Journal*, determined that 60 percent had prescribed placebos, more than half of them doing it once a month or more. Of the Israeli doctors who pre-

scribed placebos, 94 percent said they found them to be an effective means of treatment.

These are not pure placebos. The doctor can't send you to a pharmacy to get a sugar pill; after all, you might read the prescription, breaking the spell. No, doctors routinely prescribe medications that have a tiny bit of something useful in them—but its licensed use is not to treat what is ailing you.

Despite being so commonplace, it is a practice that splits the medical community. It is seen by some as unethical—dangerous, even. And not only is it practicing deception on a patient; it also forces other medical professionals to act as accomplices to the placebo-prescribing physician. After all, what do you do with your prescription? You take it along to the pharmacist. Your pharmacist then—willingly or reluctantly—tends to play along. An article in the *Journal of the American Pharmaceutical Association* even provides a script for their role. Realizing that a doctor has prescribed a placebo, the pharmacist should deliver the medication with these words: "Generally, a larger dose is used for most patients, but your doctor believes that you'll benefit from this dose." The pharmacist might then advise you of some possible side effects. Or not.

If this shocks you, you can be comforted by the fact that no one is out to fleece you. Neither your doctor nor your pharmacist is getting away with some scam. They are simply doing what they can for your health. They know that you have faith in their abilities; otherwise you wouldn't have come for the consultation. And their abilities include the knowledge that placebos work—though no one knows exactly why. You have faith in your doctor, and that faith can make you well. The nature of placebo simply means that they have to practice a tiny little deception to help it happen. Is that wrong? There is no consensus on the answer to that question.

**WHILE** the ethical issues surrounding placebo have long been debated to no conclusion, the scientific basis of the effect is a relatively new topic for research. The general conclusion here, it seems, is that the placebo effect is due to chemistry. The classic demonstration involves inducing pain in subjects; the original work was done by dentists who had extracted molars from pa-

tients. However, less drastic measures are possible. The only truly essential ingredient is a little deceit.

It all kicks off with the pain-racked patients receiving something like a morphine drip. Later, after the patients have begun to associate the morphine with pain relief, you can subtly substitute saline solution for the morphine. The patients don't know their "morphine" is nothing but salt water and, thanks to the placebo effect, they report that their pain medication is still working fine. That is strange in itself, but not as strange as the next twist makes things. Without saying anything to the patients, you put another drug into the drip: naloxone, which blocks the action of morphine. Even though there is no morphine going into the patients' bodies, naloxone still stops the pain relief in its tracks; the patients, oblivious to all that has gone on, now report that they are in discomfort again.

The only plausible explanation is that the drug that blocks morphine's pain-relieving power also blocks the saline's (placebo-based) pain-relieving power. Which means the saline really was doing something—it wasn't all in the patient's imagination. Or at least it means that imagination can have a physiological effect.

When the dentists first performed this trick, they attributed the placebo effect to a stimulation of the body's endorphins, natural opioids that act using the same biochemical pathways as morphine. The expectation of pain relief was enough to trigger an endorphin release that did the job, they concluded. Then the naloxone blocked the endorphins; that's why the pain came back. It turns out to be more complicated than that, however.

What was once considered nothing more than the fancies of the imagination is a real, repeatable, and multifaceted biochemical phenomenon. The placebo effect pulls out all the stops; the expectation of pain relief can stimulate all kinds of natural pain-relieving chemicals. Use ketorolac, a painkiller that works via a completely different chemistry from that of morphine, in the conditioning, then replace it with saline. The addition of naloxone does nothing there because the placebo pain relief is provided not by endorphins but by some other natural painkiller that your body produces. The stimulation of hormones that work in the same way as the painkiller sumatriptan is one example. The phenomenon even depends on how much pain the patient is expecting to feel. Tell ready-conditioned patients they are getting

morphine that is more dilute than usual (when in fact they were getting nothing more than saline), and introduce naloxone. Again, it doesn't block the painkilling effect of the saline because the expectation of reduced pain relief has triggered some alternate mechanism. What everyone thinks of as "the placebo effect" turns out to be a whole array of different effects, each with a unique biochemical mechanism. Our brains can fool us in any number of ways.

**THOUGH** all this seems completely convincing—by now, we are surely confident that the placebo effect is a real phenomenon—there is a fly in the ointment. In 2001 two Danish researchers published a landmark paper in the *New England Journal of Medicine*. Asbjorn Hróbjartsson and Peter Gøtzsche had begun to get suspicious about claims of the efficacy of the placebo effect. Everywhere they looked—in textbooks, journal papers, and magazine articles—authors were quoting a number the pair couldn't quite believe. According to almost everything in the medical literature, 35 percent of patients would get better if told a dummy treatment they had been given was real.

Eventually, they found the source of this much-quoted, never-questioned statistic: Henry Knowles Beecher. In *The Powerful Placebo*, published in the *Journal of the American Medical Association* in 1955, Beecher made the first loud call for the use of double-blind, placebo-controlled trials in assessing medical treatments. The paper documents his analysis of a dozen studies, an analysis that produced the magical 35 percent figure.

It wasn't enough to convince Hróbjartsson and Gøtzsche, so they carried out a meta-analysis. This is what scientists do when they are faced with a long series of conflicting answers to a question; essentially, it is a formalized way of analyzing all previous attempts to answer the question. They examine the quality of each one: its experimental methods, its biases, its statistical analyses. The idea is to get a flavor of each set of results and then put them together in a way that reflects how much weight should be given to their stated results. In the end, such a study makes some pronouncement about the overall weight of evidence for or against a hypothesis.

Hróbjartsson and Gøtzsche's meta-analysis of the placebo effect took the data from 114 clinical trials that had compared placebo-treated patients with untreated patients. Overall, there were around 7,500 patients suffering from about forty different conditions ranging from alcohol dependence to Parkinson's disease. Over this wide spectrum of complaints, they found no evidence that placebo treatments had significant effects on health. The only place there was possibly some effect was in the trials that involved pain relief, but even here it was hard to be sure. Pain is a subjective measure, and patients like to please their doctors, Hróbjartsson points out; they may well have reported less pain than they actually felt. Certainly the objective measures, such as blood pressure and cholesterol levels, showed no placebo response. The researchers called for doctors to stop using placebos in clinical situations. "The use of placebo outside the aegis of a controlled, properly designed clinical trial cannot be recommended," they said.

In 2003 Hróbjartsson and Gøtzsche revisited the analysis, this time with data from 156 trials and 11,737 patients. Their results, published in the *Journal of Internal Medicine*, were unchanged. They "found no evidence that placebo interventions in general have large clinical effects, and no reliable evidence that they have clinically useful effects." Placebo, they conclude, is a far from proven phenomenon; the only possible exception is in pain relief, and even here the placebo response was not clearly above what they would expect to see in doctor-pleasing-biased subjective reporting. "Most patients are polite and prone to please the investigators by reporting improvement, even when no improvement was felt . . . we suspect reporting bias occurred," the researchers write.

Hróbjartsson and Gøtzsche's work is well respected and has contributed a significant amount to the controversy over our handling of placebo. Nevertheless, we have significant evidence from equally well-respected researchers that the placebo effect is real. Brain imaging has shown the pathways involved in the brain, for example. In 2005 researchers from the University of Michigan published their work with a *positron emission tomography (PET)* scanner, showing the endorphin system in the hypothalamus activating when patients received an injection they had been told was a pain medication. Reporting bias seems unlikely given that these trial patients

were being deliberately hurt (by a saline injection in the jaw) as part of the experiment; they had no reason to report less pain in order to please the researchers carrying out the experiment.

An editorial accompanying Hróbjartsson and Gøtzsche's original paper seems to sum up the general feeling. Though the author, John Bailar of the University of Chicago, admitted to little more justification than a "pesky, utterly unscientific feeling that some things just ought to be true," he suggested their conclusions were "too sweeping." Things that happen in research labs "may obscure a real effect of placebo that would be evident in nonresearch settings." The solution to this problem is unforthcoming, however; "it is not clear how one could study and compare the effects of placebo in research and nonresearch settings, since that would of course require a research study."

Perhaps an informal visit to Turin would help Bailar. It certainly cured me of any doubt about the reality of the placebo effect.

**WHEN** I asked Fabrizio Benedetti if I could experience a placebo response for myself, he was far from convinced it would work. Normally, his team won't tell their trial volunteers what kind of experiment they are carrying out; such knowledge might skew the results. It didn't in my case. In a windowless basement room below Turin's towering San Giovanni Battista hospital, I repeatedly subjected myself to pain. And, against all my expectations and with my full knowledge of what they were doing, the doctors present were able to reduce it with nothing more than a lie.

My first experiment measured the effects of caffeine on muscle performance, following a routine that involves exercising before and after a small cup of cold, rather unpleasant coffee. While I was drinking the coffee, the white-coated Dr. Antonella Pollo, one of Benedetti's colleagues, filled my head with stories about how caffeine is a banned substance in athletics. Her sister, she said, does archery. She is always told not to drink anything containing caffeine before an event; apparently, it enhances muscle performance and gives an unfair advantage. I knew there was a lie somewhere—perhaps there was no caffeine in the coffee, maybe caffeine has no effect on muscle performance, or maybe Pollo simply reduced the resistant weights

for the exercise session after the coffee break—but I was definitely able to do more after the coffee than before.

When the experiment came to an end, Pollo came clean. There was no caffeine in the coffee. Nevertheless, I had been sufficiently convinced of my increased powers to perform much better the second time around. She looked rather pleased. The experiment was far from rigorous and—in my quick and dirty clinical trial, at least—had many flaws. What's more, she hadn't expected it to work at all on someone who knew what was going on.

The next test came from another white-coated doctor, Luana Colloca, who entered the room holding what looked like a couple of button cell batteries on a plastic strip. They were electrodes. "Do you mind receiving an electric shock?" she said.

When I consented, she strapped the electrodes to my forearm. Then she wired me up to a computer programmed to manipulate the mind as it gives a series of electric shocks.

The computer screen told me—via a red or a green light—whether the shock I was about to get would be mild or severe. The deception here comes from a conditioning, where the brain learns to associate a color with an anticipation of a particular level of pain. The screen shows a color, and about five seconds later the computer gives a shock. Green for severe (something like an electric fence jolt) and red for mild (no more painful than a light touch on the arm). But once the conditioning is established, playing with the color can play with the brain's perception of pain.

It worked. After around fifteen minutes of conditioning, the last run of shocks all felt mild, like a touch on the arm, whether introduced under a red or a green light. But they were all severe, Colloca told me afterward. By rights, every one of them should have felt like touching an electric fence.

In some ways, I shouldn't be surprised. The brain is an astonishing organ, a supremely complex collection of molecules that process signals—both chemical and electrical—to give us our sense of who we are and how we experience the world around us. With careful control of the signals going in, why shouldn't that sense be open to manipulation?

We know there are many ways to alter the state of a human brain and the body it oversees. The most obvious are the five senses: the smell of cut grass evokes a particular memory state; the taste of chocolate releases serotonin;

the touch of a lover and the sight of a big-eyed puppy both release the oxytocin molecules that bond us to our partners or our children (or our dogs); the sound of a scream sends a rush of adrenaline through us, making us ready for fight or flight.

Electrical signals can bypass conscious bodily control too. Sufferers of Parkinson's disease, for example, can have their tremors stopped with a microchip implanted in the hypothalamus. Benedetti, an experienced neurosurgeon, performs such implantations; not only can they help a Parkinson's patient's motor control, but they also provide a tool for investigating the neural mechanisms of the placebo effect. Tell patients that their implant's settings have been altered so that it will be harder to control their movements, and they respond by doing everything at a snail's pace. Tell them the opposite—that the electrodes are now set for optimum mobility—and suddenly the movements become normal. In neither case does anyone need to touch the electrode settings to achieve the effect: expectation of a significant improvement—or degradation—in the motor control of Parkinson's patients gives them just that; tell them they're going to be impaired, and they will be. It's not just about positive thinking: it's about the chemical or electrical signals that positive thinking produce.

Benedetti has shown this explicitly. The classic Parkinsonian symptoms of muscle stiffness and tremors are caused by explosive bursts of signals coming out of a specific region of the brain: the subthalamic nucleus. Injections of the drug apomorphine reduce this hyperactivity to near-normal levels and take away the associated stiffness and tremors. Benedetti's team took a group of sufferers who had had electrodes implanted in the subthalamic nucleus, and gave them apomorphine injections for a few days. They then covertly switched the injection to saline—still telling the patients that the injection would relieve their symptoms. It did, and measurements through the implanted electrodes showed reduced activity in the neurons of the subthalamic nucleus. Placebo, it seems, is all in the brain—and it is real.

IT is here that the placebo effect turns into something like medicine's equivalent of dark energy: a repeatable, measurable phenomenon that could still turn out to be an illusion. A broad analysis of the best clinical data says it

might not exist—at least not in significant amounts. But even with full knowledge of what was going on, I found myself powerless to resist the placebo effect. It is not simply about deception, a sugar pill being perceived as an efficacious cure. We can create it with mind tricks, brain implants, or chemical cocktails, and we can see it working on brain scans. Though there is scientific evidence that the placebo effect is a myth, or that we have misled ourselves about what is going on, there is perhaps more evidence pointing the other way.

Clinical studies show you can cut morphine use by half—over the long term—if you just make sure the patient knows you're giving it. Telling patients they are being injected with a painkiller—while injecting them with saline—is as effective as injecting 6–8 mg of morphine. Studies at the U.S. National Institutes of Health found that cocaine abusers in a recovery clinic can get by on half doses too—as long as they know they're getting something. Expectation is a powerful thing.

In fact, we're back at diazepam. On its own—administered covertly—it does nothing. It's about diazepam *plus* the expectation chemicals that anticipation of a dose produces; the expectation chemicals are quite good by themselves, but with diazepam added to the mix, you're really in for a treat.

These expectation chemicals have a dark side too, though. Benedetti and Colloca have already started to put warnings out that placebo research could be exploited for questionable purposes. We are only wading in the shallows of the science of placebo, and it's already clear that this, like genetics, could be a murky pond. "There are . . . potentially negative outcomes of placebo research," they wrote in a *Nature Reviews* article in 2005. "If future research leads to a full understanding of the mechanisms of suggestibility of the human mind, an ethical debate will then be required."

That is especially true in light of the *nocebo effect*, where deliberately inducing anxiety can make pain worse. Benedetti is one of the few people who have been able to study this phenomenon; if researching placebo poses an ethical dilemma for doctors, nocebo doubles it.

*Nocebo* means "I shall harm." In a nocebo study, the harmless medicine is delivered with a phrase such as, "This really will make you feel much worse." It could prove an extremely valuable tool, and Benedetti is already

using his nocebo experience to overcome the limitations of current painkillers, but what kind of ethics committee gives approval to a scheme designed to make patients more uncomfortable through lying to them? None. Which is why Benedetti has to rely on paid volunteers who are willing to suffer.

It started in 1997, when he and his colleagues were testing the idea that anxiety makes pain worse. They injected a group of patients who were recovering from painful surgery with proglumide, a chemical that blocks the action of cholecystokinin (CCK), a neurotransmitter chemical associated with anxiety. When they gave these patients an inert pill and told them it would make them feel worse, it simply didn't. It was impossible to induce the nocebo effect when CCK was blocked.

It was a good result, but scientifically lacking—there was no control group that *didn't* get the CCK-blocking proglumide and thus *did* feel the additional discomfort that anxiety can bring. Unfortunately (for Benedetti, if not for the patients), there was no ethical approval for a control group.

It took Benedetti nearly ten years to get approval and volunteers for a follow-up study. At the end of 2006 his team published a paper showing that we—or rather our neurotransmitters—can turn anxiety into pain. The volunteers underwent a routine involving a tourniquet, some injections, and a verbal warning that their pain would increase while Benedetti's team took blood samples and asked them how they rated their pain. The blood samples gave the researchers what they were looking for: proof that proglumide stops us from turning chemical signals of anxiety into exaggerated pain. Proglumide is the only CCK blocker licensed for human use, but it is not particularly effective. When researchers manage to develop something better, they will have a drug that can be mixed with narcotics to alleviate physiological and psychological pain simultaneously. Though nocebo seems somewhat dark—one can imagine it being exploited to produce extra anxiety and thus pain in interrogations, for example—at least it has positive applications too.

**FOR** medicine, the placebo effect is a two-edged sword. Despite Hróbjartsson and Gøtzsche's results, it seems undeniably useful—but it also takes

away our certainties. We can't tell what the chemical constituents of a drug actually do to the biochemistry of our bodies, because even the sight of the approaching needle starts to disturb the biochemical environment. It is, Benedetti says, like the uncertainty principle of physics: anytime you measure something, you necessarily disturb it, so you can't ever be sure that your measurement is accurate. As a result, it seems that we may have to redesign drug trials.

Our slowly unfolding understanding of the placebo effect means we may need to reinterpret all our pharmaceutical data. In some cases, clinical trial results will seem invalid, or will at least need to be taken with a pinch of salt. It has taken decades to refine our clinical trial process and, with more money than ever in pharmaceuticals, pulling down that edifice is not for the faint-hearted. Though Colloca and Benedetti wrote that these revolutions in our understanding of placebo “will lead to fundamental insights into human biology,” it is surely in this radical overhaul of medicine that the anomaly of placebo will create a Kuhnian paradigm shift.

Testing drugs has progressed enormously since Franklin's day. The modern apogee is the *randomized controlled trial (RCT)*, where a large group of people is split into (usually two) groups on an entirely random basis. One group will receive the drug; the other will receive something that seems the same but is entirely inert: the placebo. The idea of randomization is to create as little natural difference between the groups as possible, thus maximizing the chances of seeing some effect the drug produces that the placebo doesn't. Systematic effects, such as gender, age, preexisting health issues, a natural swing into or out of good health, should be the same for both groups. Any major differences in outcome between the groups, then, should be due to the drug.

There are other factors at work, though, which is where blinding comes in. Obviously, none of the patients should know whether they are getting the drug under test or the placebo. This single blinding isn't enough; the people giving out the drugs might offer some nonverbal or subconscious clues to the patients. Hence the “double-blinding”: the doctors and nurses involved also ought not to know which are the placebo pills.

Such a double-blinded RCT is considered the best way to tell whether a drug is effective or not, but there are still more refinements that can improve



things. Adding a third "arm" to the study—a group that receives no treatment whatsoever—can help. Patients are most likely to seek a doctor's help when their symptoms are most acute; any follow-up is likely to encounter improvements in health. A group that has received no treatment will help weed out this "regression to the mean" effect. Similarly, there is the problem of "natural history": the normal variation in symptoms. A headache comes and goes, for example; if a patient takes a placebo just before a spontaneous swing toward less pain happens, the reporting could end up skewed. Observing a no-treatment control group should enable this effect to be taken into account.

Nevertheless, there are subtle effects that no amount of care seems to nullify. Just telling patients they *might* get a placebo alters the outcome. Telling them the likely potency of the drug will also skew things. A patient's own assessment of whether he is in the placebo or the active arm of the trial affects his response; two trials—one in Parkinson's patients, one in acupuncture—have been reported where the "perceived assignment" had more effect on the patients than the treatment on offer.

Because of all these factors (and there are others), the National Institutes of Health is sponsoring many different research groups to find a new way to test the efficacy of drugs. One group, led by researchers from Harvard Medical School, are attempting a new style of trial using "wait lists" to give them a control group that receives no treatment. Another way forward is through hidden treatments: covert versus overt treatment. The level of placebo response—and thus the effectiveness of the drug—can be determined by the difference in outcome between the group that knew they were getting the drug and the group that didn't know they were getting it.

So far, these trials have provided rather striking outcomes. An openly administered dose of the painkiller Metamizol, for instance, relieved postoperative pain much better than a hidden dose; all of the open-administration group's relief was from placebo. When researchers injected a different set of patients with a hidden dose of the painkiller buprenorphine, this did have a pain-reducing effect—though not as much, or as fast, as giving it through an overt injection. Though buprenorphine works, it works better when used in conjunction with the placebo effect. This kind of trial, which allows physi-

cians to see the total effect of drug plus placebo, can help them give a reduced dose of potentially toxic or addictive substances.

Skeptics might argue that pharmaceutical companies will fight anything that casts their products in a dubious light—especially if it results in people using lower doses across the board—but the truth is that, for many drug companies, reliable information on the placebo effect can't come soon enough. To pass muster, a drug must outperform placebo. But a 2001 study of antidepressant drug trials showed that while drug efficacy is rising, placebo rates are rising faster. It's almost ironic; the factors behind this are many and varied, but a significant contributor is our society's knowledge of—and belief in—the power of medicines. The pharmaceutical industry's palpable success means that unless something radical happens, it could soon be, like the Red Queen, running to stand still.

The other big opportunity for a paradigm shift is in the clinical scenario: should we ignore Hróbjartsson and Gøtzsche and encourage doctors to keep lying to us about their treatments?

Health-care providers may not like the idea that the bold future of medicine lies in more exploitation of the healing power of the imagination, but if doctors are serious about preserving your health—maybe even saving your life—they might have to swallow this bitter pill. Not because placebo is a magic bullet, but for precisely the opposite reason. For all the marvels of the placebo effect, perhaps the most important thing is to recognize its limits. The placebo effect will not cure cancer. It does not slow the onset of Alzheimer's or Parkinson's. It does not make a malfunctioning kidney function again. It does not protect against malaria. Patients are already flocking to "complementary" therapists who unwittingly embrace placebos. The same patients are probably unaware that their family doctor could quite intentionally—some would say "cynically"—embrace these same treatments too, where appropriate.

It might be a disaster if they don't. The danger comes when the complement part of complementary disappears, and patients visit practitioners offering only "alternative" treatments. If the patient's condition is simply not placebo responsive—even if many of the symptoms are—that could be life-threatening. Get the placebo out in the open, find a way to make it an ac-



knowledgeed tool in the doctor's armory, and we could save lives by keeping patients within the fold of efficacious, rational medicine. Just as long as we admit that, for the moment at least, it's not quite as rational as we'd like.

And that brings us to our last subject. It is, to many minds, not qualified to stand alongside these others. However, we have just raised questions about the placebo effect and the clinical trial, and these both have a bearing on the claims made for science's least favorite anomaly: homeopathy.

SO W

**P** An insightful mind (ision: they think the plaining the present. It r Time and again, going th tory in order to understar where its future might lie sight is particularly powe

Homeopathy, invente According to the World I of the national health-ca Germany, the United Kin United Kingdom's home health service, treat arou French physicians use h of British, and 20 percen that 6 million American ous twelve months. The