THE PLACEBO EFFECT

by Antonio Bertoloni

The activity of rational phytotherapy is determined by the consolidated methods of classic pharmacology and comes under the scientific parameters with which the properties of the substances used in human or animal therapy are assessed. However, self-medication (and at times official medicine as well) has always used alternative phytotherapeutic methods and products that show a partial activity of practical evidence, whilst without being subjected to the process of the scientific investigation that qualifies a drug. This is the case both for the different presentations of the same traditional drug (aloe, valerian, St. John's wort, camomile, etc.) which are difficult to distinguish from one another and even more today, for the products of alternative medicine, due to the growing exchange of information between the Western world and developing countries where, due to obvious traditional and economic reasons, methods of cure prevail that are based on locally accessible plants. Independently of the fact that these new applications may show, in our countries, toxicities unknown to the original accustomed users, the greater comprehension of the new situation requires further examination of the so-called "placebo effect" as a psychophysiological effect independent of the pharmacodynamic activity (1).
As will be underlined below under point 4., the use of the placebo effect, whether unconsciously in self-medication or finalized by the doctor, can result in appreciable therapeutic advantages.

1. DEFINITIONS AND TERMINOLOGY

1.1 PLACEBO

Over the centuries, therapists have noticed that, in man, there are discreet percentages of improvement and even cure (up to 50%) through medication with substances without any pharmacodynamic effect, i.e. considered unsuitable to modify the altered metabolic reactions of the patient, restoring them to normal. Further observations show that these effects are not only influenced by the type of illness and the personality of the patient and doctor but, above all, they are not observed in a state of unconsciousness or narcosis and not even in the same tests, conducted in parallel in animals: it must therefore be a question of an effect of suggestion (2), i.e. of sensations and predispositions which are totally uncritical but typically human because conscious (3).
The Latin term of placebo, which means "I will please'", appeared in England in Quincy's Lexicon of 1757, with the definition : "A drug used more to please the patient than to benefit him" (1) but since placebo can be not only a substance but also a procedure, definitions such as the following are used today : "Placebo is any substance, the effects of which can be attributed to its use and not to its specific pharmacological properties or any therapeutic procedure that is objectively devoid of specific activity for the disease treated".
If the placebo is an inert substance, it is defined: pure placebo; if, on the other hand, it has potential physiological or pharmacological effects, which cannot influence the treatment under way, it is called : impure placebo.

1.2. THE PLACEBO EFFECT

In its turn, the placebo effect is defined: "The psychological, physiological or psychophysiological therapeutic effect obtained, independently of the pharmacological effect of the drug or specific effect of the procedure, and that acts through psychological mechanisms".
In the most frequent case, it is positive as it leads to an improvement in the state of health of the patient, but it can also be negative because it is sometimes accompanied by undesired effects such as gastro-intestinal problems, reactions of the central nervous system (insomnia, depression, tiredness, restlessness), vegetative reactions (sweating, tachycardia, pallor) or dermatological reactions (orticaria, eruptions).
The negative placebo is sometimes also defined nocebo or displacebo (3), (4).
The main characteristic of the placebo effect is the inconstancy of the therapeutic response which is on average positive in 35% of somatic illnesses and 40% of mental illnesses; however, a positive response does not mean that the problem is only psychological and, vice versa, a negative result is not evidence for an organic aetiology (5).

1.3 THE "PLACEBO" PATIENT

"Placebo-responder" patients are generally insecure, extrovert, tend to be condescending, anxious, and favourable to the therapeutic treatment; "non-responders" are, on the contrary, not very extrovert, more rational than emotional, sceptical but also, paradoxically, hyperimpressionable with a hysteric personality .

2. THE MECHANISM OF ACTION OF THE PLACEBO

After much perplexity, the observation has been reached that the positive response to a placebo appears to be linked with an increase in the secretion of endorphins (neurotransmitters of the pituitary gland with morphine-similar analgesic properties) caused automatically in the placebo-responder aware of the treatment. As counter-evidence, it has been observed that the simultaneous administration of the placebo and of an antagonist of opiates (e.g. naloxone) annuls the placebo effect (3).

3. EXAMPLES OF PREPARATIONS FOR PLACEBO

The Prescriptiones Magistrales of the Association of Swiss Chemists (6) contain some examples of preparations for placebo that can be used in different, forms, colours and flavours, in the quantities prescribed by the doctor.

3.1. Tablets

Tablets of ascorbic acid 50 mg (No. XXX)

3.2. Drops

Sodium chloride	3,0
Aqueous solution 1% of nipacombin (Aqua conservans)	30,0
Tincture of saffron or alkanet , drops	I I I

3.3. Powders

Sodium chloride	0,05
Mannitol	0,45

mixed and reduced to a powder.

3.4. Syrup (7)

Aurantii flavedinis sirupi (Syrup of exocarp of bitter orange)	100.0
Distilled water	100.0

3.5. Suppositories

Mass for suppositories (e.g. of No. X): as necessary

Observations.

In the drops, nipacombin is the classic 7:3 mixture of methyl- and propyl p-idroxybenzoate; tincture of saffron or alkanet, contained in a minimal quantity [(therefore impure placebo cannot be talked of here (see point 1.1.)], have the exclusive purpose of colouring, which takes on particular importance in the placebo. The syrup, on the other hand, is an impure placebo, because the exocarp of citrus fruits is rich in amaroids and essence, which stimulate gastric and biliary secretion and is used for digestive problems. The mass for suppositories is Adeps solidus of the European pharmacopoeia.

4. USEFULNESS OF THE PLACEBO

The benefits of the use of a placebo, both in self-medication with non-standardized preparations or alternative medicine, and on medical prescription, can be summarised in the following three considerations (3), (5).
4.1. It can represent the only valid therapy, even if palliative, for incurable illnesses
4.2 It can represent an uncertain therapeutic result obtained with drugs of proven efficacy
4.3 It can represent a valid alternative to therapies which are not tolerated due to serious side effects.
In the field of rational phytotherapy, the placebo allows a stricter control in the clinical experimentations of new drugs (8).

5. LITERATURE

(1) The following book was published early this year: Daniel E. Moermann, PLACEBO.MEDICINA, BIOLOGIA, SIGNIFICATO. Editrice Vita e Pensiero, Euro 13
(2) The following example describes how the effect of suggestion can even invert the pharmacological action. "A 28-year-old woman had suffered from periodic nausea for some months. After an opportune period of control, she was given 10 ml of syrup of ipecacuana (a powerful emetic Ed. note) directly through a tube in the stomach (to prevent her tasting it) and assuring her that the drug would have eliminated the nausea. Not only did this disappear in 30 minutes, but the gastric contractions also decreased which are normally heightened by ipecacuana" [Wolf S. "Effects of suggestions and conditioning on the action of chemical agents in human subjects –The pharmacology of placebo". J. Clin. Invest. 21 (1950) 100-109
(3) Mutschler E., "Arzneimittelwirkungen", 6th edition WVG 1991, page 99
(4) Hänsel-Sticher-Steinegger, "Pharmakognosie-Phytopharmazie" , 6th edition Springer 1999, page 1233
(5) From lessons of the Course in Pharmacology held at the University of Parma in the 1970s.
(6) Waser P.G. and Steinbach-Lebbin C., "Praktische Pharmakotherapie", Schwabe & Co. AG, Basle 1987, page 533
(7) The drug Aurantii amari flavedo is in Swiss Pharmacopoeia 8. Strictly speaking, flavedo refers to the yellow part of the peel (exocarp) of orange, whilst the white part, or albedo is called : "endocarp" and the whole peel, "pericarp".
(8) The subject lies beyond the scope of the previous discussion, therefore it is summarised here purely for the purpose of collateral information.
The placebo effect shows the need to distinguish, in a clinical test, the real pharmacodynamic effect of the product under study from any other effects independent of it. This can be done only with a comparative test in which, all conditions being equal, the new (potential) drug is compared with a placebo or a standard preparation of known efficacy (Controlled test). This comparison takes on a valid ethic character however, only if there exist therapeutic alternatives for the pathology treated because, otherwise, the placebo would represent an intrinsically dangerous and unacceptable deception for the patient.
Depending on the procedure followed, clinical tests are defined as follows:
open controlled test: when both the patient and the doctor can distinguish the drug from the placebo
blind controlled test: when only the doctor can distinguish the drug from the double-blind controlled test: when neither the doctor nor the patient can distinguish the drug from the placebo controlled crossover test, aimed at controlling two different groups of patients : first, one group of patients is given the drug and the other the placebo (according to one of the aforementioned procedures); this is then followed by a period without treatment (the so-called wash-out period) and lastly, the test is repeated inverted with the same patients in perspective tests on the other hand, the patients are divided into different groups by age, sex, anamnesis etc, before starting the test which is then carried out (with one of the aforementioned procedures) until completion, keeping the same division.