

THE PLACEBO EFFECT

THE TRIUMPH OF MIND OVER BODY

A growing body of research reveals not just psychological and perceptual components to the placebo effect but also a biochemical substrate to the mechanism.

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A neglected phenomenon

One of the most commonly used terms in medical language is the word *placebo*. The *placebo effect* is used as a scale for evaluating the effectiveness of new drugs. But what exactly is the placebo effect and what are its consequences in the deterministic structure of Western medicine?

The placebo effect has been frequently abused by health professionals to denote and stigmatise a fraud or fallacy. Alternative therapies have often been characterised as merely placebos. But the placebo effect is not a fraudulent, useless or malevolent phenomenon. It occurs independently of the intentions of charlatans or health professionals. It is a spontaneous, authentic and very factual phenomenon that refers to well-observed but uninterpreted and contingent therapies or health improvements that occur in the absence of an active chemical/pharmacological substance. Make-believe drugs—drugs that carry no active chemical substances—often act as the real drugs and provoke therapeutic effects when administered to patients.

In many drug trials, the manufacturers of the drug sadly discover that their product is in no way superior to the effect of a placebo. But that does not mean that a placebo equates to a null response of the human organism. On the contrary, a placebo denotes non-chemical stimuli that strongly motivate the organism towards a therapeutic course. That is, the placebo effect is dependent not on the drug's effectiveness but solely on therapeutic intention and expectation.

Effects of positive and negative thinking

The placebo effect has been often misunderstood as a solely psychological and highly subjective phenomenon. The patient, convinced of the therapy's effectiveness, ignores his symptoms or perceives them faintly without any substantial improvement of his health; that is, the patient *feels* better but is not healthier. But can the subjective psychological aspect of the placebo effect account for all of its therapeutic properties? The answer is definite: the placebo effect refers to an alternative curative mechanism that is inherent in the human entity, is motivated by therapeutic intention or belief in the therapeutic potential of a treatment, and implies biochemical responses and reactions to the stimulus of therapeutic intention or belief.

But placebos are not always beneficial: they can also have adverse effects. For example, administering a pharmacologically inactive substance to some patients can sometimes bring about unexpected health deteriorations. A review of 109 double-blind studies estimated that 19 per cent of placebo recipients manifested the *nocebo* effect: unexpected deteriorations of health.¹ In a related experiment, researchers falsely declared to the volunteers that a weak electrical current would pass through their head; although there was no electrical current, 70 per cent of the volunteers (who were medical students) complained of a headache after the experiment.²

In a group of patients suffering from carotid atherosclerosis, prognosis and progression of the disease were burdened when their psychological health was bad (i.e., they were affected by hopelessness or depression). In another group of carotid atherosclerosis patients, prognosis and progression were burdened not only by hopelessness but also by hostility.³ In patients with coronary heart disease, hopelessness was a determinative risk factor.⁴ Social isolation, work stress and hostility comprised additional risk factors.⁵

Positive or negative thinking seems to be a decisive risk factor for every treatment, perhaps even more important than medical intervention.

The nocebo effect appears to have a specific biological substrate. A group of 15 men whose wives suffered from terminal cancer participated in a small perspective study. After their wives' deaths, the men experienced severe grief that caused immunodepression. The spouses' lymphocytes for a period of time after their wives' deaths responded poorly to mitogenes. Grief had assaulted their immune system. The study proposed that grief and grief-induced immunodepression resulted in high-level mortality of the specific group.⁶

A short history of a small miracle

The term *placebo* (meaning "I shall please") was used in mediaeval prayer in the context of the phrase *Placebo Domino* ("I shall please the Lord") and originated from a biblical translation of the fifth century AD.⁷ During the 18th century, the term was adopted by medicine and was used to imply preparations of no therapeutic value that were administered to patients as "decoy drugs". The term began to transform in 1920 (Graves⁸), and through various intermediate stages (Evans and Hoyle, 1933⁹; Gold, Kwit and Otto, 1937¹⁰; Jellinek, 1946¹¹) was fully transformed in 1955 when it finally claimed an important portion of the therapeutic effect in general. Henry K. Beecher, in his 1955 paper "The Powerful Placebo", attributed a rough percentage of 30 per cent of the overall therapeutic benefit to the placebo effect.¹²

In certain later studies, the placebo effect was estimated at even higher, at 60 per cent of the overall therapeutic outcome. In a recent review of 39 studies regarding the effectiveness of antidepressant drugs, psychologist Guy Sapirstein concluded that 50 per cent of the therapeutic benefits came from the placebo effect, with a poor percentage of 27 per cent attributed to drug intervention (fluoxetine, sertraline and paroxetine). Three years later Sapirstein, along with a fellow psychologist Irving Kirsch, processed the data from 19 double-blind studies regarding depression and reached an even higher percentage of therapeutic results attributed to the placebo effect: 75 per cent of depression therapies or ameliorations were placebo induced!¹³

Hróbjartsson and Gøtzsche (2001¹⁴, 2004¹⁵) doubted the effectiveness of the placebo phenomenon, attributing it solely to the subjective factors of human psychology. And indeed, there is a major aspect of the placebo effect related to psychology. In two studies where placebos were exclusively administered, the placebo effect seemed to be effected from the subject's perception of the applied therapy, i.e., two placebo pills were better than one, bigger pills were better than smaller, and injections were even better.¹⁶

The placebo induced a reaction not only to the therapy but also to its form, suggesting that the placebo phenomenon is shaped according to the personal symbolic universe of the patient. Before the placebo response occurs, human perception has already interpreted the applied therapy and has prepared a certain response to it. It would appear that not only chemical but also non-chemical stimuli participate in the motivation of the human organism towards therapy.

But is the placebo reaction solely a psychological phenomenon or does it have additional tangible somatic effects?

One of the more dramatic events regarding placebo therapy was reported in 1957 when a new wonder drug, Krebiozen, held promise as the final solution to the cancer problem. A patient with metastatic tumours and with fluid collection in his lungs, who demanded the daily intake of oxygen and the use of an oxygen mask, heard of Krebiozen. His doctor was participating in Krebiozen research and the patient begged him to be given the revolutionary drug. Bent by the patient's hopelessness, the doctor did so and witnessed a miraculous recovery of the patient. His tumours melted and he returned to an almost normal lifestyle. The recovery didn't last long. The patient read articles about Krebiozen's *not* delivering what it promised in cancer therapy. The patient then had a relapse; his tumours were back. His doctor, deeply affected by the aggravation, resorted to a desperate trick. He told his patient that he had in his possession a new, improved version of Krebiozen. It was simply distilled water. The patient fully recovered after the placebo treatment and remained functional for two months. The final verdict on Krebiozen, published in the press, proved the drug to be totally ineffective. That was the *coup de grâce* for the patient, who died a few days later.¹⁷

In spite of the melodrama of the Krebiozen case, there is no single case or personal testimony that can denote or prove a therapy to be effective. Statistical studies, not personal testimonies, can verify a proposed therapy's effectiveness, and well-planned studies are able to concur that the placebo phenomenon has somatic properties.

One such study was implemented in 1997. The two study groups consisted of patients with benign prostatic hypertrophy. One group took actual medication while the control group received placebo treatment. The placebo recipients reported relief from their symptoms and even amelioration of their urinary function.¹⁸ A placebo has also been

reported to act as a bronchodilator in asthmatic patients, or to have the exact opposite action—respiratory depression—depending on the description of the pharmacological effect the researchers gave to the patients and therefore the effect the patients anticipated.¹⁹

A placebo proved highly efficient against food allergies and, subsequently, impressively effective in the sinking of biotechnologies on the stockmarket. How could that be? Peptide Therapeutics Group, a biotech company, was preparing to launch on the market a novel vaccine for food allergies. The first reports were encouraging. When the experimental vaccine reached the clinical trials stage, the company's spokesperson boasted that the vaccine proved effective in 75 per cent of the cases—a percentage that usually suffices to prove a drug's effectiveness. But the good news didn't last long. The control group, given a placebo, did almost as well: seven out of 10 patients reported getting rid of their food allergies. The stock value of the company plunged by 33 per cent. The placebo effect on food allergies created a nocebo effect on the stockmarket!²⁰ In another case, a genetically designed heart drug that raised high hopes for Genentech was clobbered by a placebo.²¹

As aptly put by science historian Anne Harrington, placebos are "ghosts that haunt our house of biomedical objectivity and expose the paradoxes and fissures in our own self-created definitions of

the real and active factors in treatment".²²

The placebo's pharmacomimetic behaviour can even imitate a drug's side effects. In a 1997 study of patients with benign prostate hypertrophy, some patients on a placebo complained of various side effects ranging from impotence and reduced sexual activity to nausea, diarrhoea and constipation. Another study reported placebo side effects as including headaches, vomiting, nausea and a variety of other symptoms.²³

The placebo effect in surgery

But how deep can the placebo effect trespass into the well-defined area of medicine? Surely it can't joust with medicine's strike force; it cannot challenge surgery. Or can it?

In 1939, an Italian surgeon named Davide Fieschi invented a new technique for treating angina pectoris (chest pain due to ischaemia or lack of blood/oxygen getting to the heart muscle, usually due to obstruction of the coronary arteries).²⁴ Reasoning that increased blood flow to the heart would reduce his patients' pain, he performed tiny incisions in their chests and tied knots on the two internal mammary arteries. Three quarters of the patients showed improvement; one quarter of them was cured. The surgical intervention became standard procedure for the treatment of angina for the next 20 years. But in 1959, a young cardiologist, Leonard Cobb, put the Fieschi procedure to the test. He operated on 17 patients: on eight of them he followed the standard procedure; on the other nine he performed only the tiny incisions, letting the patients believe that they'd had the real thing. The result was a real upset: those who'd had the sham surgery did as well as those who'd had the Fieschi technique.²⁵ That was the end of the Fieschi technique and the beginning of the documented surgical placebo effect.

In 1994, surgeon J. Bruce Moseley experimented with the surgical placebo. He split a small group of patients suffering from osteoarthritis of the knee into two equal groups. Both groups were told that they would undergo arthroscopic surgery, but only the first group got the real thing. The other group was left virtually untreated, with the doctor performing only tiny incisions to make the arthroscopic scenario credible. Similar results were reported in both groups.²⁶

Moseley, stunned by the outcome, decided to perform the trial with a larger statistical sample in order to reach safer conclusions. The results were replicated: arthroscopic surgery was equal therapeutically to the placebo effect.²⁷ The placebo had found its way into surgical rooms.

Perhaps the most impressive aspect of surgical placebo arose in a groundbreaking 2004 study. In the innovative field of stem-cell research, a new approach was taken with Parkinson's disease. Human embryonic dopamine neurons were implanted through tiny holes in the patients' brains. Once again, the results were encouraging. And once again, the procedure failed to do better than a placebo. In this case, the placebo involved tiny holes incised in the skull without implantation of stem cells. As the researchers confessed, "The placebo effect was very strong in this study".²⁸

But how can it be that the therapeutic expectancy alone often produces results equal to those from actual surgery? It appears that the mind is exerting control over somatic processes, including

diseases. The biochemical traces of this influence are only beginning to be outlined. Modern research indicates a biological, tangible substrate to the placebo effect.

Somatic pathways

In the mid-1990s, researcher Fabrizio Benedetti conducted a novel experiment whereby he induced ischaemic pain and soothed it by administering morphine. When morphine was replaced by a saline solution, the placebo presented analgesic properties. However, when naloxone (an opiate antagonist) was added to the saline solution, the analgesic properties of the water were blocked. Benedetti reached the conclusion that the placebo's analgesic properties were a result of specific biochemical paths. Naloxone blocked not only morphine but also endogenous opioids—the physical pain-relievers.²⁹

The endogenous opioids, endorphins, were discovered in 1974 and act as pain antagonists. Benedetti's suggestion of a placebo-induced release of endorphins was supported by findings produced with MRI and PET scans.³⁰ Placebo-induced endorphin release also affects heart rate and respiratory activity.³¹ As researcher Jon-Kar Zubieta described, "...this [finding] deals another serious blow to the idea that the placebo effect is a purely psychological, not physical, phenomenon".³²

Further findings support the notion that the placebo effect presents a biochemical substrate in both depression and Parkinson's disease. Analysing the results of PET scans, researchers estimated the glucose metabolism in the brains of patients with depression. Glucose metabolism under placebo presented differentiations that were similar to those caused by antidepressants such as fluoxetine.³³ In patients suffering from Parkinson's disease, a placebo injection promoted dopamine secretion in a similar way to that caused by amphetamine administration.³⁴ Benedetti

demonstrated that the placebo effect provoked decreased activity in single neurons of the subthalamic nucleus in patients with Parkinson's disease.³⁵

From numerous research findings, it is logical and rather safe to conclude that there is a biochemical substrate to the placebo effect. But what is more intriguing to it is its relation to perception. It would appear that perception and the codes and symbols that the animate computer, the brain, utilises in order to process internal and external information strongly determine the potency and form of placebo response.

In a recent study, patients were purposely misinformed that they had been infected by hazardous bacilli and they subsequently underwent treatment. However, there were no bacilli and the treatment administered was a placebo. Guess what? Some of the study subjects developed infection-like conditions that were not treatable by the placebo medication.³⁶ The mind interpreted the fictional bacilli as hazardous and instructed the body to respond to them as if they were real.

Despite the placebo's potency and its importance for a new perception of health where body and mind heavily interact, large numbers of scientists continue to regard the placebo as an insignificant systematic error, a troublesome nought. According to cancer researcher Gershon Zajick: "There is nothing in the pharmacokinetic theory which accounts for the placebo effect. In

order to keep the theory consistent, the placebo effect is regarded as random error or noise which can be ignored.³⁷

One of the most perceptive placebo researchers was Stewart Wolf, "the father of psychosomatic medicine", who as early as 1949 had given it a thorough description. Wolf not only defended the placebo as a non-fictional and very "real" phenomenon but also described the placebo's pharmacomimetic behaviour. He was perhaps the first researcher to correlate the placebo effect not only with psychology and predisposition but also with perception. More than half a century ago, he stated that "the mechanisms of the body are capable of reacting not only to direct physical and chemical stimulation but also to symbolic stimuli, words and events which have somehow acquired special meaning for the individual".³⁸

In this context, a pill is not merely an active substance but also a therapeutic symbol and thus the organism is able to respond not only to its chemical content but also to its symbolic content. Likewise a bacillus, beyond its physical properties, acquires symbolic properties that can cause an organism's reaction even in the absence of the bacillus.

The presence and extent of the nocebo effect should also be studied in regard to drug resistance. Perhaps drug resistance is a multifactorial phenomenon involving not only microbial evolutionary aptness but also human psyche mechanics. Placebo and nocebo phenomena might prove fundamental not only on the personal level but also in the public health arena. They might even provide the foundation stone for a new model of health, a new medicine that was envisioned by Wolf in the 1950s: "...in the future, drugs will be assessed not only with reference to their pharmacologic action but also to the other forces at play and to the circumstances surrounding their administration".³⁹

Five centuries ago, Swiss alchemist and physician Paracelsus (1493–1541) wrote: "You must know that the will is a powerful adjuvant of medicine." It seems that our scientific arrogance has blinded us to the teachings of the past. ∞

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Peter Arguriou was born in Greece in the summer of 1973. He studied medicine at the University of Athens Medical School, but left disappointed by the mechanistic perceptions governing medicine. Later, he briefly studied classical homoeopathy at the Aegean University under Alternative Nobel Prize winner George Vithoulkas. He writes for the Greek press and is the author of eight books (fiction, science fiction, poetry—most of them still unpublished). He is a member of the Hellenic MENSA and currently is working on a book regarding novel epidemics, bad science, the gene promise, the media travesty in coverage of science news, orchestrated propaganda and the corruption of the scientific establishment by big business and political agendas. He can be contacted by email at petrosarguriou@hotmail.com.

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