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# Placebo: Its Action and Place in Health Research Today\* – Summary and Conclusions

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## 1. The Background

Placebo (Lit. I will be pleasing or acceptable) treatments have been part of medical history since before 1785. Then the word was defined in the 'New Medical Dictionary' to mean a 'common-place method or medicine', or as its more recognisable use in 1811 by Hooper as 'an epithet given to any medicine adapted more to please than benefit the patient'. These quotations from the Oxford English Dictionary were presented by R. Smoak<sup>1</sup> of the World Medical Association who went on to note the 1801 use by John Hargrave of 'Perkin's Tractors' which were metal rods that were supposed to cure people through electromagnetic effects.<sup>a</sup> But it was not until the 20th century that the placebo controlled trial came into its own with applications of assessing the actual value of Homeopathy, Diphtheria antitoxin and Cold vaccines. The use of such trials to evaluate the potency of drugs and vaccines was largely unregulated until the full horrors of the medical experiments effected in the Nazi concentration camps were disclosed. Following the Nuremberg Code of 19 August 1947,<sup>b</sup> which sought to guide the way experiments may be conducted with humans, the World Medical Association issued the 'Declaration of Helsinki' in June 1964 that became a key event in the development of a suite of generally accepted guidelines for the conduct of medical experiments with humans.<sup>c</sup> The latest, 2000 Edinburgh version of this Declaration, is the one which seeks to define when and how placebo trials might be conducted.

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a. An eclectic array of such techniques and equipment (pictured) can be found at: <http://www.collectmedicalantiques.com>.

b. See <http://ohsr.od.nih.gov/nuremberg.php3> for the Nuremberg Code.

c. See [http://www.mja.com.au/public/issues/172\\_06\\_200300/loff/loff.html#refbody](http://www.mja.com.au/public/issues/172_06_200300/loff/loff.html#refbody) for a discussion of the Declaration of Helsinki.

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\* An International Conference held in Warsaw, April 12-13, 2003, entitled 'Placebo: Its Action and Place in Health Research Today' was attended by some 200 individuals who heard 25 presentations delivered by participants from the wider Europe and North America.

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We were then introduced to the work effected by the Council for International Organizations of Medical Sciences (CIOMS) by Juhana Idänpään-Heikkilä<sup>2</sup> who noted a 2002 publication, 'International Ethical Guidelines for Biomedical Research involving Human Subjects', that considers in full the position of the patient and the ethical aspects of using placebos. These, it asserts, should be used only when the science is sound, if no proven beneficial intervention exists, if harm is unlikely and the people involved are consenting volunteers. The issue of patient's rights was also taken up by Pēteris Zilgalvis<sup>3</sup> of the Council of Europe who noted that this was an active discussion in the Council and that a new Draft Directive Convention on Biomedical Research was to be released in 2004.

Setting these approaches to guidelines for the conduct of clinical trials in another context, Rainer Gerold<sup>4</sup> of the European Commission, explained that however a placebo trial was construed it had to comply with existing rules, be mindful of the special circumstances that pertain in Developing or Poor Countries, particularly with regard to the exploitation of patents, the manifestation of the benefits and the possible development of double standards of ethics. Also, European bodies such as the European Agency for the Evaluation of Medicinal Products (EMEA) has a wealth of information and is active in pursuing the ethical aspects of the testing and use of medicines.

## **2. Some Issues**

### **2.1 The nature of a placebo**

We were invited to consider the deeper, more philosophical, meanings of the words that we were using by Z. Szawarski.<sup>5</sup> Indeed, the concept of the placebo itself proved quite elusive. Were a new material introduced into a trial, then this may of itself produce an effect. One might regard the introduced material 'inert' with regard to any known mechanism that might ameliorate the disease state, but the introduction of a bitter, unpleasant or bad egg type of taste might radically affect the person so assailed. Again, this author introduced the notion that at very low levels of 'active ingredient' as, for example, part of a 'dose – response' experiment, one might have the equivalent of a placebo that was defined only by the absence of an 'effective' amount of the material under examination. This kind of placebo was challenged as some participants thought that it was possible that however small an amount of test material was available, all the effect observed could have been due to that small amount of material. This is an argument 'in extremis'.

As 'science' is about testing current 'best guesses' to determine how much confidence we might have in them, or their changed variants as required by the testing or experimental observations, it would seem that the most effective way of acquiring confidence in the impact of a drug on a disease state would be via an experiment which was set up to demonstrate the way the ameliorative effect was dependent on the amount of material applied to the affected person. Clearly, if a beneficial effect was observed that was independent of dose level then that effect may be thought of as a non-specific effect akin to a placebo effect. It could be that the effect varied both positively or negatively with dose level, in which case conclusions may be drawn as to the putative

medicament's use level or complete non-use. It is often the case that an effect of concentration is not observed until a particular threshold level of application has been crossed. Any ameliorative effect before the concentration dependent effect is observed may again be considered to be a placebo effect. It should also be noted that this way of testing is independent of other drugs of 'proven' efficacy. It also does not require the introduction of any new material whose effects may be difficult to control: the lowest concentration of the substance under investigation could be present at vanishingly low concentrations – or not be present at all as noted by E.A. Singer.<sup>6</sup>

## **2.2 Different scenarios where a placebo could be used**

It also emerged from the conference that we have to define clearly the different situations that could call for a placebo control to determine whether or not the material under question was an 'active' principle by virtue of its unique properties. Here we should distinguish between the examination of a drug or vaccine that is novel, unique and has not any equivalent and the same kind of material that is equivalent to other materials that have already been shown to have effects in the specific area in question. Where the material under test is completely novel the testing of such a material may involve the use of the placebo or zero concentration control except in cases where the patients in the control group are likely to be permanently damaged. Clearly, if it is not known whether or not any efficacy of the new material is likely, then the experimental group is just as likely as the control group to suffer irreversible harm. In this latter case there is a justification of the placebo control even though damage is thought to be likely. Nevertheless, it is hardly likely that a manufacturer would venture forward with a substance that was thought to be as likely to produce harm as benefit. Previous tests in animals would have had to have demonstrated some beneficial properties before a test in humans could be justified to an ethical review board. Under such conditions it would behove the manufacturer to be more concerned about the maximising of the efficacious effects by a determination of the most beneficial methods of delivery of the new material. Here, the way the drug or vaccine is delivered, the organs that receive the material, the number and timing of doses applied and their quantity of material delivered are key variables that need to be determined for every new application. Having discovered the most advantageous routes, times and methods of delivery, it would remain to discover the amount of material that needs to be delivered to achieve the maximised beneficial effects. The determination of a dose-response relationship is the way this can be achieved.

The second case devolves around the situation when a new product is generated that is held to be superior to a product that is already extant. The superiority may be in the increased degree of efficacy obtained, the achievement of the same ameliorative effect at a lower cost in either monetary terms or in terms of a decrease in unpleasant or unwanted side-effects. Here it is clear that the new challenger material should be tested in a face-to-face manner in the same test against the existing medicament. The use of a placebo control is not necessary as it has (presumably) been shown that the original material under challenge was efficacious in relation to a placebo or zero concentration control in previous trials.

A third case arises from the emergence of a drug or vaccine from patent protection. Here it is necessary for a 'Generics' manufacturer to make a product that is equivalent to that which was heretofore produced under patent protection. Tests of such Generics therefore are based on showing that they are neither significantly more or less efficacious nor do they have side effects that differ materially from that of the previously patent protected material. In these experiments it is not necessary to use a placebo control.

### **2.3 Developing country issues with placebos**

Clinical trials in developing countries cost less than those in developed countries. It may also be that the level of natural challenge in a developing country is many times more powerful than that which obtains in a developed country. Additionally, we have to consider whether the drug or vaccine under examination is relevant to the disease state of the particular developing country in which the trial is sited. If it is not relevant then the ethics of exploitation of a group of people less fortunate than those in the developed country has to be considered. They will have accepted the risk of side reactions and toxic effects in exchange for money. Ethically, there is nothing inherently unacceptable in this situation. A casuistic approach will tell us that in normal employment in the developing world in the nuclear, construction, fishing and agricultural industries there is an ever present danger of injury or death which is accepted in exchange for the going wage rate. The only additional question that is raised with regard to the developing world is the actual magnitude of the reward for the risk undertaken. As there are relatively few cash jobs in the developing world and much unemployment, the temptation to exploit this situation would be considerable. However, to drop below wage levels for jobs of comparable risk in the same circumstances would be unacceptable.

There are situations in which the drug or vaccine tested is relevant to the disease conditions in the developing country. Here the company conducting the tests is under some obligation to continue to provide the drug or vaccine if it has been shown to be efficacious. But to whom? the people involved in the trial, their families, their tribes, their region or nation state? While it is clear that some sort of preferential pricing may be readily introduced the levels set and the region of application have still to be determined. Were the ethical committees reviewing such applications to think about the communities exposed to the risks of new drugs or vaccines, then they might want to recommend that experiments be confined to defined pockets of people enabling a clear preferential treatment after the efficacy trial had been concluded.

From a utilitarian perspective, the cost to benefit ratio of taking risks in a developing country is different from that in a developed country. In a country in which HIV/AIDS infects some 30% of the 20-40 year old age group (Zambia), people are prepared to take higher risks in tests of a putative drug or vaccine than in the USA (circa 0.4% infection rate) as any beneficial effects have disproportionately large consequences. This could mean that placebo controlled tests of a putative drug/vaccine that could cure/prevent AIDS would be more readily acceptable in a developing country. There are many complicating issues that relate to testing AIDS reagents in any country. Issues of informed consent, the education of the people who enter the trial in

the advantages of safe sex and the deliberate deprivation of those who do not get into the trial of the same information come into play. A further complication is that those on the trial may believe that they are the ‘protected ones’ and engage in more unsafe sex. Were some such individuals to be in the placebo group then there would be a higher infection rate, and therefore death rate, amongst them as compared to others who had not been party to the trial. Although AIDS may seem an extreme case, similar life and death situations exist for the diseases of Malaria, Tuberculosis and intestinal and respiratory infections.

Yet were the tests to be effected in the more stricken country and the benefits accrued in the less affected country a clear injustice would have been effected. So, some of the rewards for having been exposed to higher risk should stay with those who have put themselves at such a risk. Again difficult decisions need to be made about the extent to which such rewards have to be given, but it would be inexcusable and grossly unfair were both financial profits and health care gains to be made in the developed country that produced the drug/vaccine while the country in which the hazards of the tests were incurred was left to fend for itself.

## **2.4 Placebos and Informed Consent**

It is a widely experienced phenomenon that people who once were ready to engage in a trial, when informed that they could be treated with a non-active placebo, leave the trial and seek a situation in which their condition could receive a putatively active material as noted by Jan Joerden.<sup>7</sup> It is however possible that for the acquisition of the informed consent, the details of what drugs/placebos are to be delivered may be described under a less than detailed protocol. The term placebo may be omitted as this would be sure to bias the results. Nonetheless it is clear that patients entering trial conditions should be ‘fully informed’ of what is to happen to them. This in itself exerts an effect on the way the trial proceeds. As other speakers pointed out, it is not only the materials that are given directly to the test subject that have effects it is the ambience of their delivery.<sup>8,9</sup>

While the system has to respect the ‘autonomy’, ‘self-determination’, ‘motivation by rational choices’ (Kant) and rights of the individual, the patient also has obligations to be honest, to meet commitments for appointments, permit treatments and to observe the duties and obligations of a contractee to a relationship. These requirements have been incorporated into Polish Law via the rules and regulations for implementing Informed Consent Procedures as noted in the presentation by P. Zaborowski and A. Górski.<sup>10</sup>

### **2.4.1 Ethical issues in trials of Homeopathic preparations**

A homeopathic preparation may contain a dilution of a plant extract at such a concentration that there is a probability that there is less than one molecule of the original extract in the material that is ingested or injected. In a placebo controlled trial of such a material what and how the doctor tells the patient about the course of treatment that is to be undertaken is therefore crucial to the outcome of the trial. So how is the ‘autonomy’ of the patient to be respected? If the patient is told what the doctor really thinks – that both the placebo and the test material do not contain ingredients that the medical profession believes to have any physiological or

biochemical activity – then the value of the exercise to the patient is impugned. If the doctor lies and says that he or she is testing both a putatively active material in contrast to a putatively inactive control then the doctor is in default of his or her ethical code. The crux of this issue lies in the probability that the doctor's lie could well be therapeutic and relieve suffering. It may be accepted that the overriding consideration is that it is the principle duty of the doctor to enhance the patient's well-being. In which case the ethical deficit of a lie may prove to be justified: and after all, if there is relief from troublesome symptoms the doctor may indeed not have lied for one of the unknowns in the test is whether or not there is activity associated with the materials on trial. However, the alternative hypothesis cannot be denied in that it is the visit to the doctor and the aura of the doctor-patient interaction which was the curative stimulus merely aided and abetted by the additional, yet evocative, actions of the ingestion or injection of what could easily be coloured sterile water.

In addition to the placebo controlled testing of the efficacy of the homeopathic preparation, the preparation itself may be used as an alternative to the placebo in cases of emotional disorder where it may be shown to be of therapeutic value.<sup>11</sup>

## **2.5 Placebos to be used in particular kinds of trials**

We can identify various disease (not-at-ease) state conditions that call for prevention or amelioration. Broken bones, burns, ruptured organs or blood vessels, cuts, bombshell, mine and firearm wounds, are generally unique to the individual and event and efforts to cure and treat them are not generally tested via placebo controls. Another suite of diseases are caused by infection. The two major approaches to dealing with these diseases are via prevention (vaccines) or cure (antibiotics). Vaccines that seek to protect against non-life-threatening diseases (colds due to Rhinoviruses; Coronaviruses and Adenoviruses, German Measles, Chickenpox, etc...) may well be tested using placebo controls or dummy vaccines. Other vaccines directed towards preventable diseases that would otherwise be life-threatening, such as Measles, Hepatitis B, Hepatitis A, Smallpox, Polio may or may not, as the conditions dictate, be tested using placebo controls. This often depends on the chosen end-point for the trial. Were the end-point the level of specific antibody then a placebo control could be indicated; however where the end-point was the presence or absence of disease after a defined exposure period then it could be judged unwise to expose placebo treated individuals to a life-threatening situation without protection. Generally speaking, for diseases caused by viruses recourse to medicaments is futile (except perhaps for the Acyclovir treatment of Herpes infection).

There are a number of diseases that seem to be caused by endogenous bacteria and viruses that emerge when particular states of the immune system prevail. Examples are: Herpes Simplex Virus, *Helicobacter pylori*, Papilloma virus, viruses that may be implicated in Breast Cancer, Arthritis, Myocardial Infarction and other indications. As some aspects of the functioning of the immune system seem to be under mental control (hence the new subject area 'Psychoneuroimmunology') it would be expected that placebo controlled trials of new vaccines would be in order.

Antibiotics are used to cure infections by bacteria and on occasion, fungi or nematodes. Generally it can be shown that the antibiotic is active against the infecting

agent *in vitro*. This enables the appropriate antibiotic to be chosen before general application to the diseased individual. Testing new antibiotics in placebo controlled trials may be advantageous when the disease in question is not life-threatening. However, when this is not the case and there is a real chance that irreversible harm may be done then a trial that involves a placebo would not be permitted. The efficacy, or otherwise, of the putative antibiotic would have to be ascertained in a dose-response trial. This may not give as sharp a difference from zero concentration, but added statistical power is obtainable from an expected relationship between the efficacy of the different concentrations/amounts applied.

A third category of disease state is that predicated on an ailment of the mind. Here a wide variety of diseases exist some of which are: Depression (Selective Serotonin Reuptake Inhibitors [SSRI]), Hypertension, Myocardial Infarction, Attention Deficit Hyperactivity Disorder, Schizophrenia, Headache (Migraine), Asthma, Eczema, Psoriasis, Parkinson's Disease, Seasonal Allergic Rhinitis, Gastroesophageal Reflux as well as diseases that may on occasion have a psychosomatic origin such as arthritis, diabetes, rheumatism, stomach ulcer, some cancers at particular levels of progression. Such diseases are open to being affected to a considerable extent by the suggestion that an improvement in the condition of the patient is expected by the doctor as a result of the patients' participation in a particular trial (particularly if the patient is not told that the trial is to be controlled by a placebo dose). The effects of such 'mental conditioning' could be from 30-80% of the effects of that of the material on trial.<sup>6,9,12,13,14,15</sup>

### **3. How the Placebo might work**

There is increasing evidence that the liberation of simple chemicals in the brain can cause changes in mood and levels of excitement. Dopamine, endorphins, serotonin, glutamate, opiates and other small molecules are implicated in such effects as noted by R. del la Fuente-Fernandez.<sup>16</sup> As more experiments are effected that seek to relate the secretion of these chemicals with changes in the brain as evidenced by functional-Magnetic Resonance Imaging (fMRI) or various tomographic techniques such as Positron Emission Tomography (PET),<sup>d</sup> it is becoming increasingly obvious that the above chemicals are implicated in such reactions as reward systems, expectation requirements, love, processes leading to reproduction, pleasure, depression and the fight or flight reactions. What happens between the doctor and the patient affects the excretion of these chemical messengers in the brain with consequent effects on the hormonal or immunological competence of the affected individual. The use of placebo materials to achieve similar effects therefore is precedented. When a patient believes that he or she is being treated by a respected doctor then it is likely that the small molecule balance will shift with effects that may or may not reduce the patients disease symptoms. What needs to be done is to better define the stimulus and the stimulus-response relationship between what the patient actually experiences and the way such experiences affect the small molecule balance and distribution in the brain.

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d. <http://www.bae.ncsu.edu/bae/courses/bae590f/1995/mullen/index.html>

#### 4. The Power of the Placebo

The papers presented at this conference provide powerful evidence that the administration of a placebo can be as efficacious as the provision of a putatively active medicament. Not only may amelioration of a painful condition be achieved but some such treatments may actually cause a distressing condition, in these cases A. Barsky calls the agent a ‘nocebo’<sup>9</sup> (I will cause hurt or harm). It should also be noted that there is a suite of syndromes that are particularly prone to be evoked by materials that have no known pharmacological action: headache, stomach pains, skin conditions, breathing disorders/asthma, dyspnoea, tachycardia, depression, Parkinson’s syndrome, hypertension, attention deficit hyperactivity disorder, fatigue, drowsiness, dizziness, nausea, jaw pain, rheumatoid conditions and sweating.

Insofar as this mental influence can obtrude into the way the body works, so also might placebo/nocebo type situations have some degree of effect. What becomes increasingly clear is that the power that the mind has over bodily functions is only just beginning to be explored. What we believe, and what the quality of those beliefs state is a parameter we cannot continue to ignore if we are to think in terms of preventive health care or the remediation of disease states. The next step in this progression is to learn more about the way we acquire beliefs and the factors that influence the quality of the belief as it exerts its effects in controlling via such organs as the hypothalamus the workings of the hormonal and immune systems. At this symposium F. Porzolt noted that the effect of such interventions as surgery was dependent on the way the doctor presents the case for such treatment to the patient; he called this ‘knowledge framing (Zelendesign)’<sup>8</sup>.

However we look at it, there is the potential of a revolution in the way health care is delivered to those in need of release from disease. How far these techniques will extend into the controlling of human minds in the more general interests of society remains to be seen. But these glimmerings of the possible uses to which the control of belief systems can be directed has to be a warning to ethicists who must now consider the creation of the kind of regulatory environment in which such abilities are more likely to adduce benefit than result in harm.

#### 5. Conclusion

The material presented at this conference pointed to a new dimension in the prosecution of activities that seek to relieve people of disease. While the simple instrument of the placebo may show those interested in the efficacy of physiologically active chemicals the extent to which the chemical of interest is actually active, the surprising outcome of such studies is that the placebo *per se* is worthy of more general study. This, when taken further, points to the ways in which mind can influence the matter of the body. Of course, mind itself is an activity of matter, so we may retain the experimental approach that has told us about the world outside ourselves to examine the world that is inside our brains. New techniques and approaches to these once intractable problems are now in train. Where they will lead us we cannot predict, but as with the emergence of all new tools, we have to adopt those ethics that will carry us forward with the expectation that we will maximise benefits and minimise harms.



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