

Meaning, Medicine, and the "Placebo Effect"

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of publication. The points represented by solid circles are studies of one of the first really effective treatments for ulcer disease, cimetidine (trade-name Tagamet), a drug which inhibits the production of acid in the gut. The earliest studies were done in 1975, and they continued for about ten years. But in 1981, the first studies were done of a new, "better" drug which also blocked acid called ranitidine (trade-name Zantac). Before ranitidine came along in 1981, cimetidine healed 72% of the patients treated with it in trials. After ranitidine came along, the effectiveness of cimetidine dropped so that only 64% of patients treated with it were cured; ranitidine cured 75% of patients treated with it in trials. It is, of course, research physicians (those doing these studies), not patients, who are fully aware of (and excited by) newly emerging drugs. As they convey their enthusiasm for their new drugs, they may simultaneously disparage the "older" ones, even though they may not be aware they are doing it.

In summary, what patients know (not what kinds of people they are), and what things mean, is what accounts for the effectiveness of much of medical treatment. And, of course, the single most important source of knowledge and meaning for patients is their doctors. Doctors know lots of things. Many of the things that they know they are unaware of knowing (as is true for most of us in this life). But it is the depth of their convictions which conveys to patients the power of their treatments.

5 Formal factors and the meaning response

The most important aspect of any medical experience is its *content*. Whether a physician or healer prescribes aspirin or penicillin, willow bark tea or quinine, the most crucial thing is that the drug has some sort of active ingredient which interacts with the body, the immune system, a pathogen or the like, to facilitate recovery. But the content of medicines is not the only thing that counts. We have just reviewed the effect that physicians – their knowledge, their enthusiasms – can have on treatment. The *form* of medicines, their color, shape, and amount, makes a difference, too.

Meaningful pills (pink and blue ones)

In the early 1970s, several professors at the University of Cincinnati medical school devised an interesting experiment for their students (Blackwell, Bloomfield, and Buncher 1972). Fifty-seven second-year medical students agreed to participate in what they were told was a study of two new drugs. Each student would receive either a stimulant or a sedative. They were told the ordinary effects of these drugs. For example, they were told that "a sedative drug usually makes the individual feel more relaxed, calm and easy-going, but some people react by feeling drowsy, sluggish or tired. There is a tendency toward a decrease in pulse-rate, pupil size, and arterial [blood] pressure." The students were randomly divided into four groups. These groups received, respectively, one or two pink or blue tablets; the tablets were, in fact, inert. The students filled out a form describing their mood, took one another's blood pressure, took their tablets, listened to a one-hour lecture (the professors don't tell us what the lecture was about!), and then went back to the laboratory to fill out another mood rating form and to take one another's blood pressure again.

What happened? First, students who got two inert pills had more pronounced effects than those taking only one tablet. While the effects they reported ("more drowsy," "more sluggish") were generally moderate,

among students who took one tablet, 6 of 119 responses were relatively severe, while among those taking two tablets, 26 of 158 responses were more severe. This is a statistically significant result ($p < .005$; this would occur by chance fewer than 5 times if one repeated the experiment 1,000 times).

Overall, students in the experiment felt less alert after the experiment than before. The professors attribute this to the fact that they spent an hour in class listening to that unspecified lecture. But, 66% of students who had taken blue tablets felt less alert compared to only 26% of those who had pink tablets. It is unfortunate that the professors didn't include a group of students who took no pills to see how the lecture affected *them*. But, for anyone who has ever sat through a long class, we can probably guess that the pink pills, clearly interpreted by some students as stimulants, inoculated them against some boredom!

What can we learn from this interesting experiment? First, let's consider some of the things we can eliminate. It is quite clear that the medication the students received had nothing to do with the outcome: in the first place, the tablets were designed to be inert; and, in the second place, people responded differently to the same "ingredients" depending on the color of the pills. It seems extremely unlikely that "regression to the mean" had anything to do with the results of this experiment; these students weren't sick to begin with, and although they may have been bored, since they were put into the four groups randomly, it's unlikely that the students getting blue pills were more bored to begin with than those getting pink pills. And it's unlikely that physician enthusiasm had much to do with it – presumably they were as enthusiastic about the blues as the pinks.

Clearly, the color of the pills the students took made a difference. Why? It seems pretty clear that these colors – pink and blue – have "meanings." Pinks, reds and oranges are among the colors which are called "warm" or "hot." Red is the color of stop lights, stop signs, and (traditionally, at least) fire trucks. Blue and green are "cool" colors. While one might have (or sing) the "blues," one might also listen to Jelly Roll Morton's "Red Hot Peppers" for a rather different musical experience. A study in Texas showed that red and black capsules were ranked as "strongest" while white ones were "weakest"; men had stronger preferences than did women (Sallis and Buckalew 1984). Colors are meaningful, and these meanings can affect the outcome of medical treatment.¹¹

The medical students in the experiment responded exactly as this meaningful code predicts (and as the experimenters predicted). Red

¹¹ For a fascinating analysis of Western color symbolism, see Marshall Sahlins' interesting account (1976).

tablets were uppers, and blue ones were downers. Ton de Craen, a Dutch epidemiologist, has shown that this is more generally true. He and his colleagues did a study of forty-nine medicines available for sale in Holland which affect the nervous system. They found that stimulant medications tend to be marketed in red, orange or yellow tablets, while depressants or tranquilizers tend to be marketed in blue, green or purple ones (de Craen *et al.* 1996).

Soccer and the Virgin Mary

It is not always quite this simple. In a British study, people with various anxiety states responded differently to the same drug (oxazepam, or Serax, a drug similar to Valium) depending on the color of the tablet: symptoms of anxiety were more improved when the tablets were green, and symptoms of depression were more improved when the tablets were yellow (Schapira *et al.* 1970).

Two Italian studies show that there can be gender differences in these matters of color. The studies are rather complicated and a bit hard to interpret, but they seem to show that, when men and women are given blue or orange placebo sleeping pills, the women fall asleep much more quickly than the men when given blue placebos, and the duration of sleep is much longer for women given blue placebos than it is for men (Cattaneo, Lucchilli, and Filippucci 1970; Lucchelli, Cattaneo, and Zattoni 1978). In Italy, blue pills inhibit sleep in men, or promote it in women, or both, at least compared to orange pills. I am not quite sure what to make of the British study, but there may be some sense in the Italian one. In Italy, the color blue has different meanings for men and women. For women, blue is considered to be the color of the dress of the Virgin Mary. Since the Virgin is always thought of in blue, and since the Mother of God is a very reassuring and protective figure for Italian women, it seems reasonable that blue sleeping pills should be effective for them. By contrast, for Italian men, blue is the color of Azzurri, the national Italian soccer team. Blue (or azure) means success, powerful movement, strength and grace on the field, and, generally, great excitement. So it is at least plausible that blue sleeping tablets would work less well for men than for women. Orange, by contrast, is a color without strong meanings in Italian culture.¹²

¹² For this account of the meaning of blue in Italy, I am indebted to Lola Romanucci-Ross and her husband, John Ross, MD. Dr. Romanucci-Ross has published extensively on the anthropology of Italy. Forza Azzurri has a very cool web site at <http://forzaazzurri.com/>. The team slogan is "losing is not an option," not a notion conducive to a nice nap.

Another apparent exception to the notion of blue pills as being "downers" is the interesting case of Viagra, marketed in a pastel blue pill.¹³ If anything should be displayed as an "upper," this ought to be it. The pill is prominently displayed in advertising, its lozenge shape pointing upward to the right. This is an interesting example of what Victor Turner has called "polysemy" – the notion that the same sign can represent different things at different times and contexts. So, checking the Oxford English Dictionary, one finds a long list of citations following the definition of the word "blue": "Affected with fear, discomfort, anxiety, etc. . . . depressed, miserable. low-spirited." But "blue" is also defined as "Indecent, obscene," as in the term "a blue movie," which is "libidinous." And while "blueness" may mean "indelicacy, indecency," it's also the case that "a blue-nose" is "someone who is excessively puritanical." Viagra surely partakes more of the "blue movie" than the "blue nose."

It is important to remember that, in all of these cases – the medical students from Cincinnati, and the other study subjects from Italy and Britain – the comparisons were made between people taking the same drugs, either placebo or real. The only difference was in the color. It is also important to note that these sorts of effects showed up not only when people took placebos, but also when they took real drugs. As you can see, the term "placebo effect" doesn't seem very apt here if the same thing happens whether people take placebos or active drugs. Suppose we notice that none of the sailors who eat lemons get scurvy. We call it the "lemon effect." Then we discover that no one who eats grapefruit gets scurvy. Do we still call this the "lemon effect?" We surely could, but it wouldn't be very precise.

Two is more than one

In our study with the medical students, the professors found a difference in effect not only between the colors of placebos, but also in their numbers. Two worked better than one. Given that the pills were inert and had zero effectiveness for anything, the fact that someone took two of them shouldn't make any difference, since two times zero is still zero. But it did.

In the large series of 117 studies of treatments for ulcers, there were a number of different dosing schemes. But among all the patients in these studies, 618 patients were to take their placebos twice a day, while 1,058 were to take their placebos four times a day. After 4 weeks of taking placebos, 32.5% of the patients taking two placebos a day had no active

ulcers visible in the endoscope while 38.2% of the patients taking four a day had no active ulcers; that is a difference of 5.7%. This is not a big difference, but it is a statistically significant one ($\chi^2 = 5.6, p < .02$). There is less than one chance in 50 that this outcome is due simply to chance (Moerman 2000). In a similar study with a somewhat different set of ulcer trials, and much more sophisticated statistical techniques, Ton de Craen, a researcher in the Netherlands, has shown a larger difference than this: 36.2% of 1,504 patients taking two placebos a day were ulcer free in 4 weeks while 44.2% of 1,821 patients taking them four times a day were ulcer free; that's a difference of 8% (de Craen *et al.* 1999).

Why does this happen? Well, it seems pretty simple. What's important here is the meaning of things. When my grandson was not yet three, I asked him if he wanted one cookie or two. "Two cooks," he said, not worrying about spoiling the broth, walking away, happy as could be, with a cookie in each hand. You don't need to be a rocket scientist to know that two is more than one, or that four is more than two.

Capsules and tablets; shots and pills

These matters of color and number are matters of the *form* of medicine. There are other matters of form which make a difference as well. A Canadian study with 29 patients showed that chlorthalidopoxide (Librium) was more effective against anxiety, phobias, and broken sleep when the drug was given to the patients in a capsule than when it was given as a tablet. In this study, the patients were to take pills three times per day. When they took capsules they took their pills more regularly (mean of 2.97 capsules per day) than when they took tablets (2.49 per day). Moreover, patients expressed a strong preference for the capsules: "Eleven patients requested continuation of the same treatment while receiving treatment with capsules, and on withdrawal of treatment the capsule group voiced more complaints" (Hussain and Ahad 1970). The authors conclude that both factors – patient preference and compliance – accounted for the difference in improvement.

Likewise, the route of administration of a drug (or placebo) can have a significant effect on its value. For example, it is widely recognized ("every-one knows") that shots are more powerful than pills. There is even some scientific evidence for this. In the early 1960s, a team of doctors and pharmacologists at the University of Mississippi did a very interesting experiment. They enrolled 134 patients with high blood pressure in a study of a new drug which showed promise for lowering blood pressure. They were divided into 4 groups. One group got the drug in the form of oral pills while another group got oral placebos which they took three times

¹³ Robert Hahn brought this issue to my attention, and helped solve it.

a day for 12 weeks. Another group received an injection of the drug, while the last group received an injection of a placebo (sterile saline solution) once every two weeks. The patients treated with pills didn't respond very well; their blood pressure dropped a small amount in both groups, but not enough to be clinically significant. The patients in groups which received injections had a much greater response. In both groups, blood pressure declined significantly for about a year (47 weeks in the group getting the drug injections, and 59 weeks in the group getting the placebo injections) whereupon it slowly went back to where it had been when the experiment began 3 years earlier. The authors conclude that the "inference to be drawn is that the parenteral [that is, injected] placebo is more effective than the oral placebo... [and that] more hypotensive [pressure reducing] effect is obtained from one [inert] injection every two weeks than from one [inert] tablet three times a day" (Grenfell, Briggs, and Holland 1961:129).

Taking a different approach, Ton de Craen has shown that injected placebo is more effective than oral placebo in the treatment of headache (de Craen *et al.* 2000). When the drug sumatriptan (known in the United States as Imitrex) was first introduced to treat migraine headaches, it was only available in the form of an injection; today it is still available that way, but also as tablets and nasal spray. Dr. de Craen did a meta-analysis of 35 trials, combining the data from many of them to see what the effects were. In placebo-treated patients, among those treated with a pill taken by mouth, after two hours 25.7% of patients (222 of 865) reported that their headache was better (it was gone, or mild). Of those treated with a placebo injection, 32.4% of patients (279 of 862) were better. Again, this difference is small (6.7%) but it is highly statistically significant, and could be expected to happen by chance only twice if we repeated the experiment 1000 times ($\chi^2 = 9.4$, $p = 0.002$).

What is happening here? This is one of those things which "everyone knows." The fact that we consider *all* drugs to be very powerful is probably the reason that we keep worn out medicines in the medicine cabinet in the bathroom long after their expiration dates, long after we would ever take them for anything.¹⁴ Some of them are, however, more powerful than

¹⁴ Several years ago, a student in one of my classes wanted to do a study to see just what kind of pills people thought were more powerful than others. She asked all the other students in the class to bring to her "one of each" of the pills stored in their medicine cabinets at home. Thirty students brought in so many pills that she took them home in a grocery bag. Everyone was amazed. It turned out in the study that people thought the most powerful drugs were large, multicolored capsules (especially red and white ones) and very tiny pills.

A classic (etic) account of the meaningfulness of American bathroom medicine cabinets can be found in Horace Miner's famous description of the body rituals of the

others. There are lots of things like this, things we just "know," even in the absence of evidence. We "know" that red pills are stimulants and that blue ones are depressants. We know that shots are more powerful than pills. This is the kind of thing that doctors know as well as patients (even if it isn't "true" in a particular case). We know that drugs which have to be stored in the refrigerator are more powerful than ones that can be kept in the medicine cabinet. We know that big multi-colored capsules are more powerful than white aspirin-sized tablets. We know that very tiny pills, which must be small because they have very powerful medicine in them, are stronger than aspirin-sized tablets. We know that the antiseptic medicines that we put on cuts must be red, and that wounds must be covered in order to protect them from the "air." When a sore is in a place that is hard to bandage (on a lip, for example), we cover it with grease. And we know that prescription drugs are more powerful than drugs we can buy over the counter.

There is, to my knowledge, only scientific evidence to show the first two of these are actually correct (pill color, and shots vs. pills). But the other statements are examples of the kinds of things we know which influence the way in which we interpret the meanings of our medications. And it seems that, as long as we know these things to be true, we are right.

Meaningful surgery

Another one of the things we all know is that surgery is *really* powerful. This makes excellent sense for many reasons. In a surgical procedure (what, in recent years, has come to be called "a surgery") the patient is rendered unconscious, or senseless, and a surgeon actually enters the patient's body; blood is shed (or sacrificed). The process is in its very nature dangerous. "The operation was a success, but the patient died," is a classic phrase of the surgical art, indicating the dangers surrounding even the most positive outcomes. These are powerful images. It is not surprising that they might have powerful effects on patients, and on their sickness. But, for a variety of reasons, we know very little about the meaning response in such cases.

There are very few double blind trials of surgical procedures. There are two fundamental, and closely related, reasons why this is the case. First, it is considered too dangerous. Anesthesia itself is dangerous (although much less so than as recently as the 1980s), and it is very hard to imagine that many such studies would be approved by institutional review boards,

Nacirema (Miner 1956). For a quite different (emic) take on the same situation, see J. D. Salinger's famous story "Zooey" (Salinger 1955:74-6).

or IRBs. ("IRBs" are committees of doctors, ethicists, and, often, community members who review research proposals to see that they are fair to all the patients and ethically appropriate.) But many medical procedures are dangerous; many modern drugs are very toxic and must be taken very carefully. So why is it that the dangers inherent to surgery are considered especially serious?

The reason for this, it seems to me, is rather subtle, and follows from a major difference between "medicine" and "surgery." For millennia, most drugs have been derived from some sort of natural product, usually a plant. Most of the time, there has been no obvious reason why the plant should have the effect it does on human beings. For example opium, derived from poppies, has a dramatic effect on human beings. Why would a poppy care about whether human beings get pain relief from surgery, or get high? The salicylates (precursors to aspirin, ibuprofen, and most of the other "non-steroidal anti-inflammatory drugs") are widely found in nature – in willows (the salicylates are named after the genus of willows: *Salix*), birches, and particularly in the shrubs of the genus meadowsweet (*Spiraea*), after which aspirin is named. While sometimes it is possible to speculate why plants might produce such substances (poppies are quite toxic to insects due to their opium content, and therefore are rarely eaten by them), at other times it is quite unclear. And even if it is clear what the ecological factors may be, it was still only in the 1970s that scientists discovered the *endorphins*, or "endogenous opiates" ("opiates from the inside"), which are part of the mammalian pain regulation system.¹⁵ Generally it is the case that our experience with drugs is based on "empirical experience." Most of the time there is only very little real understanding of how drugs work. It is, for example, still not clear exactly how aspirin works, although it surely does. And so there is ample reason to devise tests which show us clearly and convincingly that some substance from whatever source *really does* stop headaches, or heal ulcers, or whatever it might be that we want to treat.

Surgery is quite different. Surgical procedures do not come from plants. They are not done for empirical reasons, but for *logical* reasons. It seems perfectly logical to put pressure on a cut or wound to stop the bleeding, to clamp down on a ruptured artery, and to forcibly remove a loose, decayed or broken tooth. Without offense, it does not require great insight or imagination to think that one might set a broken arm or remove a decayed or broken tooth. Indeed, there is evidence of chimpanzees removing the loose teeth of others using small sticks (McGrew and Tutin 1972).

¹⁵ When this was discovered, many were extremely skeptical, unable to believe that the body could or would produce substances to which it might become "addicted." But it does.



5.1 Belle removes a loose tooth from Bandit by using a small stick while Shadow looks on. Delta Primate Center, Covington, Louisiana, 1972.

While it doesn't make much sense that willow bark tea relieves headaches (since, after all, willows don't even have heads), it makes perfect sense to take out a diseased organ – an appendix, a spleen – that one might get along without; for people who are comfortable describing blood vessels as "plumbing," it makes perfect sense to put shunts around blocked arteries, as in a coronary bypass operation. As we will see, at least occasionally, it turns out that these procedures work just fine, but not necessarily because of the logic behind them. We will take a look at the logic of a very important related set of illnesses and see where it leads.

Coronary artery disease

One of the most common causes of death in the United States is myocardial infarction, or heart attack. The traditional biomedical understanding of this disease is that it is caused by *ischemia*, a lack of adequate blood flow to some region of the heart, which is in turn caused by *atherosclerosis*, which is a build-up of lipids or fatty tissues in the coronary arteries, the arteries which supply blood to the heart itself; most people have three coronary arteries, while a few have four or five. These fatty tissues, of course, are said to be due to excess cholesterol in the body, due