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THE POWER OF PERSUASION AND THE PLACEBO RESPONSE

Key Words: Poisonings, blinded and double-blind studies, ancient placebo remedies, "active-controlled trials", nocebos, surgical placebos, medical ethics, conditioned responses

A curious thing happened to me on the way to writing this Newsletter. The Health Journal section of the February 18 issue of the *Wall Street Journal* was entitled **"Doctors Advise Parents To Throw Out Ipecac"**. That seemed strange, if not heretical. Administering syrup of Ipecac to poisoning cases has been standard treatment in Emergency Rooms for decades. Home medical texts, and baby-care books almost always advise keeping syrup of ipecac in the medicine cabinet.

ALSO INCLUDED IN THIS ISSUE

Many pediatricians have routinely supplied bottles of ipecac to new parents to keep on hand for emergencies. Poison-control and health centers all around the country also recently distributed free samples of ipecac syrup to commemorate March as "Poison-Prevention Month". **What is responsible for this sudden reversal?**

Someone in the U.S. is poisoned every 30 seconds with over a million cases reported annually. It is not known how many cases are not reported, but over two thirds of those that are occur in children under the age of six, most of whom are less than two years old. Nine out of ten poisonings occur at home and about 70 percent of these are managed by Poison Control Centers over the telephone. Their advice is often to immediately give syrup of ipecac followed by at least four to eight ounces of water. The dosage differs for infants, children, and adults, but if vomiting has not occurred within 20 minutes, the procedure should be repeated.

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Ipecac As A Placebo?

Ipecac is derived from the dried roots of ipecacuanha, a plant found in Brazil and central America, and has been used in medicine for centuries. Up until 1960, pharmacists mixed their own ipecac remedies which were often up to 15 times more potent than the current version. Since some patients occasionally received a dose that was dangerous or lethal, the present pre-mixed syrup was introduced and quickly became a household item. Anyone can buy a one-ounce bottle of syrup of ipecac for about $2 without a prescription. Sales were $1.6 million in 1999, up more than 10 percent from the previous year. Since this ipecac product is quite safe and may possibly have saved thousands of lives, why are we now being told to throw it out?

The major reason for getting rid of ipecac stems from an extensive review of the literature on treatment for poisonings that appeared in the journal of toxicology. This comprehensive analysis, which was done under the auspices of American and European toxicology and poison control center groups, revealed that patient outcomes were not significantly affected by administering ipecac in cases of suspected poisonings.

In some instances, giving ipecac might actually interfere with other treatments that could be beneficial. The survey also reported that other treatments like pumping out the stomach or giving activated charcoal were of little value if administered more than an hour after a poisoning. However, this review focused on hospital records, and most of these patients were treated more than 90 minutes after ingesting poison. Many experts disagree with its conclusions because they do not apply to the home use of ipecac to induce vomiting shortly after a poison was ingested.

How does ipecac work? Under normal circumstances, periodic contractions of the stomach help propel its contents to the small intestine. When these stomach contractions cease or significantly diminish, a feeling of nausea results, which, if severe enough, may be accompanied by vomiting. The emetic action of ipecac is thought to be due to its direct irritant effects on the stomach that reduce these contractions. This results in nausea and vomiting, depending on the dose.

What does any of this have to do with persuasion or placebos? After all, if infants consistently vomit following the administration of ipecac, it is not likely to be a placebo phenomenon. Placebo effects are generally attributed to either the patient's belief in the efficacy of the treatment or faith in the power of the individual who has prescribed it. The physician's expectations may also play a role, which is why the gold standard for evaluating the efficacy and safety of a new drug is the double blind trial in which neither the patient or physician knows whether a real or look alike dummy product is being administered. It is conceivable but doubtful that a placebo effect could influence an infant's response to ipecac. It would also not seem necessary to perform double-blind studies to confirm that nausea and vomiting are predictable pharmacological properties of ipecac.

However, it's not that simple, and the current controversy reminded me of experiments performed by Dr. Stewart Wolf at New York Hospital over 50 years ago that could never be repeated today.

Tom And Morning Sickness

Wolf had already reported numerous observations on the reaction of the stomach to various emotional, chemical, and physical stimuli that he was able to visualize. This was made possible by a subject named Tom who had a complete obstruction of the esophagus due to a stricture that made it necessary for him to ingest all food through a large gastric fistula. An arrangement had been worked out for Tom to perform janitorial and other duties in the laboratory, in return for making himself available for various scientific studies. As a result, it was possible to actually visualize the effects of emotions, antispasmodic drugs, and emetics on gastric motility and secretion.

In a 1949 paper, Wolf reported that when 23 healthy subjects ingested 10 cc of ipecac, 20 of them experienced nausea and 16 vomited. In every instance, a mild, cramping, epigastric pain that persisted for 5- 10 minutes preceded the nausea. However, when he had Tom swallow ipecac and allowed it to remain in the blind end of the esophagus for an hour, there were no adverse symptoms. Applying drops of ipecac syrup directly to various sites in the stomach did not produce either nausea or evidence of any local reaction. When 5 cc of syrup of ipecac were introduced into Tom's stomach, the only symptom was a slight cramp 25 minutes later. Wolf repeated this with progressively larger doses of ipecac and was able to show that when more than 7 cc were administered, there was a decrease in stomach contractions and acid production followed by nausea, abdominal pain, and increased secretion of mucus and saliva.

However, Tom did not experience symptoms of nausea until the ipecac reached his duodenum. There was very little evidence to suggest that its emetic effects had anything to do with direct irritation of the stomach, which was the standard explanation of how it worked. This raised the question as to whether some of the emetic effects of ipecac might be partially due to the expectations of the patient and/or the physician, and would therefore really represent a placebo effect.

To test this hypothesis, Wolf studied a patient who was suffering from the severe nausea and vomiting often seen in the early stages of pregnancy. As anticipated, measurements of her stomach contractions showed that they were significantly decreased. She was then told that she would be receiving a new medication that would promptly make her nausea and vomiting disappear. In actuality, she was given a dose of ipecac that normally would have worsened her nausea and induced vomiting. Instead, her stomach contractions rapidly returned to normal and her nausea disappeared until the following morning. Was this an isolated instance that was possibly due to the fact that this patient was unusually susceptible to suggestion or the powerful persuasive abilities of Dr. Wolf? Such an experiment could never be repeated today in an academic setting because of ethical considerations. However, individuals certainly differ markedly with respect to the ease with which they can be hypnotized. Some are resistant while others routinely fall into a trance in seconds because of their extreme sensitivity to suggestion.

To evaluate this, Wolf did a subsequent study on twenty-seven healthy young subjects who were given ipecac on two separate occasions. They were told they would receive ipecac and what to expect; one hundred percent experienced nausea on each of these exposures. The majority also vomited both times. The same dose of ipecac was then given seven successive times. In each instance, this was preceded by administering a placebo the participants were told would prevent any symptoms of nausea or vomiting. Nausea failed to occur in many instances, and when experienced, was described as being much less severe than on the first two occasions.

It was not possible to predict the likelihood of placebo relief in any individual. Every one of the subjects reported an absence of nausea during one or more of these last seven trials. This was in sharp contrast to their unanimous experience of nausea in both of the first two trials without placebo premedication.

Why Is Placebo A Dirty Word?

Placebo is derived from the Latin verb *placere*, to please. It means, "I shall be pleasing or acceptable". *Placebo Domino* is in the opening verse of the vespers for the dead in Roman Catholic church rites. This was often chanted by paid professional mourners who never knew the deceased, and placebo became a pejorative synonym for a sycophant or flatterer. Its initial use in medicine appears to have been in 1811 to describe a remedy or medication given more to please than benefit the patient.

The first use of an inert substance physically indistinguishable from an active ingredient to serve as a control was in Rivers' 1908 study designed to evaluate the influence of various drugs on fatigue, although the term placebo was not used. Some investigators subsequently began to follow this approach, usually using small amounts of tasteless substances like lactose to serve as an identically appearing but inactive control. Although such trials to assess the efficacy of drugs began to increase over the next few decades, the AMA's Council on Pharmacy continued to rely on reviews by experts to determine therapeutic efficacy. The first mention of placebo as we now use it was in Torald Sollman's 1930 paper "The Evaluation of Therapeutic Remedies in the Hospital", which strongly urged the use of an inert control or placebo. "Apparent results must be checked by the 'blind test', i.e. another remedy, or a placebo, without the knowledge of the observer, if possible. The placebo, if expectant treatment is permissible, also furnishes the comparative check of the natural course of the disease; comparison with another remedy helps toward a just perspective."

The major impetus for using placebos in clinical trials came from Harry Gold who started doing this in 1932 and continued the practice for two decades. As he later noted, **"The commonly accepted belief was that placebos were given to deceive patients . . .** doctors were criticized for giving 'dummy pills'." The phrase "blind" trials Gold used allegedly came from the "Take The Blindfold Test" for Old Gold cigarettes, in which blindfolded smokers compared their taste to other brands.

Few physicians knew what a placebo meant, and nobody talked about a "placebo effect" save for Gold's group. When the subject came up, it was usually ascribed to the power of "suggestion". **Giving placebos or "dummy" pills implied that the patient had to be some sort of retard, imbecile, or moron. Doctors who dispensed placebos were considered to be quacks,** which is not surprising.

For centuries, standard medical treatments were bleeding, cupping, leeches, enemas, plasters, purging, catharsis, and even incantations to rid the body of "evil spirits". Egyptian physicians prescribed crocodile dung and similar equally outlandish treatments were common in other parts of the world. We now view all of these as being essentially worthless, and to prescribe or promote them would be quackery. However, they obviously helped many people or they would not have persisted for so long. The most plausible explanation was that they represented "placebo effects", and quackery and placebo soon became synonyms.

The desire to take medicine or receive relief from a healer is one of the features that distinguishes humans from other living things. It is evident in the ancient written and pictorial records of every culture going back well over 6000 years. The earliest Babylonian cuneiform tablets mentioned 250 drugs of vegetable and mineral origin. Still others were derived from different animals, and particularly their excrement. The Ebers Papyrus later listed 700 of these in 842 prescriptions, varying from grated human skull and the teeth of swine, to lizard blood and the urine of menstruating women. Each of these had specific indications.

Placebos also permeated Western medicine, which allegedly began when the Greek god Apollo handed his healing powers to his son Asclepius, whose daughters Hygeia and Panacea represented health and healing. Their belief in what caused and could cure illness was rooted in mind/body relationships. . The four humors theory subsequently became the core of Hippocratic medicine. This doctrine culminated with Galen, whose influence dominated medicine well into the 19th century, and also relied heavily on the power of placebos.

Is It Ethical To Give Placebos?

Think about it. If you were suffering from severe migraine, hypertension, depression, or schizophrenia, would you be willing to enter a trial to evaluate a new treatment, knowing there would be a 50 percent chance that for months, you would be receiving something that couldn't possibly help? During this period you would also be forbidden to take anything that could provide relief. In addition, your physician would not know until the study was over whether you were receiving something that might be beneficial or an identical but worthless dummy. A growing number of physicians, researchers, patient advocates and other critics feel that such double blind placebo controlled studies (which the FDA usually requires to approve new remedies), are unethical and outmoded. They also violate the spirit of international codes that were adopted to protect human research subjects from harm or the horrors of Nazi medical experiments. One prominent scientist believes that "the placebo is just an easy out. It's an intellectually lazy approach to the evaluation of drug efficacy", arguing that "we cannot deprive patients of effective treatment and live up to our ethical guidelines." Another agrees that "it is just not necessary to put patients into the position of having to suffer for science."

What physicians and patients really want to know is how a potential new drug compares with some standard effective treatment that is readily available, not an inactive placebo. Regulatory agencies in Europe and Canada have already approved alternative "active-controlled" trials in which patients who don't get the promising new drug do receive a proven treatment rather than something that clearly will not work.

However, **most researchers feel strongly that the placebo-controlled trial is the preferred way to test new drugs and devices because it is the only way to establish whether they work at all.** If 20 percent of volunteers get better with a placebo compared to 65 percent of the potentially active pill group, it's obvious that you have something that is really effective. Such a statistically significant difference would be very unlikely if something active had been given instead. Substituting an active drug for a placebo could lead to an increase in the approval of inferior medications, according to an official at the FDA's Center for Drug Evaluation and Research.

This debate has now become international, as the World Medical Association, the International Conference on Harmonization, and the Council for International Organizations of Medical Sciences are considering whether they should issue new policy statements or revise existing ones. The Helsinki Declaration, an international set of medical ethics guidelines, currently recommends the use of placebos only if there are no proven therapies for the condition, and mandates that physicians should "obtain the subjects' freely-given informed consent, preferably in writing."

The proposed revisions would call for a placebo whenever "justified by a scientifically and ethically sound research protocol" even if there are already proven therapies for the disorder being studied. It would not require written informed consent if a research ethics committee found any risks to be minimal. Everyone agrees that placebo-controlled trials are not ethical for bacterial infections that can be treated with antibiotics, or cancers that could benefit from chemotherapy and/or radiation.

The FDA has relaxed its position, stating those patients with active rheumatoid arthritis, who are doing poorly on standard drugs "are usually not appropriate candidates for placebo-controlled trials." They are also reviewing prior double blind trials in 100,000 hypertensive patients to determine if those treated with placebos may have had a significantly higher incidence of stroke.

Even though trials are blinded, if it becomes evident that some patients appear to be doing much better than others, the code is broken prematurely to see if this occurred only in the active group. In this event, the study is stopped so that all patients can receive the drug's benefits. This recently happened in the trial of a new beta-blocker to treat heart failure.

The Bountiful Benefits Of Belief

But how do placebos work? Some patients who get better with placebos (as well as standard therapies) would have done so on their own because of the natural course of certain disorders. Placebos do seem to be most effective in conditions like depression, mild hypertension, anxiety disorders, and some pain syndromes which tend to fluctuate over time. But placebo therapy is not the same as no treatment, In addition, this assumption would not explain why:

- Depressed patients rarely improve while awaiting treatment, but 70 percent did get better from just taking aplacebo.
- In a study to assess the effect of a beta-blocker on mortality after a heart attack, those taking the placebo regularly had half the death rates compared to others who skipped doses.
- Schizophrenic patients in remission who took placebos were much less likely to relapse than those receiving nothing.

Another theory is that placebos somehow stimulate the secretion of small brain peptide messengers like the endorphins that have strong effects on mood and sensitivity to pain. Although there are no measurements to confirm this, support comes from the observation that placebo pain relief is diminished by the administration of naloxone, which blocks opiate effects and also reduces the analgesic response to acupuncture. However, this does not explain why:

- An allergy vaccine allowed 75 percent of patients to eat foods not previously tolerated - but so could 75 percent of the placebo group.
- A genetically engineered drug let patients walk 26 seconds longer on a treadmill-but the placebo group could walk 42 seconds longer.
- 86 per cent of men taking a baldness drug had increased hair growth – but forty two percent of the placebo group did just as well.

Stimulation of endorphin secretion alone would not explain all of these other wide-ranging biological benefits. **The common denominator appears to be the belief, faith, or expectation of a favorable outcome, which provides a sense of control that reduces stress.**

Stress, Control, And Expectations

Stress can contribute to or aggravate the course of almost any illness. However, it is difficult to define because it differs for each of us. A steep roller coaster ride that is severely distressful for some can be a pleasurable thrill for others. The difference is due to the degree of control over the event that each participant perceived. While nobody had any more or less, the feeling of control fosters positive expectations. Just as **the feeling of having no control is always distressful**, the sense of control is a powerful stress buffer. **Placebos can provide a sense of control** for many, and **the resultant expectation of a positive result may be related to their benefits**. Consider the following:

- Patients with physical complaints but no identifiable disease were told either that no serious disease had been found and that they would soon be well, or only that the cause of their ailment was unclear. Two weeks later, 64 percent in the first group had recovered, compared to 39 percent in the other.
- Volunteers were given an alcohol-free drink but were told that it contained alcohol; most reported a tendency to feel intoxicated.
- A bronchodilator was found to be far more effective for asthmatics who were told it would open their airways and make it easier to breathe, than when they heard it would cause constriction that would make breathing more difficult.

Conversely, **nocebos that produce negative expectations can have harmful results.**

- When asthmatics were given an inhaler with salt water but told it was an irritant allergen, airway constriction increased and they had difficulty breathing. When told that the same inhaler had a new asthma medication, airways opened up and breathing quickly improved.
- When 13 people extremely allergic to poison ivy were rubbed on one arm with a harmless leaf but were told it was poison ivy, all broke out in a rash at the point of contact. When poison ivy was applied to the other arm but they were told it was a harmless leaf, there were only two reactions.

Could placebos work by reducing stress and thus increase positive expectations?

It's Not All In Your Head

Many factors can influence the power of placebos, including their size, shape, and especially color. Red placebos are better for depression while yellow or blue are preferred for anxiety disorders. In one study, medical students were told they would be participating in a test of either a powerful new stimulant or tranquilizing medication, but would not know which they were receiving. Each student took one or two blue or red inert placebo tablets, and an hour later filled out a questionnaire to indicate their reactions. The red pill group reported being energized and "high", while the blue pills had sedative effects and resulted in making subjects feel "down" and sad. Those who took two pills had stronger responses in both groups. One student who took two blue pills had such a depressive reaction that he had to be admitted to the health service.

Big tablets and capsules work better than small ones, injections are more potent than pills, and surgery is the most powerful placebo. The first proof of this came during the 1950's, when a popular treatment for angina was tying off the internal mammary artery. Proponents claimed that this increased blood flow in the coronary arteries because of collateral circulation that developed as new vessels grew in. There seemed to be little doubt that many patients benefited, but some surgeons were skeptical. In one study, they selected patients with similar degrees of angina and performed identical bilateral skin incisions under local anesthesia. The internal mammary was ligated in some but not in others, although the patients were not aware of this.

Six weeks later every patient who underwent sham surgery reported a decreased need for nitroglycerine and an increase in exercise tolerance, compared to three out of four of the ligated group. Improvement persisted on 6 to 8 month follow-up in sham surgery patients. A second experiment involved ten patients with equal degrees of angina. Five underwent ligation and five had only the skin incisions. Both groups reported about 40 percent improvement 6 months later, but **the most impressive results were seen in two of the fake surgery patients.**

It is not likely that such studies could be performed today because they would have to be approved by Institutional Review Boards, ethics committees, patient's right groups, fiscal intermediaries, etc. Critics would also quickly complain that this violates the most important part of the Hippocratic oath "First, do no harm to the patient." However, one such study was done only a few years ago in ten middle-aged men scheduled for arthroscopic knee surgery - and with their consent. All were draped and anesthetized in the operating room, and sent home after surgery with crutches and a painkiller. Two had the standard procedure of scraping and rinsing the knee, three had only the rinsing, and five had the same skin incision but nothing else. The surgeon didn't know what procedure was being perforemed until he opened an envelope from the anesthetist just before making the incisions.

The placebo worked. Six months after surgery, the patients still didn't know what had been done. All of them reported much less pain and none were unhappy with the outcome of their partiular operation.

Another surgical attempt to reduce angina was the Vineburg procedure, in which the internal mammary artery is implanted into heart muscle to improve the coronary circulation. Patients also improved following surgery despite the fact that subsequent angiograms failed to demonstrate any increased coronary blood flow. Coronary bypass surgery is very successful in relieving angina and increasing exercise tolerance and these benefits often persist for years. Nevertheless, follow-up angiograms often show that many of these vessels have become completely occluded again after only 6-12 months. Why does improvement persist if the original problem that led to the surgery recurred?

There is a sharp disparity between what patients feel subjectively, and what physicians observe objectively. **Illness and disease are often used as synonyms, but they are not the same.** A greater appreciation of this distinction may provide important insights into why placebos work.

Placebos May Improve Illness Symptoms, But Can They Also Cure Disease?

Athough angina was significantly reduced in the artery ligation studies, there was no corresponding improvement in any patient's electrocardiogram. Whether placebos can actually reverse disease is a tricky question that gets into allied subjects such as the ability of a strong faith and "intentionality" to reverse cancer and other fatal diseases. In one famous case, a patient with terminal cancer who required oxygen to walk a few steps was given a new drug he was assured would cure him. His tumors quickly "melted like snowballs on a stove", symptoms disappeared, and he was even able to fly his own plane alone. He remained in excellent health for more than a month, when it was announced that studies had now shown the drug to be worthless. He quickly deteriorated and died two weeks later.

Socio-cultural differences can also affect placebo responses. In a comparison of over 100 double-blind placebo-controlled ulcer studies with the same drug and the identical placebo pill, placebo healing averaged 32 percent overall and in the U.S. It was 60 percent in Germany, 21 percent in neighboring Denmark and The Netherlands, but averaged only 6 percent in Brazilian trials.

Just as Pavlov's dogs learned to salivate at the sound of a bell that had previously signaled feeding time, **some placebo effects may be conditioned responses.** If an inert but identifiable substance is given along with a drug, it may subsequently be able to reproduce the same effect, including immune system suppression, pain relief, central nervous system stimulation, and improved physical activity. When asthmatic children were given a sniff of vanilla along with a squirt of medicine from a bronchodilator twice a day, the vanilla odor alone was later able to significantly improve their breathing because it had similar bronchodilator effects. Consulting a physician often provides a sense of control that reduces stress, but the associated symbols and rituals of the encounter (white coat, stethoscope, physical examination with its associated instruments, personal touch and laying on of the hands, etc.) may also provide benefits via conditioned responses that resulted from prior experiences.

Almost any complaint can be shown to be influenced by a placebo. This is not necessarily limited to administering an inert injection or pill along with the suggestion that improvement will follow. A placebo can restore sexual function to nonorgasmic women hooked up to a biofeedback machine that measures vaginal blood flow, which increases with sexual arousal. When shown explicit sexual stimuli that would arouse most females and 30 seconds later receive a false biofeedback signal that their vaginal blood flow has increased, they promptly reported becoming genuinely aroused, and they are.

The power of a placebo can obviously be influenced by many factors, the most important being the faith and expectations of the patient. Placebo effects are achieved by many mechanisms involving different circuits. Some believe this could include signals transmitted via pathways such as the "electrical circulatory system" proposed by Nordenström, or by meridians that conduct the flow of *chi*. Documented faith healing with or without direct contact may also be mediated via such subtle energy conduits. All of the above issues will be thoroughly discussed at our next Congress - so stay tuned.

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