4: Explanatory mechanisms for placebo effects: cultural influences and the meaning response

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Summary

In this chapter, I reconceptualize elements of the "placebo effect" as the *meaning response*. The meaning response is defined as *the physiological or psychological effects of meaning in the treatment of illness*. Much of what is called the placebo effect – meaning responses elicited with inert medications – is a special case of the meaning response, as is the "nocebo effect". Several implications of this reconceptualization are described, and emphasis is placed on the idea that meaning effects accompany *any* effective medical treatment.

Introduction

A few years ago, Anne Harrington wrote that there was a tension in studies of placebos, a tension between the cultural or hermeneutic sciences, those concerned with "meaning", and the natural sciences, roughly committed, she said, to explanations in terms of "mechanisms". "Because placebos as a phenomenon seem to hover ambiguously at the crossroads between these two perspectives, they are at once a frustration and wonderful challenge".[1] In this chapter, I plan to "hover at the crossroad", trying to connect meaning with mechanism.

Definitions

Placebo effects are, today, most commonly recognized in research medicine where they are among the reasons for the requirement for the randomized controlled trial (RCTs). It is commonly the case that patients

who are given inert medications ("dummies", "placebos") in RCTs get well just as do the patients given the drug under study (the "verum"). For this reason, the "placebo effect" is often defined as the response of patients to inert treatments. This definition leads quickly to paradox and ambiguity,[2] largely because it involves a confusion of correlation with cause. All the control group patients had inert tablets, therefore the inert tablets caused their improvement; and similarly, in the experimental group, all the patients had active treatments, therefore the drug caused their improvement. Neither, of course, is a valid claim. I take an alternate approach and define the *meaning response* as *the physiological or psychological effects of meaning in the treatment of illness*; when these responses are elicited after the use of inert or sham treatment, these responses, although still meaning responses, can be called the "placebo effect" when they are desirable and the "nocebo effect" when undesirable. Note that this definition excludes several elements that might help to account for the improvement of some patients in either arm of an RCT that might include "natural history" (some things might "go away by themselves") or regression to the mean, experimenter or subject bias, systematic error in measurement or reporting, and the like; under certain very special and unusual circumstances some improvement may be attributable to "conditioning". Notice that this definition is not phrased in terms of "non-specific" effects; while many elements of the meaning response or placebo effect may seem to be non-specific, they are often quite specific in principle once they are understood. Several examples may make clear what this definition entails.

Medical treatments are meaningful

One, two; pink, blue

A group of medical students was asked to participate in a study of two new drugs, one a sedative and the other a stimulant.[3] Each student was given a packet containing either one or two blue or pink tablets; the tablets were inert. Later, the students' responses to a questionnaire indicated that the red tablets tended to act as stimulants while the blue ones acted as depressants; and, two tablets had more effect than one. The response of these students was not to the inertness of the tablets, and cannot easily be accounted for by natural history, conditioning or regression to the mean. Rather, they can be accounted for by the "meanings" in the experiment: pink or red means "up", "hot", "danger", while blue means "down", "cool", "quiet". And, two means more than one.

Branding

In a British study, 835 women who used analgesics for headache were randomly assigned to one of four groups.[4] One group (D) received aspirin labeled with a widely advertised brand name ("one of the most popular … analgesics in the United Kingdom widely available for many years and

supported by extensive advertising"). The other groups received the same aspirin in a plain package (group C), or placebo marked with the same widely advertised brand name (group B), or unmarked placebo (group A). The women took the pills when they had headaches, then reported how they felt an hour later on a 6-point scale (from −1 for "Worse" to +4 for "Completely better"). "Mean pain relief after one hour for each group … was: group A (unbranded placebo) 1·78, group B (branded placebo) 2·18, group C (unbranded active) 2·48, and group D (branded active) 2·7". These differences were statistically significant; the active treatment groups reported more pain relief than placebo groups ($F = 40{\cdot}96$, $p < 0{\cdot}001$), and branded preparations provided more pain relief than did non-branded ones ($F = 18{\cdot}84$, $p < 0{\cdot}001$).

In particular, for 435 headaches reported by branded placebo users, 55% were reported as improved after an hour (rated two, three or four on the scale) while only 45% of 410 headaches were reported to be that much better by unbranded placebo users ($\chi^2 = 6{\cdot}76$, $p < 0{\cdot}01$). Aspirin relieves headaches. But so does the knowledge that the pills you are taking are good ones, which you learned on TV.

Aerobic exercise

In a study of the benefits of aerobic exercise, two groups carried out a 10-week exercise program. One group was told the exercise would enhance their aerobic capacity while another was told the exercise would enhance aerobic capacity and psychological wellbeing. Both groups improved their aerobic capacity; but only the second improved in psychological wellbeing (actually "self-esteem"). The researchers call this "strong evidence … that exercise may enhance psychological wellbeing via a strong placebo effect".[5]

In the red versus blue pill study, we can correctly (if not very helpfully) classify the responses of the students as "placebo effects". But in the second study, the presence of the brand name enhanced the action of both the inert and the active treatments. It does not seem reasonable to classify the "brand name effect" as a "placebo effect" since there need not be any placebos involved. And calling the consequences of authoritative instruction to the exercisers a "placebo effect" could only come from someone who believes that words are inert, and do not affect the world, someone who has never been told "I love you", or someone who has never read the reviews of a rejected grant proposal. It seems quite reasonable to label all these effects (except, of course, of the aspirin and the exercise) as "meaning responses".*

* As this was written during the fall of 2000, I saw a similar use of language in discussions of the effect of new "drag free" suits which might give an edge to Olympic swimmers. *US News and World Report* said "[S]wimming officials aren't convinced this is anything more than the placebo effect. Swimmers excel because they *think* they've got an edge" (Aug 21, 2000, p. 55). "Thinking", in my view, is not inert.

Chinese astrology

Such fateful effects of meaning can occur in much broader and more diffuse contexts than simple experiments. A large study examined the cause of death of 28 169 adult Chinese Americans and nearly half a million randomly selected matched "white" controls, all from California. It was found that "Chinese Americans, but not whites, die significantly earlier than normal (1·3–4·9 yr) if they have a combination of disease and birth year which Chinese astrology and medicine consider ill fated".[6] For example, among the Chinese Americans whose deaths were attributed to lymphatic cancer (n = 3041), those who were born in "Earth years" – and consequently were deemed, by Chinese medical theory, especially susceptible to diseases involving lumps, nodules, or tumors – had an average age at death (AAD) of 59·7 years; among those born in other years, AAD of Chinese Americans also suffering from lymphatic cancer was 63·6 years, nearly four years longer. Similarly, for Chinese Americans who died of illnesses related to lung diseases (bronchitis, emphysema and asthma), those who were born in "Metal years" – "the Lung [is] the organ of Metal"[7] – had an average AAD of 66·9 years; among those born in other years, AAD of those dying from such lung diseases was 71·9 years, five years longer. Similar differences were found for other sorts of cancers, for heart attack, and for a series of other diseases. No such differences were evident in a large series of "whites" who died of similar causes in the same period; the difference in age of death, for example, from lung diseases for whites born in "metal years" and those born in other years was 0·07 years (26 days). The intensity of the effect was shown to be correlated with "the strength of commitment to traditional Chinese culture".

It is clear from this case that these significant differences in longevity among Chinese Americans (up to six or seven per cent of length of life) is not due to having Chinese genes, but to having Chinese ideas, to knowing the world in Chinese ways. The effects of meaning on health and disease are not restricted to placebos or brand names, but permeate life.

Sociosomatics

I hope that by now my argument has indicated that the "placebo effect" is only a tiny portion of a much larger field linking social and meaningful processes with human biological ones. Arthur Kleinman has characterized an aspect of these relationships as "sociosomatics",[8] which he describes as "the fundamental dialectic between the body and the social world".[9] While the placebo effect is only a very small piece of that dialectic, it is an important one since it is subject to experimental observation. One can randomly give people inert pills or real drugs and see what happens; one cannot randomize half a group to be Chinese and the other half to be Tahitian.

Dimensions of the effects of meaning in medicine

The meaning response has many dimensions in medical care.

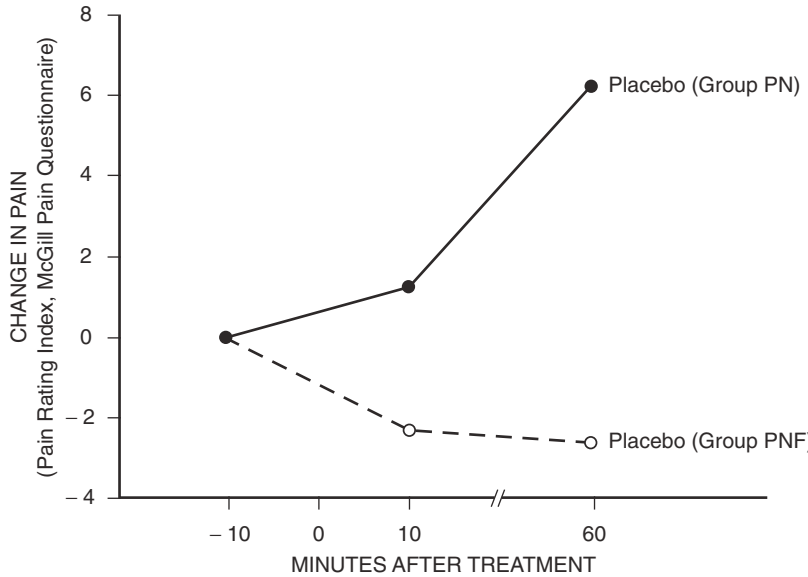
Meaning permeates medical treatment

Insofar as medicine is meaningful, it can affect patients, and it can affect the outcome of treatment. Most elements of medicine *are* meaningful, even if practitioners do not intend them to be so. The doctor's costume (the white coat with stethoscope hanging out of the pocket),[10] manner ("enthusiastic" or not), style ("therapeutic" or " experimental"), and language are all meaningful and can be shown to affect the outcome;[11] it has been argued that diagnosis itself is an important form of treatment.[12] Many of these factors have recently been reviewed by Gracely.[13]

Many studies can be cited to document aspects of the therapeutic quality of the practitioner's manner. Perhaps the best of these compared four different factors contributing to the placebo effect: status of the communicator of drug effects (dentist versus technician), attitude of the dentist and attitude of the technician ("warm" versus "neutral"), and message of drug effect ("oversell" versus "undersell"). By far the most significant of these effects was the last. A strong message of the effect of a drug (actually an inert capsule) substantially reduced the patients' reports of the pain of mandibular block injection compared with a weak message, and those who received the weak message reported less pain than a group that received no placebos and no message at all.[14]

In a more recent study of general practice consultation, Thomas showed the effect of a "positive" manner compared with a more matter-of-fact approach on the part of the physician. A series of 200 patients with symptoms but no abnormal physical signs (characteristic of roughly half of office visits to the general practitioner), were randomly assigned to a "positive" consultation with or without a prescription (of a generally neutral drug, 3 mg tablets of thiamine hydrochloride), or a "negative" consultation with or without the same prescription. In the positive consultations, "the patient was given a firm diagnosis and told confidently that he would be better in a few days". In the negative consultations, the doctor said "I cannot be certain of what is the matter with you". In a survey of patients two weeks later, 64% of positive consultation patients said they were better, while only 39% of those who had negative consultations thought they were better ($p < 0{\cdot}001$). Receiving a treatment in this study made no difference; physician attitude overrode any considerations of the pills patients might have received.[15] The physician had an effect but the placebos did not.

Such physician attitudes can be conveyed to patients in extremely subtle and delicate ways. Gracely has described a phased experiment in which dental patients were told they would receive either placebo (which might reduce the pain of third molar extraction, or might do nothing), naloxone



Change in pain rating index between baseline (10 min before injection) and 10 and 60 min after administration of placebo.

PN = group that could have either received placebo or naloxone.
PNF = group that could have received placebo, naloxone, or fentanyl (PNF).

Figure 4.1 Physician effects in placebo treatment can be very subtle.[16]

(which might increase their pain, or do nothing), fentanyl (which might reduce their pain, or do nothing), or no treatment at all. Subjects were all recruited from the same patient stream, with consistent selection criteria by the same staff. In the first phase of the study, clinicians (but not patients) were told fentanyl was not yet a possibility because of administrative problems with the study protocol, yielding the PN group. In the second phase, clinicians were told that patients might indeed receive fentanyl, yielding the PNF group; see Figure 4.1. Placebo treated patients during the second phase experienced significant pain reduction from their inert treatment while those in the first group did not.[16] The only apparent difference between the two groups was that the clinicians knew that the first would not get fentanyl and the second group might (although none represented in the figure actually did; they all received only placebo).

It is often suggested that one should use drugs quickly before they lose their effectiveness (this quip has been attributed to several people, among them the 19th century French physician Armand Trousseau[17] and William Osler[18]). In particular, there is evidence to suggest that the effectiveness of drugs declines as new drugs come along. In Figure 4.2, the results of a large series of studies of two different treatments for peptic ulcer disease are plotted by year of publication. It is, of course, research physicians, not patients, who are aware of the significance and possible value of new drugs.

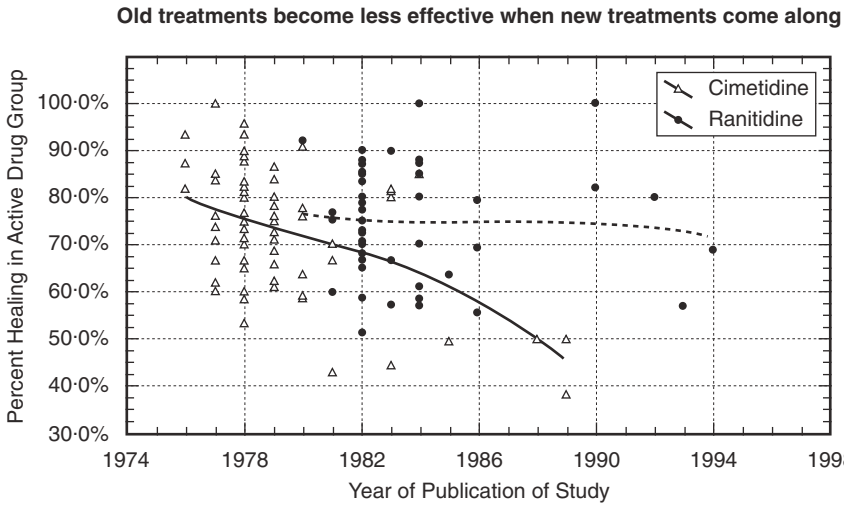


Figure 4.2 Two sets of trials of treatments of peptic ulcer disease.[44]

While there is strong evidence for such "physician effects", there is little to show that "patient effects" are very important. A mass of research in the 1970s designed to identify "placebo reactors" produced only inconsistent and contradictory findings.[19–21]

Physician and patient need not share the same meanings

It is interesting that, in some of these cases, doctor and patient may not share the same system of meaning. Traditional Chinese Medicine is based in large part on the manipulation of *chi* using a combination of herbal treatments, acupuncture and so on.[7] Acupuncture, in particular, has become quite popular in the West.[22] Yet few Western patients know much about *chi* or its manipulation, and most would have difficulty fitting such knowledge into their school-based understanding of physiology – nerves, blood vessels, and so on. Their knowledge of oriental medicine in general and acupuncture in particular is probably based on their watching Bill Moyers on public television, where they may have learned that "acupuncture works" although for no evident reasons. Cassidy has found that, even after six months of acupuncture care, American patients still have a very sketchy understanding of the system, at least in terms authentic to oriental medicine, yet they are very enthusiastic about their care which they deem extremely effective.[23]

In conventional medicine, too, the conceptualization of illness is often quite distinct for patient and physician. The contrast of the physician's view of "hypertension" ("a disease of unknown origin, a risk factor for stroke") and the patient's view of "hypertension" ("a physical illness characterized by

excessive nervousness caused by untoward social stress") is a case in point.[24] This suggests that the strength of a physician's convictions is more important than the convictions themselves.

Regardless of the style of medicine (conventional, complementary) or what the fit is between physician and patient understandings of the system, it is important to recognize that, until there is clear evidence to the contrary, it makes most sense to expect that the effectiveness of *any* form of medical treatment will include some component of meaning response, whether or not it is the meaning the physician intended.

Meaning responses can be demonstrated in surgery as well as in internal medicine

BIMAL

The classic example of surgical placebo effects comes from two studies of the bilateral internal mammary artery ligation (BIMAL) as a treatment for angina;[25,26] in this procedure, the idea was that ligating the mammary arteries would increase the amount of blood flow to the heart via a set of arteries postulated to exist for a variety of (rather obscure) reasons which were (none the less) easy to convey to patients. Combining these two studies, 24 of 33 patients (73%) showed substantial improvement on patient and physician assessment while nine did not. Patients in both studies showed increased exercise tolerance and reduced nitroglycerine consumption. Patients who received the sham surgery (local anesthesia, chest incision, and artery exposed but not ligated) did somewhat better overall as 10 of 12 (83%) showed substantial improvement. While the operation, which was becoming quite popular at the time, quickly disappeared from practice after publication of these two studies, it is worth noting that these effectiveness rates (and those reported by the proponents of the procedure at the time, for example, see Kitchell, *et al.*[27]) are much the same as those achieved by contemporary treatments like coronary artery bypass or beta blockers; to my knowledge, no double blind trials of the former have been carried out.

TMR

Meaning responses may occur in the most contemporary forms of heart surgery:

> "PLC, The Heart Laser, opening new *bloodlines*: What are *bloodlines*? *Bloodlines* are conduits created by the Heart Laser through the wall of the left ventricle. These *bloodlines* allow oxygen rich blood to saturate the oxygen-starved heart tissue".

At least that is what it says on the website of the company that makes the laser, PLC Medical Systems, Inc.[28]

Transmyocardial laser revascularization (TMR) is the most recent surgical approach to angina. A company spokesperson told me that they

estimate they were approaching a total of 6000 procedures worldwide (in Spring 2000) explaining that, after the procedure was covered by Medicare, it quickly gained widespread acceptance in the medical world (Floody P, personal communication).

Elements of transmyocardial revascularization

In TMR, an incision is made in the side of the chest between two ribs. The pericardium is removed, and the myocardium is exposed. A laser (several different types are used) is touched to the surface of the heart, and a laser beam is fired into the heart, presumably to make a channel thru the heart. Usually 30 to 50 such channels are made. The idea is that this will make a sort of substitute artery, a "bloodline" in the terms of one company, thru which blood will flow providing oxygen-rich blood directly to the heart muscle. The pericardium is replaced, and the chest is closed. More recently, a less invasive version of the surgery, using a catheterized version of the laser (percutaneous transmyocardial laser revascularization), has been developed, for example see Bortone, *et al.*[29]

By the mid '90s, a number of fairly large trials had been carried out. The procedure was reserved for people who were not healthy enough to be treated by the standard techniques (CABG, angiography), and who had very serious, unstable end-stage angina, that is, for very sick people. The results were quite remarkable: success rates were in the range of 75% to 90%. Successful improvement in these studies required a two stage improvement in the four stage Canadian Cardiovascular Society system; that is a lot of improvement for such very sick people.

For a history of the procedure, see Kantor B, *et al.*[30]

The interesting thing is that no one really knows how or why this operation "works". The "bloodlines" close up in a matter of hours, and there is no evidence that the myocardial blood flow actually increases by the best type of evidence, perfusion imaging.[31] But people do get better (see box). Why? Some say that the laser beams disrupt the nerves of the heart, and denervate the affected areas[32] but others seem to show quite clearly that this is not the case.[33,34] There is some reason to believe that the scarring process may lead to angiogenesis, but there is little evidence that this has any effect on angina.

A number of observers suggest that, by analogy with the bilateral internal mammary artery ligation, the improvements observed may be due to the meaning response (or in their terms, the placebo effect), for example see Kantor, *et al.*, Lange, *et al.*[30,35]

While surgeons remain enthusiastic about the procedure,[36] one interesting study showed that, in sheep, TMR led to angiogenesis in lased channels, but "failed to improve myocardial function";[37] one would not expect much of a meaning response from sheep.

And most recently, Dr Martin Leon and a group of colleagues from across the US have enrolled 300 patients in a placebo controlled trial of a related procedure similar in form to angioplasty. A laser catheter is inserted in the femoral artery and threaded up into the left ventricle; the laser pulses are administered from inside out; this requires much less invasive surgery. These patients were very sick:

- all were rated as class III or IV on the 4-stage Canadian scale
- 90% had previously had bypass surgery
- 65% had previously had heart attacks
- all had had angioplasty within the previous 4 months
- yet they were relatively young people, averaging about 62 years in age.

Patients were randomly assigned to one of three groups, a high-dose group (20–25 laser punctures), a low-dose group (10–15 laser punctures), or a mock procedure with only simulated laser treatment. All three groups displayed similar impressive improvement six months after surgery on all objective and subjective measures which were observed. Exercise tolerance was increased in all three groups. The percentage of patients who improved two or more classes on the Canadian scale ranged from 25% (high dose) to 33% (placebo) to 39% (low dose). Frequency of angina declined, and physical functioning and disease perception scores increased, in all three groups. None of the modest differences between the three groups was statistically significant.[38]

A few years ago, before the FDA approved this laser treatment, Dr Alan G Johnson, in an article titled "Surgery as a placebo" in the *Lancet* said (with notable prescience), "Electrical machines have great appeal to patients, and recently anything with the word 'laser' attached to it has caught the imagination".[39] It may be worth suggesting that doctors, as well as patients, find their imaginations fired by lasers.

Other placebo surgery

Similar results – 70% improvement in objective and subjective measures in both surgical treatment and surgical sham groups – have been shown for Meniere's disease (an inner ear disturbance causing loss of balance where patients tend to fall towards the affected ear), with a three year follow up.[40]

In a review of 2504 diskectomies for lumbar disk disease, 346 patients were found to have no herniation (this might then be called a "diagnostic diskectomy"); regardless, many of these patients subsequently experienced partial (38·4%) or complete (37·0%) relief of sciatic pain (total = 75·4%) after their surgery.[41]

More recently, in a prospective, randomized placebo controlled trial, patients with osteoarthritis of the knee were given one of three arthroscopic procedures. The placebo patients were put to sleep, draped, examined,

injected with local anesthetic, and given three stab wounds in the skin with a scalpel. No arthroscopic instruments were inserted, but "a standard arthroscopic debridement was simulated as closely as possible in the event the patient was not totally unaware during the event".[42] This surgery was compared to standard arthroscopic debridement and to arthroscopic lavage (a diagnostic arthroscopy). In this pilot study, the five patients receiving the sham procedure responded essentially the same as did those who received the full surgical treatment, and as do similar patients in normal clinical practice: they "reported decreased frequency, intensity and duration of knee pain" six months after surgery. A full scale study is currently underway with 180 patients.

While studies such as these are rare, their results are consistent with the notion that medical acts are meaningful, and that meaning has an effect on patients. Surgery is particularly meaningful: surgeons are among the elite of medical practitioners; the shedding of blood is inevitably meaningful in and of itself. In addition, surgical procedures usually have compelling rational explanations which drug treatments often do not. The logic of these procedures ("we'll clean up a messy joint", or "we'll get more blood to your heart") is much more sensible and understandable, especially for people in a culture rich in machines and tools, than is the logic of non-steroidal anti-inflammatory drugs ("which may block the production of prostaglandins which seem somehow to be involved in the inflammatory process").

Meaning responses can be extremely variable

It is common for researchers to cite Beecher's famous paper of 1955 to the effect that placebos are effective 35% of the time.[43] House officers have been shown to estimate placebo effects as occurring less frequently than that, averaging about 20% while nurses estimate much lower still.[44] (My experience over the years teaching these issues suggests that nurses are among the very hardest to convince that inert medications, or meaningful interactions, can affect illness or disease.) Indeed, inert treatment can be effective far more often than either of those estimates, or, indeed, Beecher's estimate. In a series of 117 RCTs of cimetidine or ranitidine for treatment of endoscopically diagnosed ulcer, ulcer healing (also endoscopically confirmed) after four or six weeks of therapy with inert pills ranged from 0% to 100% with a mean of 35·5 and a standard deviation of 16%.[45] To say that "the placebo group healing rate is 35%" under these circumstances is rather like saying "American men are five feet ten inches tall" because that is the mean adult stature.

In these 117 studies, the drug group healing rate is also highly variable, from about 38% to 100%. The correlation between the placebo rate and the drug rate is 0·43 ($p < 0·0001$); the higher the placebo effectiveness, the higher the drug effectiveness.

Formal factors account for some variation

What sorts of factors account for this variation? The research on this issue is in its infancy, and much remains to be learned. There are formal factors which seem to make a difference: capsule or tablet size or color can make a difference in the effect of drugs.

Color

In addition to the study with medical students already mentioned, others have shown such variations. In one study, the tranquilizer oxazepam relieved symptoms of anxiety better when presented in a green tablet, while depressive symptoms were relieved better when the drug was presented in a yellow tablet.[46] A Czech study of patients with a variety of somatic and psychological problems showed that capsules with warm colors acted as stimulants and cool ones acted as sedatives.[47] This finding has been found generally; a systematic review "suggests that green and blue may have more sedative effects and red and orange may have more stimulant effects".[48]

But meaning can be more complex than this. In an Italian study of the sedative effect of inert tablets, while women preferred blue tablets (as is ordinarily the case), men did not; blue tablets prolonged their time until sleep.[49] In Italy, the color blue seems to have different meanings for men and women. For Italian women, blue is the color of the dress of the Virgin Mary; since the Mother of God is a very reassuring and protective figure for many Italian women, it seems reasonable that blue sleeping pills should be effective for them. By contrast, for Italian men, blue is the color of Azzurrii, 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 Italian men than for women. Another apparent exception to the notion of blue pills as tranquilizing is that of Viagra, marketed in a blue pill, prominently displayed in advertising, its lozenge shape usually pointing upward to the right. The Oxford English Dictionary, reflecting the racy aspect of the color blue notes that it can mean indecent or obscene, smutty or libidinous, as in a "blue movie".* Particular cultural details, like soccer team names, can disrupt otherwise widespread relationships of meaning; but the inherent polysemy of richly meaningful symbols also requires close attention to detail.

In any case, a recent Dutch study has shown that stimulant medications tend to be marketed in "hot" colors – red, yellow, or orange tablets – while depressants tend to be marketed in "cool" colors – blue, green, or purple tablets.[48] One can consider "one-a-day" vitamins to be among the most neutral of medications; they are not imagined to have immediate or dramatic effects. Observations suggest that vitamins are usually marketed

* Robert Hahn suggested this line of thought.

in tablets with pale pastel tones. Whether these marketing decisions are made consciously or otherwise, they are amenable to a rational analysis.

Number and type

In addition to the study with medical students, several others have shown that two pills work better than one.[50] One study showed that patients receiving three different placebos for two weeks each did better than patients receiving the same placebo for six weeks.[51] Similarly, a study of antacid treatment of ulcers had an interesting element.

> Seven patients were switched to a [randomly selected] second batch of medications because of continuing peptic discomfort of high intensity after three days of therapy. Due to lack of pain relief after the first switch, one patient was switched twice. The sequence of switching was from placebo to placebo to placebo again. On the third batch of placebos, the patient obtained pain relief and his ulceration healed after four weeks of therapy.[52]

The number of placebo tablets taken can have real clinical significance. In 71 RCTs of cimetidine or ranitidine for endoscopically diagnosed ulcer disease, control group patients took placebos for four weeks. In studies where they took two placebos a day, 249 of 751 patients (33%) were healed (endoscopically verified) while in studies where they took four placebos a day, 427 of 1129 (38%) were healed; this difference is statistically significant, $\chi^2 = 4{\cdot}26$, $p < 0{\cdot}05$.[45] This same proposition has been demonstrated for the same condition (four placebos per day: 44·2% healing rate; two per day: 36·2%) but with much more statistical precision in a formal meta-analysis.[53] In this study, the authors very carefully considered other variations between the studies which might have accounted for the differences; none of the adjustments they could make – given the published data – diminished the difference. For example, patients in the 4 per day trials were "slightly more often male, were somewhat younger, and were more often smokers. Male gender, younger age, and smoking have been associated with lower healing rates [for ulcer disease], so adjusting for these baseline characteristics would have resulted in a larger rather than smaller healing rate difference". The authors note that, although they adjusted for all possible confounding factors for which data were available, they could "not rule out that in this non-randomized comparison the observed difference was caused by some unrecognized confounding factor or factors". Regardless, given what is currently known about these differences, the Number Needed to Treat for a beneficial effect, the NNT_B, for four placebos a day versus two per day is 13.

In addition to the number of pills, other factors can modify efficacy. One study has shown capsules of chlordiazepoxide to be more effective against anxiety than tablets of the same drug,[54] and parenteral placebo has been shown to be more effective than oral placebo several times, for hypertension,[55] rheumatoid arthritis,[56] and migraine headache,[57] among others.

Cultural factors account for some variation

Again looking at 117 ulcer trials, three studies from Brazil demonstrate that placebo healing rates there are much lower than in other countries. The placebo healing rate is seven per cent in Brazil versus 36% in the rest of the world ($t = 3{\cdot}13$, $p = 0{\cdot}0016$). Similarly, the placebo healing rate in six studies in Germany averages 59%, twice as high as in the rest of the world ($t = 3{\cdot}88$, $p = 0{\cdot}00018$) and three times that of two of its neighboring countries, Denmark and the Netherlands, where, in five studies, it averages 22% ($t = 3{\cdot}21$, $p = 0{\cdot}011$). For ulcer patients taking placebo, the NNT_B for being German (not Danish or Dutch) is 3.*

The placebo effect is not always high in Germany. In a series of 32 comparable trials of treatment of moderate hypertension, active drug treatment reduced diastolic blood pressure (DBP) by an average of 10·9 mm Hg (range 7 to 21) while placebo treatment reduced DBP by 3·5 mm Hg (range –5 to 9; in two studies, placebo-treated patients had an increase in mean DBP). The clearest international variation in these data is opposite to the findings in the ulcer data. The mean placebo group change in DBP in four German trials is 0·25 mm Hg, while in the remaining 29 trials it is 3·9 ($t = 2{\cdot}6$, $p = 0{\cdot}013$); one study that showed an *increase* of 5 mm Hg in DBP with placebo treatment was done in Germany. The drug group change in the German studies is the same as in the remaining trials. Hence, Germany, with the highest placebo healing rates in ulcer disease, shows the least improvement in placebo treatment of hypertension. High rates of placebo effect seem to vary by medical condition within national cultures.[45]

That there should be such substantial differences in outcome with the same treatments for the same conditions in places with such deeply shared traditions of the life sciences and biomedicine seems surprising until one becomes more aware of the deep differences in understanding of illness between these closely related cultures. Thus the German experience of hypotensive drugs may be affected by their broad concern for a condition – *Herzinsuffienz* – which generally does not exist in the United States, France, Great Britain, and so on. This syndrome and its scope have been described in some detail;[58] suffice it to say that German physicians routinely treat low blood pressure and other symptoms of "heart insufficiency" in a very large proportion of older adults, treatment which, in the US, would probably be considered malpractice. The French have their *crise de foie*, *fatigué*, and *spasmophilie*,[59] while the Americans have their nearly unique infatuations

* Such differences found in different countries could have additional explanations. There could be systematic differences in study populations or disease characteristics. Ulcer disease is now known to be due in part to infection with *Helicobacter pylori*; if Brazilians had a much higher prevalence of such infection than Germans, it might account for some of these differences. When these studies were done, the role of *H. pylori* was unknown. While this might account for some differences, it seems unlikely that it would account for the differences between the Germans and the neighboring Dutch and Danes.

with "sinus", "low-grade viruses", and multiple personality (or dissociative identity) disorder.[60] These different understandings of illness and suffering can have as significant an effect on medical treatment as can the more familiar (and exotic) "culture bound syndromes" from around the world like *susto*, *amok*, and *latah*, all of which, Hahn reminds us, encourage a focus on the ways in which "culture, psychology and physiology [are] … mutually relevant across cultural and nosological boundaries".[61]

"Adherence" and placebos

One of the strangest examples of variation in the effect of inert medication comes from a series of studies which show significant difference in outcome depending on the amount of medication patients consume. Table 4.1 summarizes five such studies. The first row in the table gives the results from a very large study of the use of cholesterol-lowering drugs by individuals who had experienced myocardial infarction. After five years, there was no difference in the 5 year mortality rates for patients taking clofibrate and those taking placebo (20·0% v 20·9%; z = – 0·60, p = 0·55). However, good adherers to the clofibrate regimen (those who took more than 80% of their drugs; three tablets three times per day) did much better than poor adherers (15·0% v 24·6% mortality). And, good adherers to the placebo regimen likewise did much better than poor adherers (15·1% v 28·2% mortality). The other cases – infection after chemotherapy for cancer patients, one year relapse for schizophrenia, and beta blocker treatment for men and women who had survived a serious myocardial infarction – show similar results.

These results are hard to interpret for a number of reasons. The most significant one is that patients can not be randomly assigned to good versus poor adherent groups; the groups are, somehow, self selected. And, interestingly, not much is known about how and why people do, or do not, adhere to drug regimens. In most of the studies reported, there were no apparent differences between the adherent and non-adherent segments of the samples; for all factors (except the study outcome) the groups looked as if they *had* been randomly assigned. In the case of the clofibrate trial, there was some evidence that the less adherent patients had "a somewhat higher prevalence of baseline factors [associated with mortality]".[62] Controlling for these factors with a multiple regression analysis adjusted the five year mortality for adherent placebo patients to 16·4% versus 25·8% for less-adherent patients; that is, it made practically no difference. The Canadian study of amiodarone for survivors of acute myocardial infarction, with similar outcome, considered a broad range of medical and social factors to attempt to account for the differences; no single factor predicted the difference in both placebo and drug groups.[63] This is a very compelling problem for which, at the moment, there is no reasonable explanation. Adherence may be associated with several other important factors in health and meaning, considered next.

Table 4.1 "Adherence" and response to drug and placebo.

Drug tested	N	Outcome	Drug group		Placebo group		Source (ref. no.)
			Adherent*	Not adherent	Adherent*	Not adherent	
clofibrate	3760	5 year mortality	15·0%	24·6%	15·1%	28·2%	62
antibiotics	150	infection after chemotherapy	18·1%	53·0%	32·2%	64·0%	99
chlorpromazine	374	1 year relapse	13·0%	57·0%	40·0%	80·0%	100
propranolol (men)	2175	1 year mortality	1·4%	4·2%	3·0%	7·0%	101
propranolol (women)	602	1 year mortality	4·5%	8·7%	6·8%	19·0%	102
amiodarone	1141	2 year all cause mortality	7·4%	14·8%	8·8%	18·7%	63

*Adherent patients took more than 75% or 80% of medication (65% in amiodarone study); non adherent patients took less.

Disclosure

In the 1980s, James Pennebaker began a series of experiments with college students. He randomly assigned half of a group of them to write for about 20 minutes about their very deepest thoughts and feelings about the most traumatic experience of their whole lives. The other half of the group was asked to write about everyday, ordinary phenomena: to describe the laboratory, or the furniture in it, etc. The students in the first group took to the task with intensity and imagination, often writing long and complex stories, and displaying significant emotional responses; many students cried while writing. Even so, most reported that they enjoyed the experiment, and would readily do it again. It was psychologically positive. Pennebaker followed up on the students for the rest of the school year. He found that, among other things, the emotional writers were admitted to the student health service significantly less often than students who had written about everyday items.[64]

This experiment has subsequently been repeated many times around the world, with corporate executives, prison inmates, medical students, people with chronic pain, men laid off from their jobs, and Holocaust survivors. Almost always the results are the same: there is a positive health effect of some sort. In more recent work, Pennebaker has analyzed the content of such writing, and compared it to the outcomes (which are, inevitably, variable). Those with the most health improvement are writers who construct the most coherent stories and express most clearly their negative emotions.[65] In our terms, they are the ones who create the most meaningful story out of their pain, deciding most effectively what to leave out, and what to put in.

Self-assessed health

Nearly 7000 Californians over 60 were asked one question in 1965 "In general, would you say your health is: excellent, very good, good, fair, [or] poor?". Nine years later, adjusting for their ages, men who had rated their health as excellent were 2·33 times as likely to be alive as were men who rated their health as poor; women were 5·1 times as likely to be alive when they rated their health as excellent.[66] In a follow up study 17 years after the study began, the combined, age-adjusted advantage for those who had rated their health as excellent remained: those who professed excellent health were 2·3 times as likely to be alive as were those who rated it to be poor.[67]

The most subtle work on this issue has been done by Ellen Idler of Rutgers University and her colleagues. She has tried to tease out just what it is that causes this effect, trying to find what personal characteristics people have who report excellent health compared to those who do not. She had similar results in a study of 2800 men and women over 65 living in New Haven, Connecticut.[68] Men who rated their health as excellent were nearly seven times less likely to die within four years than those who rated it as poor; women with excellent self-rated health were 3·1 times as

likely to die as those with poor self-rated health. Idler included a whole range of other factors in her analysis; among them were the subjects' disease history, age, smoking behavior, and weight; their medical history and health status: whether they had recently been hospitalized or in a nursing home, and the number and kind of medications they took; the support they had available, the number of friends and family, their religious activity and religiosity, their attitudes and moods. Several of these (age, smoking) predicted some portion of four year mortality, but none had as much effect as did global self-assessment of health. "Self-rated health", Idler writes,"appears to have a unique, predictive, and thus far inexplicable relationship with mortality". Other research like that by Maruta[69] shows that there is a general relationship between optimism and longevity; but Idler's work shows that there is only a modest relationship between the *specific* evaluation of one's health, and the *general* assessment of one's attitude to life.

Idler suggests two explanations for these observations, first, that the story people tell about themselves is a self-fulfilling prophesy, that the attitude itself is protective of health, and, second, that people simply know themselves better than anyone else does. These need not, of course, be mutually exclusive. And, as with Pennebaker's work, your answer to the question "What is the overall status of your health?" may just be one of the shortest, and most meaningful, stories you can tell.

A number of these factors – adherence, disclosure, self-rated health – may be related. It may be, for example, that those with lower self-rated health have lower levels of adherence than others; some studies might be interpreted as saying that "knowing" that their health is poor, patients may feel it is a waste of time to take medication.[70] This is obviously testable. It may be that medicine simply has less meaning for patients who take less of it. There may be cultural differences in compliance, or in self-rated health, or in the consequences of these matters. These and several other combinations offer a number of testable hypotheses.

Meaning responses may be higher in clinical than experimental settings

There is little evidence available to indicate that what happens in clinical trials has much relationship to what happens in actual medical practice. There is some evidence to indicate that treatment may be more effective in practice than it is in research.

Abandoned treatments of angina pectoris

Benson and McCallie reviewed the reports of a number of treatments for angina pectoris which, in the period before the widespread adoption of controlled trials, were widely utilized, but then later abandoned. They summarized the results of treatment of angina pectoris with methyl xanthines, khellin, vitamin E, ligation of the internal mammary arteries

(mentioned above), and Vineberg's implantation of the internal mammary artery. Data from the 13 studies they cite "reveal that subjective improvement was seen in 82·4 ± 9·7 per cent (mean ± SD) … In addition to subjective improvement, objective changes occurred: the placebo effect increased exercise tolerance [in four studies], reduced nitroglycerin usage [in three studies], and improved electrocardiographic results [in two studies] … [and in seven studies] relief [lasted] for a year or more".[17]

Other abandoned treatments

In a similar study of treatments "once considered to be efficacious by their proponents but no longer considered effective based upon later controlled trials", Roberts and co-workers looked at a series of reports on glomectomy for bronchial asthma, levamisole for herpes simplex virus (HSV) infection, photodynamic inactivation for HSV infection, organic solvents (ethyl ether and chloroform) for HSV infection, and gastric freezing for duodenal ulcer. "Despite our current understanding of the inadequacy of these five treatments, enthusiastic adherents reported good or better outcomes for patients ranging from 45% … for gastric freezing (N = 598) to 89% for photodynamic inactivation (N = 169) … For a total of 6931 patients treated by these five methods, 2784 (40%) were reported to have had excellent outcomes, 2049 (30%) good outcomes, and 2098 (30%) poor outcomes".[71]

In these cases, apparently inert treatments (but not "dummy pills") seem to have been satisfactory (that is, good or excellent) 70% or 80% of the time, not 35% of the time. The difference between the two circumstances is primarily the attitudes of the physicians. In the studies described by Benson and by Roberts, the providers of these treatments were enthusiastic about them; they had physiological theories they believed in, and treatments which made sense to them, which they could explain to their patients. In RCTs, the same is true, but only half the patients will benefit from this new improvement; and all the patients have had to provide informed consent.*

Chiropractic and conventional treatment of low back pain

A somewhat different comparison yields a similar result which indicates how context can affect meaning responses. Kaptchuk and colleagues have reviewed the evidence for efficacy of a number of areas in complementary medicine including chiropractic medicine.[74] In nine studies of spinal manipulation therapy for low back pain "three show no difference between manipulation and a sham …, two are positive for manipulation …, one is clearly positive for manipulation plus injected drug …, and … three trials could be construed as showing some benefit for manipulation over sham

* Research on the effects of informed consent on active or inert treatments has had highly variable results; compare, for example Kirsch, *et al.*[72] with Sprafkin, *et al.*[73]

during some course of the complaint". It is, from this perspective, difficult to say that chiropractic manipulation is "better than a placebo". Another meta-analysis of eight studies of chiropractic manipulation comes to similar conclusions: "the available RCTs provided no convincing evidence of the effectiveness of chiropractic for acute or chronic low back pain".[75]

But other comparisons can be made. If there is little evidence that chiropractic is "better than placebo", there is ample evidence to indicate that it is better than conventional medicine for this complaint. In a survey of members of a HMO (Health Maintenance Organization) which provided both types of care, "chiropractic patients were three times as likely as patients of family physicians to report that they were very satisfied with the care they received for low back pain (66% [of 348] v 22%)".[76] In a half dozen such surveys, from 65% to 85% of chiropractic patients express such satisfaction.[74]

Similar results are seen in a Dutch study which randomly assigned patients with low back and neck pain to manual therapy, physiotherapy (exercise, massage, ultrasound, etc.), general medical care (analgesics, home exercise, bed rest), or placebo treatment (detuned shortwave diathermy and detuned ultrasound). At six week follow up, physiotherapy and manual therapy had very similar outcomes and were significantly better than general medical care. Placebo treatment was intermediate, somewhat less effective than the active treatments (only one of four measures was statistically significant), and somewhat better than treatment by general practitioners on two measures (one significant, one not).[77]

One might be able to show that the analgesics and muscle relaxants of general medical care are more effective than placebo for pain and muscle stiffness. So here the paradox is that care which cannot reliably be shown to be better than placebo seems to work better than care which can. Why?

Whatever the details of treatment may be, there is one huge difference between the care one typically receives for low back pain from an MD and from a chiropractor: its *meaningfulness*. Participant observation on my part suggests that the approaches of chiropractors and physicians vary dramatically for this condition; see also Oths.[78] The chiropractor immediately carries out a focused, pointed, attentive examination asking pertinent questions about history, injury, mobility and so on, asking you to bend this way and that, usually taking *x* ray films and showing them to you, pointing out misaligned vertebrae, explaining the course of treatment, its goals and likelihood of success. The walls in a chiropractor's office are frequently hung with large posters displaying the spine, explaining its function and workings; there are colorful brochures explaining the history and value of chiropractic treatment. Occasionally one finds articles, popular or scholarly, photocopied perhaps, showing the results of studies on the effectiveness of chiropractic. One may even see a model of an actual spine with simulated spinal nerves arrayed along it, hanging from a doorknob. The entire experience is validating, encouraging, supportive and positive. We have not yet had an adjustment and we feel better already. The

adjustment, on an elaborate adjustable table, is itself replete with satisfying pops and snaps, rolling over, and just enough pain to suggest that something good may come from it.

Contrast this with the physician's attitude. No diagrams. No spine on the doorknob. The advice usually is of the order of "take aspirin, rest in bed, take it easy". Of course, the patient has been doing that for ten days before the appointment, and is there because those things have made no difference. *The Merck Manual* uses the word "malingering" twice: once in the phrase "pathologic malingering", a synonym for Munchausen syndrome, and once in its discussion of low back pain. While it is said to be uncommon, "Inconsistent historic and physical findings on sequential examinations may make one suspicious of this diagnosis". If your back problem is anything but linear and does not heal up quickly, you are suspect. "When suspected, [malingering] can only be established by garnering evidence that the patient is faking". Under these circumstances, the doctor's approach should become that of the lawyer, not the healer. "Direct evidence of malingering may best be acquired by someone other than the physician". The *Manual* does not say more, but one imagines a detective is in order to expose this fraudulent patient.[79]

It is striking that the same symptoms could elicit such varying responses. But surely it is clear which approach is likely to be more meaningful, and hence potentially effective, for the patient with back pain, regardless of what studies about the effectiveness of specific treatments may have found. In this way, the case of chiropractic is similar to the abandoned treatments discussed earlier: 70% or 80% of patients achieve satisfactory treatment outcomes marked by measurable subjective and objective improvement with enthusiastically employed techniques – rich in meaning – which seem not to be substantially more effective than sham treatments in blind trials.

Meaning responses in other medical systems

It is sometimes suggested – as I suggest for chiropractic – that some medical systems have, over the generations, elaborated their meaningful elements in order to enhance the meaning response; it seems as if many of them do little research to extend the specifics of their systems, and most contemporary research is designed to demonstrate the effectiveness of existing treatments, not to develop new or better ones. (One may wish to say the reverse of conventional medicine, that it has enhanced the specific effectiveness of the system through persistent research in pharmacology and physiology at the same time as it has generally neglected the meaningful; that is not to say the meaningful is not there, but it is not there as the result of deliberate study.) While such a proposition seems plausible, it is hard to demonstrate convincingly in general terms.

Navajo medicine

Consider an extreme case which points up the difficulties. One of the most complex forms of medical treatment is that developed by the Navajo of the American Southwest. There are a dozen or so major treatments known as Blessingway, Evilway, Holyway and so on, each with many variants. For an example, see Wyman's account of the Blessingway;[80] Sandner gives a rich account of Navajo medicine from a clinician's perspective,[81] and Silko gives the perspective of an artist.[82] Many family members and friends gather for such an event which can last for a week or ten days, and which involves the singing of dozens of complex chants by several highly trained medicine men who also create a series of beautiful drypaintings (or "sandpaintings") – which, in effect, concentrate beauty – on which the sufferer sits. Different herbal infusions are used several times, each containing 30 or 40 different plant medicines which are drunk and rubbed over both the sufferer and all the attending medicine men and other visitors, family and friends. The focus of the event is twofold: the intention is to banish evil, and then to re-establish the beauty (*hózhó*) which has somehow been lost from the sick person's life.[83] This form of healing is "likened to a spiritual osmosis in which the evil in man and the good of deity penetrate the ceremonial membrane in both directions, the former being neutralized by the latter";[84] it is, then, a powerful social experience suffused in meaning.

To determine just which elements of this rich treatment were "active" and how they interacted would require an extraordinary series of studies which compared this system with one lacking the meaningful elements (Placeboway?). Such a scheme would not be Navajo medicine, rather like psychoanalysis without talk, or surgery without the knife. But thinking about a medical system so different from the one we are immersed in – where the meaningful elements are so apparent – might allow us to gain a sense of the fullness of the meaningful dimensions of our own approach to healing.

Mechanisms in the meaning response

It is, of course, very difficult to specify the mechanisms involved in these processes. This is often the case in internal medicine, and, while undesirable, is not generally a serious problem. For example, it seems plausible that non-steroidal anti-inflammatory agents have their effects by somehow interfering with prostaglandin production, but that this is not clear in detail does not reduce the effectiveness of drugs ranging from willow bark tea to naproxen. The mechanisms of action of the opiates were unclear until research in the 1970s uncovered the endogenous opiates; the drugs were as useful before as after those discoveries. One need not know how a treatment works in order to use it effectively.

Pain

There is one area where 25 years of (intermittent) research has shown us something of the mechanisms involving meaning responses, namely in pain. Since the pioneering work of Levine and Fields in the late 1970s,[85–87] it has been reasonable to argue that some forms of placebo analgesia involved the production of endogenous opiates which could be blocked by the opiate antagonist naloxone. The matter was not a simple one, and Gracely showed that there may have been more complex mechanisms involved.[88]

More recently, Italian researcher Fabrizio Benedetti has carried out an elegant and ingenious series of experiments clearly showing that one can induce significant analgesia with inert substances, that these effects can be reliably blocked by naloxone, and that they can be enhanced by the cholecystokinin antagonist proglumide (as naloxone blocks opiate action, proglumide has been shown to enhance it); he has also shown that one can induce placebo hyperalgesia (a "nocebo" effect) which can be blocked by proglumide.[89,90] The clear inference here is that the symbolic and meaningful experience of a saline injection can somehow engage the production of endorphins in the brain.

In another study, this same team has shown very clearly that there need not be any placebos in order to evoke these responses. Surgical patients were either given pain medication openly by a physician, or by hidden injection from a pre-programmed infusion machine without any clinician in the room. Patients in the open injection groups (receiving four different analgesics) reported substantially less pain than patients receiving similar doses of hidden analgesic. "By eliminating the placebo component of analgesia by means of hidden injections, … the effectiveness of … these analgesics [was] significantly reduced".[91] In this study, since there were no placebos, it seems unwise to call these differences "placebo effects". In an editorial accompanying the paper, Donald Price notes that although the increases in analgesia were not huge – 1 to 1·5 units on a pain intensity scale, and might not be clinically significant taken alone, "both pain research scientists and the pharmaceutical industry go to the ends of the earth to make improvements of this magnitude. Adding one or two sentences to each pain treatment might help to produce them".[92] Those two sentences are not placebos, but are sources of meaning.

Immune response

There is also evidence to show that several of these factors can influence the immune system. In one study, medical students were randomly assigned to write about personal traumatic events or control topics on four consecutive days. Following the writing, they were given vaccinations for hepatitis B. "Compared with the control group, participants in the emotional expression group showed significantly higher antibody levels against hepatitis at the four and six month follow up.[93] Similarly, it has

been known for 25 years that death of a spouse depresses lymphocyte function in the elderly;[94] similar findings have been shown in suddenly bereaved parents.[95]

These studies of pain, disclosure and bereavement do not explain how experience can move biological systems. But they surely indicate that they *can* move them. Understanding how this happens is far off; it seems to me that, today, we know about as much about how information and experience are encoded in the brain as we knew of the genetic code in 1950. This seems to me a hopeful analogy.

Thinking about causality

There is a clear relationship between these meaning responses and active drug effects; I hope I have made it clear that meaning responses adhere not only to inert treatments, but also to active ones. That was the take home message from one of the first studies mentioned in this paper which showed that branded placebo was more effective for headaches than unbranded placebo, and branded aspirin was more effective than unbranded aspirin. Kirsch and Sapirstein have shown an astonishingly high correlation between drug effects and placebo effects in treatments for depression; in 19 trials, the correlation was $r = 0{\cdot}90$ ($p < 0{\cdot}001$).[96] These results come from comparing group results, but they can also be shown for individuals. Amanzio and Benedetti have shown that under a half dozen different conditions in patients treated with either morphine or ketorolac and then treated with saline, that there is a strong correlation between the drug effect and placebo effect in individuals; the correlations under six different experimental conditions range from 0·554 to 0·855, with a mean of 0·679.[90]

I have shown a similar relationship in RCTs of peptic ulcer disease treated with cimetidine or ranitidine. In 83 studies of treatment of duodenal ulcer, the correlation between the endoscopically verified healing rate in the control group and in the inert treatment group was $r = 0{\cdot}49$* ($p < 0{\cdot}000003$; see Figure 4.3).[45]

While the relationship is clear, it is not so clear how to account for it. Several different approaches to this might be taken. It seems reasonable to infer that we cannot account for such variations by referring to conditioning theory. Ader has suggested that there is heuristic value in considering "a pharmacotherapeutic regimen as a series of conditioning trials".[97] But in these cases, the various individuals, or study groups, each had identical (or at least very similar) regimens, and yet the outcome

* In 37 comparable trials of treatment of generalized anxiety disorder, the correlation between drug and placebo group improvement rates is 0·39 ($p = 0{\cdot}017$). But this is not always the case. In 32 studies of treatment of hypertension, the correlations between drug and placebo improvement were 0·20 for systolic blood pressure, and 0·10 for diastolic blood pressure; neither was statistically significant.

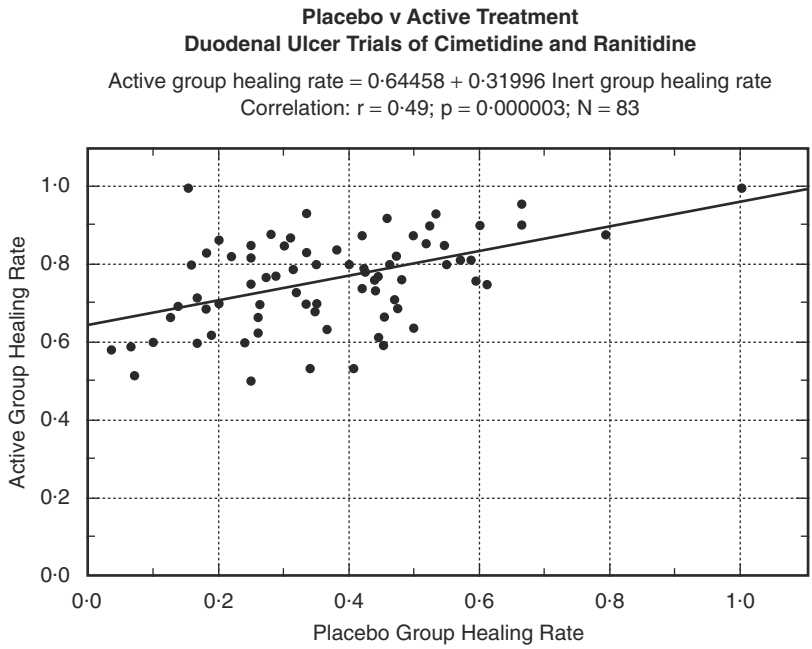


Figure 4.3 Relationship between active and inert treatments in duodenal ulcer disease.[45]

varied; patients, or study groups, with low responses to inert drugs had similarly low responses to active drugs, and vice versa.

In cases where drugs of differently appreciated "power" or "intensity" are at issue, one is drawn to an explanation based on the influence of the physician; it is s/he who best understands the varying powers of the pharmacopoeia. A similar argument may apply to the situation where older drugs seem to lose their power as newer ones come along.

But the most common approach to this issue seems to me to be somewhat more subtle and ambiguous. When these sorts of things are reported, the language usually is something like this: "the larger the active drug response, the larger the placebo response". And graphically, these things are usually represented so that the drug effect is displayed on the x-axis (usually conceived of as the "independent variable") while the drug effect is displayed on the y-axis, suggesting that $y = f(x)$, that the placebo effect is dependent on, is a function of, the drug effect. Figure 4.4 serves as an example; the graph shows the relation between responses of individuals to morphine injections and then later to either saline (filled circles) or naloxone (open circles). The key here is not the data itself (interesting as it is), but the structure of the data, the way it is displayed, which, in standard scientific argot has the independent variable on the horizontal axis.

Since the 1980s, morphine has been considered an "exogenous opiate", in contrast to the "endorphins", or "endo[genous morph]ins". Proglumide

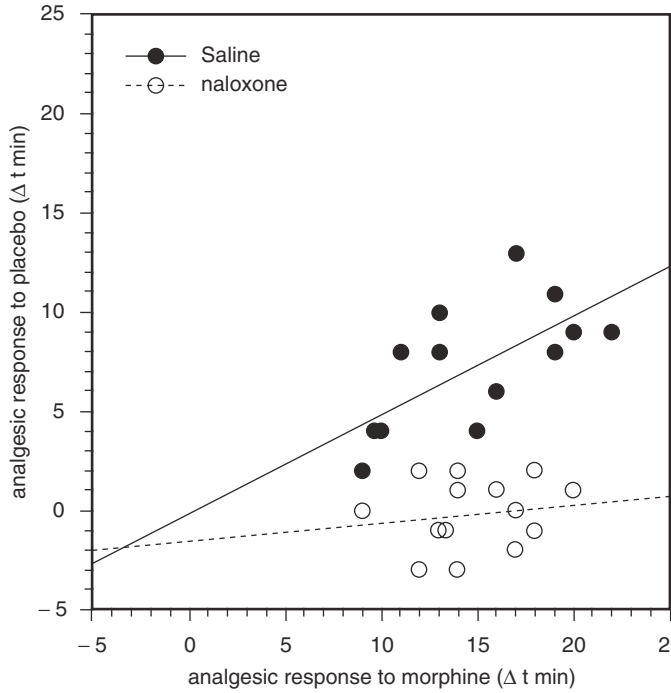


Figure 4.4 Relationship between active and inert treatments in pain. (Figure 5A from[90])

is, by contrast, considered an opiate agonist, while naloxone is considered an opiate antagonist. The data in Figure 4.4 might better be interpreted as showing that morphine is an endorphin agonist. Morphine is derived from phytochemicals which evolved in poppies to affect (negatively) the nervous systems of insect and vertebrate browsers; the endogenous opiate process preceded the exogenous one, and is the independent variable in the system (it seems clear that poppies evolved in response to the pre-existing nervous systems of browsers rather than vice-versa). From this perspective, it makes much more sense to say "the larger the placebo response, the larger the morphine response", and to reverse the axes on the graph (as was done on Figure 4.3). The enthusiasms of doctors are still real factors here, but from this perspective, it is clearer on what that enthusiasm is acting.

One implication which I intend here is that, at least on some occasions, the biology of the meaning response probably accounts for the effectiveness of some very common and very useful drugs. That we don't understand this biology very well does not change the fact that it happens, and ought only to be a challenge to understand better some of these human – that is, *meaningful* – dimensions of life. And this perspective brings to the fore one of the most important unresolved issues in this whole research area, one which has enormous potential to improve medical care around the world:

why is it that, in study after study, only a third to a half of patients are able to experience a meaning response? Why is a majority of the population (more often than not) unable to experience the benefits of a beneficial response to a meaningful interaction? Solving this problem would get my vote for a Nobel Prize.

Conclusions

The application of a focused, meaningful theory to injury or disease – angina, back pain, peptic ulcer or bad knees – can make a huge difference for patients in the objective and subjective dimensions of their illness, regardless of the effectiveness of the specifics of the treatment. In all likelihood, highly effective specific treatment effects can be amplified (or damped down) by meaningfulness (this seems evident in the data on ulcers presented earlier, where a doubtless effective therapy is still highly variable in its outcome around the world). A magic bullet is useless (or worse) in the hands of someone who cannot shoot straight.

But the evidence also suggests that treatments do not need very powerful specific effects to energize highly effective therapeutic systems; the use of minor tranquilizers for generalized anxiety disorder may be such a case. Similarly, Kirsch, reporting a meta-analysis of the effects of antidepressant medication, state that the "data indicate that 27% of the response to medication was a pharmacologic effect, 50% was a placebo effect, and 23% was due to other 'nonspecific' factors".[96]

In general, the way meaningful and pharmacological effects interact is a very complex and difficult problem which requires substantial research.[98] If you are interested in characterizing the forces needed to smash a rock with a sledge hammer, a simple design will suffice. If you are interested in characterizing the forces which move the tides, more subtle experiments will be needed, not because the forces involved are smaller or less significant, but because there is nothing against which you can compare the forces. And when forces this different interact, extremely subtle work will be required to understand the matter.

It seems nonetheless undeniably the case that doctor and patient can establish a dynamic meaningful relationship which can often materially affect illness. The meaning response – the desirable effects of meaning in the treatment of illness – (of which the placebo effect is a small special case of treatment without active ingredients) is a crucial clinical and research issue, complementary to all forms of medicine.

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