

Placebo, beliefs and knowledge, to achieve humane clinical care

We have all come across clinical cases which are surprising, gratifying or disturbing where we observed that a medicine prescribed for the patient had an inexplicably positive if not miraculous effect, which we can't explain by what we might have expected or by results previously seen with the treatment we prescribed. We confirmed clinical improvement, even cure, and so we said: 'This patient was malingering' or 'it was a placebo effect.' We often recall these clinical cases.

For me, it was an encounter about ten years ago with a woman around 40 years old who had had headaches for more than 20 years and who, when she came back for her 3-month follow-up, told me that she had had an extraordinary improvement such that her daily headaches had all but disappeared and she thanked me for listening to her problem. On asking her whether she was taking prescribed medication, she then told me, showing me her prescription carefully stored in her bag, that she hadn't taken it and she was keeping it carefully in case she might one day need it! I never saw her again...On recounting my experience with this patient to a work colleague, he said to me; 'That woman was a hysteric, and probably exaggerated her headaches and her pain.' This therapeutic effect of a placebo is quite mysterious. Beliefs or knowledge, the heart of this subject provokes much debate.

It is this journey into our mysterious clinical histories which I would like to evoke with you just as I would like to share my reflexions. I will invite the Bible, Saint Jerome, Montaigne, Jesus, C. Cungi, O. Peper, C. Bernard, A. Trousseau, Bevenetti, Decetty, Paul Tournier and Hippocrates in order to arrive at a better understanding of this placebo effect with regard to this ill patient.

I am going to tackle three elements of this subject which filled many books, so I will be reducing and simplifying a complex question, which is attempting the impossible. I will address in turn; the placebo, its definition and history; current knowledge about the placebo; clinical applications of the placebo in our everyday care and medicine of the person.

The word placebo comes from the Latin verb 'placere' in the first-person future; 'I will please'. This word can be found for the first time in the Vulgate translation of the bible by Saint Jerome in psalm 116 verse 9: 'I will please the Eternal in the world of the living.' We should also note here that the translation by Saint Jerome is not found in our bibles and that it is a bad literary translation of the Jewish word which is expressed better in the translation; 'I will walk before the Eternal, in the world of the living.' We can ask ourselves if this is a fault in the translation or an incentive for the reader transcribed by Saint Jerome.

History tells us that, in 14th Century England, this psalm was chanted during the vespers for the office of the dead by young monks chanting 'the placebo' in order to harvest the gifts of the family of the deceased, and, so, the word took on a significance associated with flattery.

In the 14th Century, Montaigne described in 'The Essays' the importance of the imagination and of trust in the process of healing; *'Why do doctors, who already have the confidence of their patients, practise with so many false promises of cure, if it isn't so that the effect of the imagination can supplement the deception of their decoction? They know what one of the masters of their profession had already written, that there are men who just need to see the medicine for it to do the trick.'*

'A woman thought that she had swallowed a pin with her bread and was in agony from an unbearable pain in her throat, where she thought it was stuck; but because there was no swelling or change visible externally, a clever man, having made the judgement that it was just imagination and opinion...made her vomit and secretly threw into her vomit a twisted pin. The woman, thinking she had brought it up suddenly felt relieved of her pain.'

The sense of flattery- stroking in the direction of the fur- is very much of the period.

The word placebo will appear in the medical world in 1795, then in 1811, in the English medical dictionary *'Motherby's New Medical Dictionnary'* defined as 'any medicine adapted more to please than benefit the patient.' So, it came to mean something different for doctors, something banal or common, a definition taken up and established by O. Peper in 1933.

The doctor is not blameless in the therapeutic relationship. For the caring doctor, there is therefore a notion of pleasing the patient so as to do them good, and if possible heal them. Are the effects induced by our treatments always rational? The placebo and how it is used will colour the relationship between carer and patient. We find again these notions in the modern definition of the 'therapeutic alliance' as defined by Charly Cungi. We will develop it further later in this talk.

Doctors have always studied the effects of drugs on the body of the sick person, that's what pharmacology is: a branch of the medical sciences which studies the chemical properties of drugs and their classification (according to the Larousse dictionary). The properties of an inert substance are contained within the **placebo effect**. The inert substance is called **verum**. This verum resembles a real drug and has an effect of its own. The trivialization of the placebo effect in modern times has extended the verum, or the vector of the placebo effect to lotions, perfumes, music... It's thumbing one's nose at semantics for the word to simply refer to 'Ave verum corpus' signifying 'Greetings, true body.' Let us listen to this choral piece, in order to feel all its beneficial effect on our spirit and on our body. It is an effect of the verum or of the placebo : feeling emotion and well-being through music. Is it not the result that is important?

There is reference here to miracles and to miraculous healing. If we open again our bible, we will find ourselves amidst miracles, the ancestors of the placebo effect.

In John 9, 11: *He replied: 'The man called Jesus made mud, spread it on my eyes and told me; 'Go to the pool of Siloam and wash yourself.' I therefore went, I washed myself and I could see.'*

In the account of this healing we find the basis of the placebo effect;

A doctor; in this case Jesus is carer of the body and the spirit, a patient: blind from birth who believes, a placebo; saliva (with healing powers) and mud seemingly without any particular power and finally a miraculous healing which bears witness, and therefore is pleasing to God.

In the 19th Century, Claude Bernard wants to experiment with drugs and in his book *'Introduction to the experimental method'* in 1855, he explains; *'A doctor who tries a treatment and who heals his patients is led to believe that the healing is due to his treatment. Every day, we can have the biggest of illusions about the value of a treatment if we haven't had recourse to comparative experiments.'*

The doctor Armand Trousseau (1801-1867) will be the first in France to administer placebos to his patients telling them that they are active drugs. He is also the first to compare their effectiveness to that of real medicines. This brings him to make a fundamental therapeutic discovery: **the effectiveness of a treatment is determined by the confidence the patient and the doctor have in it.**

In 1958, in the Dictionary of Technical terms in medicine, a new definition is disseminated: *the placebo effect will be attributed to any inert substance which has a psychophysiological effect on the subject leading to their healing.*

There are several questions about this placebo effect which have acquired importance in modern medicine. The most important lever in my opinion is Evidence Based Medicine (EBM). This is about influencing prescribing using studies, more and more precise and powerful, individual studies or meta-analyses. This requirement has led to a proliferation of studies and to the promotion of a medicine practised according to the proofs provided by clinical experiments. We therefore have an obligation to treat our patients by following recommendations with a sufficient level of proof of efficacy. This has distanced us from the Art of medicine, reduced to a compassionate relationship. In a study of a drug, the comparison of that drug to a placebo is indispensable and precedes the comparison to other drugs. But that simple comparison is rightly regarded as dubious and obliges one to perform double blind studies. The doctor doesn't know if he is prescribing the placebo or the drug under scrutiny, the verum, the patient doesn't know which he is taking. Hippocrates, who made the patient and the doctor partners against the disease, talked of '*fight and farce involving three people: the patient, the doctor and the disease.*' This is truly the case for the placebo effect : Is it comparable to a verum? Does it have an action of its own? Is it linked to the attitude of the doctor prescribing it? To the patient taking it? Probably to the two people in this setting of a medical relationship. Is the substance also inert? This effect of an inert substance has been known since antiquity (cf. Egyptian medicine) and very recently its effectiveness was compared and found to be identical to the effect of homeopathy. This effect is measurable; for the treatment of pain, it has been found to be effective in 30-40% cases and the same when treating asthma, eczema, duodenal ulceration...for all the illnesses said to be psychosomatic. Modern medicine, artificial intelligence or medicine practised without a doctor, computerised decision aids, can they make use of the placebo effect? How reliable are the 'data' which are going to accumulate millions of results based on premises open to discussion? Many questions and few answers, 'small islands of certainty in a world of uncertainty' (E. Morin).

Neurosciences and the placebo effect : a new adventure.

Concerning the questions asked, it was necessary to try and understand better what was involved in the placebo and its effect.

First distinction: the **nocebo effect**, the capacity to harm which has been observed administering both verum and placebo. So, it was observed that the response can vary by 30% depending on the mood or the negative attitude of the doctor : 'I am going to give you a small tablet, I hope that it won't give you any side effects'. The competent doctor, working in a hospital, recognised expert, for whose care people will travel many miles, will be much better at inducing a placebo effect, particularly if he is naturally optimistic. And depending on the patient, the response will vary with his trust in the doctor, his understanding of the treatment, his compliance with the prescription ('What if this medicine doesn't work? If I get stomach ache? If it makes me feel faint?'). An expectation that something won't work will reduce the therapeutic result and will create new symptoms allied to the administration of the drug.

'The response to a placebo depends more on factors relating to context than to the individual's predisposition' (Lasagna et al, 1980). These studies have shown the importance of context.

The context has been defined by numerous studies on the placebo effect :

- The size of the pill: the big ones have a greater effect
- The taste of the pill: the more bitter it is, the more effective
- The colour of the pill (studies done by industry)
 1. Blue and pale pink: anxiolytic
 2. Red: stimulant
 3. Maroon: laxative.....
- The way the drug is administered: the more technical the method, the more effective
- The cost of the medication: the more expensive it is, the better it is. Freud understood this well!

...and many observations which the expert clinician will have noticed but for which there is no proof.

If there is an answer, where will it come from? Knowledge of the functioning of the brain by functional MRI, by tomographic emission of positrons using the PET scanner, by imaging of cerebral connections will give some answers and also bring about many questions.

Pain was to serve as a basis for such research. J.D. Levine et al. published in 1978 'The mechanism of placebo analgesia' in the Lancet. This article took as a model toothache reduced by 39% with a placebo, the effect being blocked by the administration of naloxone (a powerful opiate antagonist). The conclusion was that the placebo effect is dependent on endorphins. Its effectiveness would therefore depend on the quality of the endogenous opioid system.

Numerous studies were to show that the brain, in the deep grey matter, but also in the brain stem, secretes endogenous opioids while the placebo effect is happening. The studies of Benedetti, very well known in the realm of the placebo, ('Potentiation of placebo analgesia by proglumide', in Lancet) showed that the system of transmitters which accompanies the placebo effect can be activated by blocking cholecystokinin.

It was shown in models of pain and in patients with Parkinson's that the placebo effect was linked to the secretion of dopamine in the corpus striatum. Dopamine and opioids are the agents which stimulate the emotional component of pain. Rangville, in Canada, obtained similar results with patients given a painful stimulus and put under hypnosis. We can extrapolate that all techniques which use relaxation and control of emotions will augment this placebo/opioid effect. Thus, it is an effect which we should use and which forms part of the therapeutic response.

The studies which explore *empathy* were also to specify the function of the brain and the placebo. Empathy is defined as the sharing of emotions with another, the experience of a distinction between self and other, the regulation of one's emotions. Imaging explores an immediate and automatic emotional empathy in every individual vis-à-vis the suffering of the other person. The studies of Decety (2010) and Benedetti (2015) would show that the therapeutic response is amplified by an attitude of empathy. It would lessen pain, the discomfort associated with it and the suffering which accompanies it.

There again, the miraculous healing of the leper relies on the placebo effect and Jesus' empathy for he who suffers.

In Mark 1, v 40-44:

*'A man with leprosy came to Jesus and begged him on his knees, 'If you are willing, you can make me clean.'
Filled with compassion, Jesus reached out his hand and touched the man. 'I am willing,' he said. 'Be clean!'
Immediately the leprosy left him and he was cured.*

Jesus sent him away at once with a strong warning: 'See that you don't tell this to anyone. But go, show yourself to the priest and offer the sacrifices that Moses commanded for your cleansing, as a testimony to them.'

Finally, from these different studies, we can say that the placebo effect is dependent on endorphins (pain) and on dopamine (coordination) in relation to the nucleus accumbens (the reward). Science teaches me very

little, but it rationalises, it specifies, it can give authority to the clinician, convince those who don't believe what they see and finally poses plenty of other questions without answers...

The placebo and the clinic

We use the placebo effect every day wherever we practise simply by the way we greet another, respond to their suffering and listen attentively; but, as in 'Le bourgeois gentilhomme' by Moliere, Monsieur Jourdain is successful without setting out to be so.

A recent study showed that the patient in Europe has less and less time to talk about their illness and their needs, just a few minutes before the doctor cuts them off and starts asking questions. The works of Sigmund Freud had shown well the quality of the relationship between the doctor and the patient: he used the words 'mechanism of transference.'

The placebo effect is directly linked to the quality of our relationship with the patient. It depends on the relationship we have with the sick person, not with the diseased organ. Through this relationship we make an alliance with the person and we make a contract with them to fight the illness or to avoid damage by it if it is a chronic disease. This contract cannot be broken by the doctor. Charly Cungi urges us to form this '*therapeutic alliance*' and to be therapists while being professional (our knowledge of medical science is indispensable), empathetic (sensitive to the suffering of another), warm (liking people) and authentic (speaking the language of truth). This last point seems to me to be essential. We have too often seen or heard carers using the placebo in a shocking way: 'I emptied the capsule, gave it to him and he calmed down: he wasn't really in pain ! Conclusion: it was all a big act!' The poor care-giver, challenging the suffering of another, blind to his therapeutic effectiveness, sullyng human relationship!

In truth, as Paul Tournier writes in his book 'Medicine of the person' citing Hippocrates, it is probably '*nature who heals, in other words the life-giving strength which God gives to mankind.*'

We are, with humility, only doctors who allow our patients to be 'always heard, often relieved, and sometimes healed' (Louis Pasteur). All possible weapons against their disease can be suggested to the patient, it is up to us to choose with them the most appropriate, without expecting miracles, but with the desire to correct errors in the life of the patient, the loss of meaning and purpose, which led them to come and meet us. A unique encounter between a doctor and another person!

We don't know all the effects of our prescriptions. The placebo covers with its veil of uncertainty our hazardous predictions. May they do good to those who put their trust in us!