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Placebo — the forgotten drug

by Harry Boström[1]

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The placebo effect is seen in patients who have been the target of intervention believed to lack specific action. This effect seems to be an important, and possibly the only, contribution to the positive effect of alternative medicine sometimes reported. The risks involved in the uncritical utilization of the placebo effect are, however, great and must be carefully considered. Most of the information available on this effect has been obtained from double-blind studies in connection with the introduction of new drugs. Depending on the kind of effect that is expected, improvements of up to 30% or more can be noted. Many attempts have been made to explain the nature of the placebo effect. Thus it has been suggested that a placebo acts by decreasing anxiety. Another explanation is that a placebo acts by meeting the expectations of the patient. It has also been proposed that the human placebo response has characteristics of a conditioned response.

Key terms alternative medicine, complementary medicine, placebo effect.

My clinical career as an internist began in the early 1950s after some years of basic research in medical chemistry. I got a position as junior assistant to the chief physician at one of the city hospitals in Stockholm, and during most of my first year I assisted him in his private ward. The patients in this particular ward were recruited from his large private clinic. This situation was in contrast to that of the patients in the general wards, who, in most cases, were admitted through the emergency ward.

My task was to prepare and keep the records, to keep the patients happy between the daily ward rounds, and, if necessary, give them aspirin or some barbiturate in the evening. This was why the junior doctor in this position was called the Aspirin Waiter (Albylkypare in Swedish) by the senior staff. After some time I found that not all of our patients suffered from life-threatening diseases or any other internal medical disease described in my medical books. Many of our patients (artists, middle- and upper-class housewives, local politicians) were complaining of tiredness, palpitations, headache, gastrointestinal discomfort, and so on. In spite of a careful clinical evaluation we were not able to make a proper somatic diagnosis in many of these cases.

After 2 or 3 weeks the patients were dismissed in the same or often perhaps in a somewhat better shape than when admitted. The end and high point of the hospital stay was a closed door session with the chief. After this session the patients came out with a prescription in their hands and then left the hospital happily. I became increasingly curious about the pills that my chief prescribed for these patients and asked him to tell me his secret. He then gave me a prescription that contained about 10 different substances, such as caffeine, quinidine, belladonna, strychnine theophyllamine, arsenic, and other drugs. All the drugs were prescribed in clinically and pharmacologically ineffective doses mixed with a large amount of lactose. Later, I tried to treat a few of my own patients in the same category with these gray pills. The results were excellent.

After the mid-1950s I had a 5-year period of full-time research. When I returned to a university clinic in a more senior position, I had lost the copy of the prescrip-

1 Professor Harry Boström, Tiundagatan 11, S-752 31 Uppsala, Sweden.

Year	Discovery
2010	Gene therapy
2000	Immunosuppressive drugs
1990	Cytostatics
1980	Ulcus drugs
1970	Diuretics, antihypertensive drugs
1960	Cortisone
1950	Penicillin
1940	Liver extract – B_{12} – Sulfa
1930	Insulin
1920	Salvarsan
1910	Thyroid extract
1900	

Figure 1. The discovery and introduction of new specific drugs during the 20th century.

tion. I had become a great believer in scientifically based medicine and a very determined critic of unscientific medicine, alternative medicine, and all kinds of charlatanism. I kept this attitude over the years also in my teaching until I retired from the chair of internal medicine at Uppsala.

In the early days of human society, going back thousands of years, the placebo was probably, with few exceptions, the only kind of treatment available for doctors to make their patients feel better. In contrast to the old-timers my own generation of doctors has had the privilege of witnessing and benefiting from the remarkable development not only of new diagnostic methods but also of the introduction of a fantastic arsenal of new, very effective drugs. Before the end of the 19th century, very few specific medicines for the treatment of well-defined diseases were available. Extract of Folia digitalis for the treatment of dropsy due to cardiac failure, according to Withering, 1785, was of course known but very difficult to handle even in the 1950s when I started.

In my opinion the introduction of thyroid extracts for the treatment of myxedema represents the very beginning of the new era of science-based therapy (figure 1). The discovery of insulin, and its use in the treatment of juvenile diabetes, is still an all time high in this series of achievements. Similar to the treatment of myxedema, the treatment of diabetes with insulin represented an effective specific treatment of a well-defined disease. The effect of the other types of medicines listed in figure 1 is not always as dramatic as in the case of diabetes and myxedema. In the case of infectious diseases, some strains of bacteria may, for instance, develop resistance against some antibiotics, and some of the modern antihypertensive and diuretic drugs sometimes have serious side effects. All types of leukemia cannot be cured by cytostatic drugs, and so on. Nevertheless, in conditions with a known physical basis, the list of medicines in figure 1 illustrates in a most impressive way the strength and capacity of medicine based on modern science. Because of the progress in medical research, there seems to be very little need or room for placebos and so-called alternative medicine. Nevertheless, and in spite of the remarkable achievements of modern medicine, there is still a great and seemingly increasing interest in alternative or complementary medicine in developed countries (called Nicht Schulmedizin in German, or practiques paralelles in French). This interest is not limited to the handling of functional disorders, it also concerns the diagnosis and treatment of many serious, sometimes life-threatening well-defined diseases for which successful treatment is now available within the field of scientifically based medicine. More than 300 methods of diagnosis or treatment are used in the United Kingdom by practitioners of alternative medicine. In Sweden at least 183 methods are used according to a report of the Swedish Parliamentary Commission of Alternative Medicine (1). Table 1 lists examples of various types of alternative medicine.

Table 1. Some methods in alternative medicine.

Type	Method
Spiritual	Faith healing/prayer
Pharmacological	Homeopathy
	Herbalism
	Megadose vitamin C
Physical/physiological	Acupuncture
	Auricular acupuncture
	Zone therapy
	Iridology
Devices	Magnets
	Soft laser
	Bioresonance
	Ozone generators
Mixed	Anthroposophic medicine
	Vegatest
Occult	Numerology
	Scientology

The use of alternative methods in the treatment of diseases with a known physical basis, and for which generally accepted and effective treatment is available, is unethical and not without risks; in most cases it is identical or very close to mere charlatanism. To illustrate this point I refer to a study done in 1989 under the auspices of the Swedish Society of Medicine (2, 3). This study was performed to some extent in opposition to the recommendations given in the report of the Swedish Commission of Alternative Medicine. The report summarized 4 years of extensive and intense work. It was based on trips to the Far East and on studies of the activities of healers, herbalists, and other representatives of traditional medicine in the Philippines, India,

and China. On the basis of long experience from my own department I hypothesized that the health of many patients might be negatively affected by alternative treatments. These are cases in which representatives of alternative medicine intervene with the treatment of severe and well-defined diseases known to respond to treatment within conventional medicine. This practice can result either in the interruption of adequate treatment or in a delay of the correct diagnosis. In order to launch a detailed study on the subject, we contacted all Swedish heads of hospital units of internal medicine, pediatrics, neurology, rheumatology, and oncology. They were asked for case reports (with identification data deleted) in which alternative medical treatment had resulted in a delayed diagnosis or deterioration of the clinical condition as a consequence. The cases were confined to the period 1984—1988. The base-line data on 123 reported cases indicating the types of therapy and ensuing consequences are given in table 2.

A considerable number of the reported side effects was related to intervention by so-called health resorts managed by lay people. Fourteen of 27 patients needing intensive hospital care for life-threatening complications had been treated in health resorts. Luckily, a few of these places have been closed in recent years. Table 2 shows some data on the 23 cases admitted to the intensive care units. Four were diabetic children treated at a health resort. Their insulin doses had been reduced or withdrawn and substituted by a vegetarian diet resulting in severe weight loss and growth retardation. Cases of para- and tetraplegia after chiropractic intervention, uremia and serious vasculitis in systemic lupus erythematosus (SLE), and pulmonary empyema and pneumothorax following acupuncture were also reported in this material.

After I had published this study, I received letters containing other case reports. In one case from Finland, also reported in Scandinavian newspapers, an alternative therapist withheld insulin treatment from a diabetic child. The child died in a classical diabetic coma. In another letter an interesting case of two-sided pneumothorax following acupuncture for asthma was reported. The diagnosis, made for a cyanotic unconscious patient, was indeed very difficult, but eventually the patient recovered.

Many definitions of the placebo effect are given in the literature. One of them reads as follows: "The placebo effect is the effect seen in patients who have received an intervention which is believed to lack a specific action". Since the placebo effect seems to give an important and possibly the only contribution to the positive effect of alternative medicine sometimes reported, it is appropriate in this context to exemplify the risks involved in the uncritical utilization of a placebo alone in the treatment of sick people. In some cases even a nocebo effect might occur under these conditions. This was also demonstrated in my investigation. For obvious reasons my personal experience with the deliberate use of the placebo in my work as clinician is very limited, except at the very beginning of my career, as I mentioned earlier.

It is estimated that the British Library data base contains at least 55 000 articles on the subject. Most of these articles have been published in journals unknown to ordinary doctors. Therefore I was very much relieved to find—as an introduction to this literature—a series of informative, well-balanced and up-to-date articles on placebos published in *The Lancet* in 1995. Most of the rest of my presentation was inspired by the facts and thoughts discussed in these papers (4—10).

Initially it must be stressed that in an individual case it is not easy to know whether the outcome of a particular treatment is due to a specific effect on the disease or to a nonspecific effect. In fact this delineation is very

Table 2. Side effects from different alternative therapy modalities.

Therapy	Number of cases				
	Total	Direct damage by therapy	Death (cause)		Intensive care
Health resort	44		1	(anorexia, sepsis)	14
Homeopathy	17	1	1	(Wilson's disease, spleen rupture)	3
"Naturopathy"	15	1			4
Unknown alternative	15	5	2	(hypernephroma + chronic myeloic leukemia, missed diagnosis)	
Acupuncture	6	2	1	(myocardial infarction, missed diagnosis)	1
"Alternative nutrition"	6				
Thymus extract	5	1	1	(chronic myeloic leukemia)	
Zone therapy	4				
"Alternative medicine"	3				
"Health consultant"	2				
Chiropractic	2	2			2
Iriscopy	1				
Advice from magazine	1				
Others	2				
Total	123	12	6		27

difficult in the case of both scientific and unscientific medical treatment. Under certain conditions, for example, diabetic coma, it is obvious that the probable survival of the patient is achieved by the administration of insulin. Also in the case of Wilson's disease it is not possible to replace an effective chelating agent by homeopathic pills. Such a substitution was nevertheless made in one of the cases referred to in table 2. However, in other situations, such as a self-limiting condition, or in the steady state of a painful chronic disease like rheumatoid arthritis, any treatment might give a better outcome than no treatment at all. Then it does not matter whether treatment is given with conventional or alternative medical methods. There is, therefore, good reason to believe that nonspecific or placebo effects are involved in both types of treatment. The effect of the conventional therapy given by doctors in the past was mainly nonspecific. The effect of modern therapy is mainly specific, but not always. The placebo effect has thus served the medical profession well from ancient times to the present. The mixture of specific and nonspecific effects occurring in most therapeutic situations makes it difficult, as already pointed out, to estimate the effectiveness of placebos and most alternative therapeutic methods in an individual case.

Basic research on an acceptable standard in this area is rare. Most information is obtained from double-blind studies in connection with the introduction of new drugs. Depending on the kind of effect expected, for example pain relief, increased mobility, or improved mental performance, substantial improvement of up to 30% or more may be noted. Many attempts have been made to explain the nature of the placebo effect. Thus it has been suggested that a placebo acts by decreasing anxiety. Another explanation is that a placebo acts by meeting the expectations of the patient. It has also been proposed that the human placebo response has characteristics of a conditioned response. In addition, various psychoanalytical theories on placebos have been presented. Although there is some experimental support for some of the various theories, I regard it safe to state that, at present, the nature of the placebo effect is a matter of controversy. The limited interest in or neglect of the placebo phenomenon among doctors seems to be based on various erroneous doctrines, as shown in table 3.

Table 3. Patients treated by intensive care after alternative therapy.

Age (years)	Diagnosis and complication	Alternative therapy
13	Diabetic coma	Health resort
16–20 (3 cases)	SLE vasculitis	Health resort
13	SLE uremia	Homeopathy
46	Wegener's granulomatosis	"Alt. drug" company
16–78 (2 cases)	Uremia	Health resort
25–38 (3 cases)	Fulminant colitis, colectomy	Health resort
65	Neck pain, paraplegia	Chiropractic
20	Hodgkin's disease stage IA	Chiropractic + "naturopathy"
17	Anorexia nervosa	Homeopathy
50	Status asthmaticus	Zone therapy
50	Severe bronchial asthma	Homeopathy
60	Pulmonary empyema, needle puncture	Acupuncture
42	SLE with uremia	Thymus extract clinic
70	Skeletal tuberculosis	"Naturopathy"
15	Juvenile rheumatoid arthritis	Health resort
55	Neck pain, tetraplegia	Chiropractic
38	Neurinoma, paresthesia	"Naturopathy"
20	Status epilepticus	"Naturopathy" + homeopathy

It seems obvious that there is very little evidence in the literature that any of the therapies listed in table 3 are appropriate. What should modern doctors with access to the whole arsenal of modern science-based therapy know about placebo? First of all, they should be aware of the fact that whatever they do to a patient, for example, communicating in the consulting situation, measuring blood pressure, giving an injection, removing some organ surgically, or applying fancy instruments for investigation or treatment, nonspecific placebo and unfortunately sometimes also nocebo effects act along with the expected specific effects. All doctors are not born with this knowledge. Medical students and young doctors should therefore be taught some basic facts about the placebo phenomenon. They should know that the doctors themselves might be the most important placebo. Their general attitude, their verbal and nonverbal communicating techniques, their own confidence in what they are doing, the quality of their information they give to the patient, especially about the prognosis of the disease, has an impact on the strength of the placebo effect of their performances. In some primitive cultures the patients think that the healer should not ask any or too many questions, because he should know intrinsically the nature of the illness. Such an attitude of a healer with a very strong placebo effect may occur in some subcultures of alternative medicine, such as iridology and zone therapy, but it is not recommended in the practice of scientifically based medicine. In my opinion, the use of the placebo effect by an ordinary doctor is permitted only within the strict rules of the law and according to acceptable rules of ethics. First of all, it must be remembered that all doctors are obliged to give their patients, to the best of their ability, correct information about the nature of the disease and the treatment available. This is a rule of ethics, but it is also directly specified at least in the Swedish laws on health care. Therefore, there is no room for the kind on incorrect information that seems to be a requisite of many types of alternative medicine.

The doctor is not permitted to lie to his patient and possibly not even allowed to use so-called benevolent

lies. These last-mentioned "white" lies might be particularly tempting under two main conditions. It has been estimated that, in general practice or primary care, about 50% of the patients complain of symptoms that cannot be explained on a rational basis. Neither can a definite diagnosis be made. These patients have been named temporary dependent patients by some authors. In a careful study on a large group of such patients no difference was found in the outcome when some patients were given a symptomatic diagnosis and medication and other patients were told that they required no treatment because there was no evidence of disease. In the care of incurable cancer, the administration of various forms of placebos seems to have played a central role in the past. However, also in this area, modern views on patient treatment are based on straightforward information and qualified palliative care, including effective preventive treatment of pain, emotional stress and depression, and there is left little room for alternative and placebo treatment.

I would like to finish by quoting Patrick D Wall in the *Textbook of Pain* (11). "The placebo effect is clearly powerful and infiltrates all aspects of therapy. It represents a practical, ethical and scientific challenge. If a patient seeks relief from a self-proclaimed faith healer, so let it be. However, if a patient approaches a physician of the traditional classical established school, the patient assumes that the recommended therapy is based on a rational, tested scientific scheme which has been validated and which is part of the hugely successful progress of modern medicine. If the physician prescribes a placebo, he is utilizing the patient's expectation which is created by the reputation and overt success of the best of modern medicine. This act goes beyond the physician's personal charisma and authority. It is a lie [p 1297] ."

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