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Placebo, a historical perspective

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Abstract
Substances and interventions with no specific therapeutic effect have been in use since the dawn of history. The term *placebo* has first been mentioned in the Scriptures, but it was not until the 19th century that it appeared in a medical context. Although lay people like Voltaire, and physicians such as Sir William Osler, have raised the possibility that much of what physicians did had no specific therapeutic effect, this notion was not shared by the public at large or by the medical profession. It was only by the end of the 18th century that a placebo-controlled trial has been conducted, repudiating the therapeutic effect of mesmerism. The advent, in the late 1940s, of effective treatments, which also had serious adverse effects, made the distinction between placebo and putative, active drug effects more relevant and urgent, and cleared the way for double-blind, randomized, placebo-controlled trials. This in turn triggered an ethical debate on the use of placebo, both in research and in clinical practice. Anthropologists, sociologists, physiologists, and medical researchers are all focusing their efforts on understanding the mechanism, role and modulating factors of placebo.

1. Introduction

The term placebo defines a therapy which is used for its non-specific psycho-physiological or presumed effect, but is without actual effect on the condition being treated. Placebo response is the difference between the non-specific beneficial response and that attributed to the natural history. Placebo effect is the (beneficial) effect which is derived from the context of the encounter – the rituals, the settings, and the clinician/healer-patient relationship – which is common to all treatments, as distinguished from therapeutic benefits, produced by the specific or characteristic pharmacological or physiological effects of an active compound or intervention. The first mention of "placebo" is in St. Jerome's mistranslation of the first word of the ninth line of Psalm 116. The Hebrew for "I will walk before the Lord", was translated by him into "*Placebo Domino in regione vivorum*" ("I shall please the Lord in the land of the living") (Jacobs, 2000). Pleasing has a central meaning to the notion of placebo: placebo is associated with the pleasing of the patient by the therapist, of the therapist by the patient, or both.

Since very few treatments with recognized and consistent beneficial effects have existed until the beginning of the 20th century, the history of medicine is the history of placebo. Effective placebo remedies have been ubiquitous in all societies and cultures, from the ancient Egypt (Shapiro

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and Shapiro, 1997) to today's multi-billion-dollar alternative medicine (Singh and Ernst, 2008). From crocodile dung poultices, practiced by ancient Egyptians, to acupuncture, practiced today at the top medical centers all over the world, the placebo effect continues to be a trusted ally to the practicing clinician and an unavoidable hindrance to the clinical investigator.

2. Ancient times (B.C.)

Dating back to 2100 B.C, In Babylonia and Assyria, we find that the modus operandus of the sorcerer (*ashipu)* and the physician (*asu*) was based on providing patients with empathy and comfort along with the ''specific'' remedy, thus taking full advantage of the placebo effect (Shapiro and Shapiro, 1997). The Egyptians were pioneers in writing medical texts, using medical terminology, exploring anatomy, and keeping records of procedures such as applying splints and bandages (Estes, 1989; Majno, 1975). One of the most valuable medical papyri, *Ebers Papyrus*, estimated to have been written around 1500 B.C., contained 842 prescriptions, though 700 were definitely medically worthless and the rest of questionable value (Estes, 1989; Kremers and Urdang, 1940). The ancient Egyptians were also the first to use the long-lasting technique of bloodletting in an attempt to purify the body (1000 B.C.) (Seigworth, 1980). The technique has survived for 2500 years, despite its ill effects. Same as in our time, techniques were constantly modified - from cutting to cupping to leaches - though the concepts behind them were seldom placed under scrutiny. Egyptian medicine had a great impact on the ancient Greeks, who added purges and dehydration to the medical toolbox. The history of Chinese medicine lists 4785 drugs, prescribed in four times as many (16,842) modes of prescriptions (Hume, 1940; Morse, 1934). Despite the fact that many of these drugs are used in current practice in China and the current popularity of Chinese medicine outside China, attempts to test these drugs' effectiveness using modern trial methodologies have rarely proven them superior to placebo. Acupuncture, more than any other treatment, has gained the dedication of the Chinese and interest worldwide. Unfortunately, its vast popularity notwithstanding acupuncture still lacks biological plausibility and proper scientific evidence of effectiveness (Manheimer et al., 2005).

3. The first eighteen centuries

Galen's *Pharmacopeia*, with its 820 remedies, has dominated treatment for 1500 years and disappeared only in the 19th century, under pressure from the emerging scientific approach to medicine. Galen's *Pharmacopeia* included any substance and mixture made of plants, bacteria, worms, reptiles, fish, human organs, tissue, bones powder, excretion, or extract in any phase, with or without the involvement of *force majeure*, magic, witchcraft, or any other intentional or unintentional action. Faulty deductive logic provided invaluable support to Galen's placebo effect. ''*All who drink of this remedy recover in a short time except those whom it does not help, who all die. Therefore, it is obvious that it fails only in incurable cases.*'' *Galen* (30–200 AD).

During the 16th century Mithridatum, medicine's universal remedy, later known as Theriac, was one of the oldest and most expensive drugs. It was concocted from dozens of substances and took six months to prepare (Majno, 1975). The legend tells that it was developed in the ancient Hellenistic kingdom of Anatolia (today's Turkey) by the king Mithridates VI of Pontus, who was concerned about being poisoned. It is not clear whether he was trying to develop a universal medicine or an antidote for poison. When the Romans defeated him, his medical notes fell into their hands. Andromachus, Emperor Nero's physician, added viper's flesh to the mix as a main ingredient (Hodgson, 2001), and opium was often stirred in for good measure. In the 16th century Mattioli, an Italian physician, concocted an antidote for poison and for the plague from 230 ingredients, including opium and theriac Andromachus.

Bezoar stones, believed to be the crystallized tears of a snake-bitten deer, turned out to be gallstones in the stomach of the deer. Bezoars spread from the Arab world of medicine to Europe and were used as a universal antidote. Emerging from Chinese, Indian, and Western literature, the mythological unicorn, with its spiraled horn, has become a symbol of purity and grace. It was believed to have the power to heal and to render poisoned water safe. Ground unicorn horn was among the most expensive placebo substances in the history of medicine and an important ingredient in 16th century medicine (Shepard, 1930). In fact, the substance was the left upper incisor tooth, spiraled indeed, of a narwhal whale. The absurdly high trading value gave rise to frauds and fakes, and records exist of individuals being tried and punished for such offenses.

Again, faulty deductive logic proved an ally to placebo. Antonio Durazzini, active in Tuscany in 1622 during a most deadly epidemic, reported to his superiors in Florence that the poor peasants seem to be more robust and immune to disease than the rich. He based his observation on the fact that during epidemics the poor, who could not afford his bloodletting treatments, were less likely to die from the ravages of the epidemic than the rich, who could afford it. Despite faulty deduction, the limits of the medical sciences and the power of placebo were well understood, as evidenced by the words of Ambroise Paré (1510–1590): *the physician's duty is to ''cure occasionally, relieve often, console always''* (*Guérir quelquefois, soulager souvent, consoler toujours*).

God's touch, already mentioned indirectly in the bible, was said to heal blindness, leprosy, and insanity. In ancient and medieval times, it evolved into belief in the ''royal touch''. It was practiced in Greece and Rome, and later by the English, French, and Spanish monarchies. In his 25-year reign in the 17th century, King Charles II has touched almost 100,000 individuals, some of whom no doubt achieved instant and long-lasting health. Richard Wiseman, the king's doctor, who bore witness to the many hundreds of cures performed by the king's touch (Bloch, 1973), remarked that in that period of English history more people have died of scrofula than ever before (Haggard, 1929). The belief in the royal touch faded in the 18th century, in parallel with social unrest and skepticism of the ideas of supernatural personae and of absolute monarchy. Eventually the skepticism spread to all areas of life, dismantling the entire social order (Bloch, 1973).