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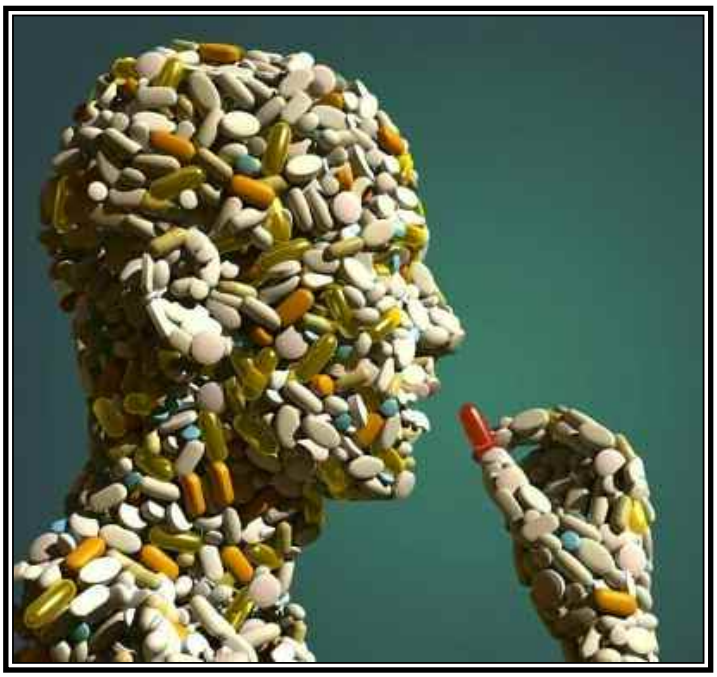

THE PLACEBO EFFECT

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EDITORIAL

THE PERPLEXITY OF THE UNSEEN

The body is a device to calculate the astronomy of the spirit.
Look through that astrolabe and become oceanic.
RUMI, *Mathnawi*.

DO NOT BE SURPRISED BY a pale aesthetical glance, beauty is still one of the best veils to look throughout this world. Beauty encompasses all, all and everything, like Truth and Goodness. Once freed from time we wander to the accomplished deed immune to all illness. Having accomplished its mortal function, the physical body returns to its forming elementals whilst the soul progresses to its further mansion, the house of *misericordiæ* endowed with prophethood. Indeed, there is no 'time' if there is no 'be', and surely there is no 'die' if there is no Thee.

Taxi downtown to uncover what really matters: there are more invisible things than visible ones. It is not what we see, that is of importance, but what we do not see that is the real substance. There is only one possible equation valid for all planes of the being, where each particle is shaped by the sublime fashioner of the wor[l]d, an exquisite sense of the phrase, a lace vaulting in a vacuum.

→| IN THIS ISSUE

Come, do not stop at the gate: Life and Death, the two guardian angels, will transmute into the Guardians of the Threshold, and let you in. There lies Beauty, Truth, and Goodness, the attributes of Love, and the primeval promoter of life who subtly affects the whole being. I will be grateful if you could spread the good news: "Come Death, I'm waiting for your call." Realistic models should be integrated in the vision, they are needed as long as we partake of this dimension. What needs to be reviewed after all? The inexplicable that not even the finest degree of angels could disclose to itself? Be my guest, I request you to step in: therein no abyss from where to surface, indeed nothing is there, neither time nor space, nothing, Nothing at All. Still the dualistic vision is creeping in this momentary dimension in which we all live. Placebo.

Ut placet in mente dei? An apophatic utterance uncovers the world: get rid of all fears and statements of joy. No ground around, no glamour, breathe deeply and plunge into the Unknown: "Hallo, who are you?" You or me?!? Definitely a day to celebrate and rejoice, *hallelu-yah* – a dynamic shared field of awakened awareness in the higher collective consciousness is at play.

Once the top-down stream of consciousness has been granted, the *U* conversion of the energy occurs and all blessings are gathered into the humane dimension. A new chapter is being chiselled into the soul: long seated marks are eradicated in a purification process to get rid of all rights – only the physical death will temporarily procrastinate freedom. The human soul is bound to transit through the realm of quantity to progress further; it needs to experience its 'physical' body as an essential step to reach up anew – only because we dwell on the relative realm of time and space this process is perceived as bottom-up. A conversion of energies akin to the one taking place at puberty or conversely at old age, when the life energy inverts its polarity, changes direction – the superabundance of a force inevitably produces its opposite. On a different level, this parallels the principle of equilibrium in the natural world in which any extreme is opposed by the system to restore balance. "Cold things warm, warm things cool, wet things dry and parched things get wet," enantiodromia, an old acquaintance of mine used to say. The ensuing plans of the being are plainly passages from one stage to the next, at times ignited by rites in the human endeavour. In consciousness *(cit)*, it is a shift, a leap into a new state. In Reality, in absence of time, the past, the present and the future are condensed into the 'now', that means that the shift already happened, is taking place and will occur, altogether at the same time, its awareness depending from which state of our individual consciousness we are witnessing it. Placebo. Here is not the unrestrained surge of the unconsciousness into consciousness at work, as the villain maintains, rather their simultaneously merging into oneness. To contemporarily perceive the two fluxes is certainly vital, but being aware of the action while displaying the 'activity' without interfering in the process is definitely a step ahead. When the performance of an action is one with its intention *(imma)*, if there is no meaningful *iatus* or temporal diastema between intention and execution, that action is effortlessly attuned with the flow of the *dharma*, is one with it. In the occasion, even the freewill vanishes, as it is one and the same with the cosmic will. The intention is a focused attitude toward a well defined goal, a pro-tension to its realization by virtue of its own entelechy to advance further and overcome all limits; in other terms, the perennial drive of life pro-tensed towards its fulfilment. The kernel is that the two energies and their actions – anode and cathode, or *ruh-illofi* and *ruh al-kuds* or whatever other combination of opposites it may be – are really simultaneous, and actually the same; if observed through the binary manner to perceive the world of the thinking mind, they appear to be two, for duality houses in time, but in the dimensionless gathering place of the soul they are one, just one.

In the midst of all this, by sightseeing randomly in the groove of the path, we gladly report of a few landmarks along its landscape, certainly not of the inexplicable goal. We all are mixed blood, we are all bastards, it depends from which stance we are looking at ourselves. To the body, it may look like health, to the spirit, as spiritual health, in between, as a spiritual-material wealth. Placebo: something pleases and soothes the wounds and recovers them to their original state. The way in which the synapses communicate in our brain counterparts our social networking. This parallelism of planes may be applied to the whole of the manifestation, as all entities are connected through their dimensionless centre by the *axis mundi* crossing in every possible direction. Devoid of time and space, no direction is at bay, everything happens contemporary in the present, every and nowhere. The thinking mind is unable to grasp this hierophany, this *darshan*, unless it affords to be one with its own working process and lifts its hold on it, only then intuition

emerges as an insight in the heightened consciousness. Seen from the realm of quantity, intuition looks faster and finer than thought: the manipulator of matter. Placebo.

Harmony is a palintropos in a reflexive tension, like the bow and the lyre. To be in a reflexive tension, to be self-reflexive is to be re-flexed in oneself. The entire matter lies on the capacity to be utterly empty, aloof from the whole lot, yet gladly allow the energy to flow by its own course, according to its own pace, synchronic to the rhythm of the body: the inner and outer are here focused in a spiritual-material alliance. Certainly consciousness is not made up of matter, it is much finer, deeper and higher than matter, is an assembly of relations in a reflexive tension. Indeed, what really matters in all human affairs are the quality of the relations, not its su[o]bjects *(persona)*, for, the former – being immaterial – will last; while the latter will perish. Yesterday I would have liked to give you a rose, not solely a rose but a flowering rose in your pose, in your improbable chest. But you were not present, emptiness around, not even the bristle of a leaf, or the cry of an angel, nor the glance of your eyes I once thought blue. The whole universe couldn't compete with that hue: a triumph could not have been better, certainly no better than you. How long should I stand at your dazzling face before joining with you? Placebo. Pinocchio identified himself with his dream and became human. Who for God's 'shake' (quiver, *spanda*) would prefer a placebo instead of a real shot? "The spiritual life is knowledge in the time of trial": a charming thought in actual fact, which certainly needs a skilled cryptographer to endorse it as a whole. Nothing can exist without movement, yet the ultimate movement takes place in consciousness where time has no grip: an endless cycle of expansion and contraction, of internalization and externalization of consciousness itself, relating to the most elevated plane *(citananda)* of the manifestation.

At times it appears as the direction is nowhere to be found: no longer faiths nor religions to cling to, no more containers of a long lost content, just the reality that inspires and sustains them is here. No sound came out of their tongues but their hassle to slaughter each other: fundamentalist to their roots, who lost connection with the original life. Be assured, everything passes and changes, they too soon will be gone. Let's swing the ladder to the encounter of the two seas. Prospero or Papageno? Even though these bastards deserve a diamond as crown, for now I can only offer them a leaded basin and a blade of red iron lore – transmute… transmute… Thought and self-awareness are the two parts of the same unfolding process of doing, the non-discursive state of consciousness can hardly, if ever, be conveyed into words. A good intention is not enough; action must follow. Placebo.

Theory, poiesis, praxis… *theà horào*, yes, we all saw the goddess, but global thought and local action are now needed, at least in ourselves to start with. Where has it gone that ability to keep together and jointly strive for a clear direction? Where has Politics vanished? Still busy with old credentials, with models, concepts and visions of old, from ten to one, and then bottom up. A thousand of existence ago 'ten' was deprived of its wholeness and became 'one'. If 1 is equal to 0, if uniqueness in wholeness is attained, if one is the whole, then the tensorial membrane between the two worlds within consciousness self-shapes itself according to its own inborn input, and the world is informed by matter. To transmute into its further stage, the soul links spirit to matter into a whole.

The whole manifestation is nothing but how we perceive our own projection on it, the projection of our particular 'self' in its reflexive mode. A paradox, a *koan*, no doubt, contrary to any opinion and beyond any reasonable doubt. Indeed the paradox has always been a powerful device to explore the reality: by unveiling it, the opposites are reconciled: inside and outside become paler and all boundaries are loosened and lost. The 'apparent' movement between the two polarities makes consciousness spark and it gives rise to the whole. An *itinerarium animi* in which an inclusive reform of the I, and of the ability of the soul to manifest the reality is most in demand. The middle world between spirit and matter, the *mundus imaginalis*, links *ta physica* to *ta meta*, in its 'imaginal' geography – not a *phantasys* – the tensorial membrane – and the soul – receives the 'impressions' of the spiritual world and reverberates them into the world of matter as mundane outcome – let us not forget that to show is not to perform.

Not a novel vision for sure, but one former to the dissection of spirit and matter in time, a compound which still grants to placebo its effect, that, according to the followers of the divided reality, shouldn't indeed be there. Spear me to detail further, we could disperse a few. Enjoy the issue. ▣

We live our lives, for ever taking leave.

RAINER MARIA RILKE, *Duineser Elegien.*

THE MANY PLACEBO EFFECTS

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→I OVERVIEW

"The miserable have no other medicine but only hope."

WILLIAM SHAKESPEARE

INTRODUCTION

A PLACEBO EFFECT IS A psychobiological phenomenon occurring in the patient's brain following the administration of an inert substance, or of a sham physical treatment such as sham surgery, along with verbal suggestions (or any other cue) of clinical benefit (Price *et al*, 2008). Therefore, the effect that follows the administration of a placebo cannot be attributable to the inert substance alone, for saline solutions or sugar pills will never acquire therapeutic properties. Instead, the effect is due to the psychosocial context that surrounds the inert substance and the patient. We now know that there is not a single placebo effect, but many, with different mechanisms and in different diseases, systems, and therapeutic interventions (Benedetti, 2008b; Enck *et al*, 2008). In other words, different processes may be at work in the patient's brain in different conditions. Sometimes it is anxiety that is modulated, at some other times reward mechanisms are involved, and in some other circumstances different types of learning, or even genetic variants, may take place in placebo responsiveness. In this sense, the placebo effect is a melting pot of neuroscientific concepts and ideas, ranging from anxiety and reward mechanisms to Pavlovian conditioning and social learning, and from neurogenetics and neurophysiology to clinical practice and neuroethics. The terms placebo effect and placebo response are often used as synonymous, thus both terms will be used here.

EXPECTATIONS

Most of the research on placebos has focused on expectations as the main factor involved in placebo responsiveness. In general, expectation is aimed at preparing the body to anticipate an event in order to better cope with it, and as such offers a clear evolutionary advantage (Kirsch, 1999). There are several mechanisms through which expectation of a future event may affect different physiological functions. For example, the expectation of a negative outcome is aimed at anticipating a possible threat, thus increasing anxiety, whereas the expectation of a forthcoming positive outcome may reduce anxiety and/or activate the neuronal networks of reward mechanisms (Price *et al*, 2008).

Indeed, anxiety has been found to be reduced after placebo administration in some studies. If one expects a distressing symptom to subside shortly, anxiety tends to decrease. In brain imaging studies reduced activation of anxiety-related areas during a placebo response can be observed (Petrovic *et al,* 2005). The best evidence that anxiety takes part in placebo responses is shown by the nocebo effect, which is opposite to the placebo effect (Benedetti *et al,* 2007). In order to induce a nocebo effect, an inert substance is administered along with negative verbal suggestions of clinical worsening, e.g. pain increase. Overall, expectations of a negative outcome, such as pain increase, may result in the amplification of pain, and several brain regions, like the anterior cingulate cortex, the prefrontal cortex, the insula, and the hippocampus have been found to be activated during the anticipation of pain in a variety of studies. Nocebo hyperalgesia has been studied in some detail also from a pharmacological perspective, in order to identify possible neurotransmitters that are involved in anxiety-induced pain increase. By using an anxiogenic nocebo procedure, it was shown that cholecystokinin (CCK)

plays a crucial role. In fact, the pharmacological blockade of CCK receptors prevents the occurrence of nocebo responses.

Not only can expectations of future events modulate anxiety, but they may also induce physiological changes through reward mechanisms. These mechanisms are mediated by specific neuronal circuits linking cognitive, emotional, and motor responses, and are traditionally studied in the context of the pursuit of natural (e.g., food), monetary, and drug rewards. There is compelling experimental evidence that the mesolimbic dopaminergic system, the main reward network, may be activated in some circumstances when a subject expects clinical improvement after placebo administration. This was observed in Parkinson's disease (de la Fuente-Fernandez *et al* 2001), depression (Mayberg *et al* 2002) and pain (Scott *et al* 2007). In the case of the placebo response, the reward can be conceptualized as the clinical improvement.

Several neuropharmacological and neuroimaging studies investigated neither anxiety nor reward mechanisms, making it impossible to state specifically whether the observed placebo responses were attributable to a reduction in anxiety or to the activation of the reward circuitry. In all probability, here too anxiety and/or reward mechanisms play a role, depending on the experimental condition. In any case, these studies have provided evidence that a complex neural network is involved during the placebo analgesic and the nocebo hyperalgesic responses (for a detailed review, see Zubieta and Stohler 2009; Tracey 2010).

LEARNING

Learning is another mechanism that is central to placebo responsiveness. Subjects who suffer from a painful condition, such as headache, and who regularly consume aspirin, can associate the shape, color and taste of the pill to pain decrease. After repeated associations, if they are given a sugar pill resembling aspirin, they will experience pain decrease. Not only can shape, color and taste of pills be associated to clinical improvement, but countless other stimuli as well, such as hospitals, diagnostic and therapeutic equipments, and medical personnel features. The mechanism that underlies this effect is conditioning, whereby a conditioned (neutral) stimulus, e.g. the color and shape of a pill, can become effective in inducing the reduction of a symptom if repeatedly associated to an unconditioned stimulus, i.e. the active principle contained in the pill.

Conditioned immune responses can be obtained both in animals and in humans. For example, Goebel *et al* (2002) showed that behavioral conditioning of immunosuppression is possible in humans. Repeated associations between cyclosporine A and a flavored drink induced conditioned immunosuppression in healthy male volunteers, in which the flavored drink alone produced a suppression of the immune functions. In the endocrine system, similar effects can be found. The hypoglycemic effects of insulin can be conditioned by pairing insulin with a conditioned stimulus in animals and in humans, and several other hormones, such as the growth hormone and cortisol, can be conditioned as well (Benedetti, 2008a, 2008b).

More complex forms of learning can be involved in placebo responsiveness, whereby different cognitive factors play a crucial role. For example, social learning is a form of learning, whereby individuals in a society learn from one another by observation and imitation. Placebo effects may involve social learning as well. In other words, the mere observation of others responding to analgesics may lead to robust placebo analgesic responses (Colloca and Benedetti 2009).

GENETICS

A central issue in placebo research is whether an individual in whom a placebo works possesses one or more specific characteristics, which can reliably identify him *a priori* as a "placebo responder", with important implications for both clinical trials design and personalized therapy optimization. Results have so far been rather inconclusive, with demographic, psychosocial, personality, and behavioral variables all proposed to play a role, but all inconsistently present across different trials. Recently, however, some genetic variants have been found that are particularly responsive to placebo treatment. For example, there is some experimental evidence that some genetic variants affect placebo responses in psychiatric disorders, such as social anxiety (Furmark *et al,* 2008) and depression (Leuchter *et al,* 2009). In social anxiety, it was found that the reduced stress-related activity in the amygdala which accompanied the placebo response could be observed only in subjects who were homozygous for the long allele of the 5-HTTLPR or the G variant of the TPH2 G-703T polymorphism, but not in carriers of short or T alleles. In depression, subjects with monoamine oxidase A G/T polymorphisms (rs6323) coding for the highest activity form of the enzyme (G or G/G) had a significantly lower magnitude of placebo response than those with other genotypes.

NO PREFRONTAL CONTROL, NO PLACEBO RESPONSE

Benedetti *et al* (2006) studied Alzheimer patients at the initial stage of the disease and after one year, in order to see whether the placebo component of the therapy (an ever-present part of the drug effect which makes the overall outcome greater than that produced purely by the intrinsic principle) was affected by the disease. The placebo component of the analgesic therapy was correlated with both cognitive status, as assessed by means of the Frontal Assessment Battery (FAB) test, and functional connectivity among different brain regions, as assessed by means of electroencephalographic connectivity analysis. It was found that Alzheimer's patients with reduced FAB scores showed reduced placebo component of an analgesic treatment. In addition, the disruption of the placebo component occurred just when reduced connectivity of the prefrontal lobes with the rest of the brain was present. The loss of these placebo-related mechanisms reduced the overall effectiveness of the treatment, and indeed a dose increase was necessary to make up for this loss in order to produce adequate analgesia.

According to this view, the impairment of prefrontal connectivity would reduce the communication between the prefrontal lobes and the rest of the brain, so that no placebo and expectation mechanisms would be triggered. In recent years this notion has been supported by the deactivation of the prefrontal cortex in the experimental setting. On the basis of previous experiments on the blockade of placebo analgesia by the opioid antagonist naloxone, Eippert *et al* (2009) conducted a study to investigate the location of naloxone action in the brain. By combining naloxone administration with functional magnetic resonance imaging (fMRI), these authors found that naloxone reduced placebo effects as well as placebo-induced responses in the dorsolateral prefrontal cortex and the rostral anterior cingulate cortex. Therefore, as it occurs for prefrontal degeneration in Alzheimer's disease, placebo analgesic responses are disrupted by the pharmacological blockade of prefrontal opioidergic functioning in the experimental setting.

Prefrontal degeneration in Alzheimer's disease and pharmacological blockade of prefrontal opioidergic transmission are not the only conditions in which placebo responses are disrupted. The inactivation of the prefrontal cortex, particularly the dorsolateral prefrontal cortex, by means of repetitive transcranial magnetic stimulation (rTMS) has the same effect (Krummenacher *et al,* 2010). Therefore, the inactivation of prefrontal regions by transcranial magnetic stimulation has the same effects as those induced by pharmacological blockade or prefrontal degeneration in Alzheimer's disease. On the basis of all these studies, a normal functioning of prefrontal areas appears to be critical for placebo responsiveness. In the presence of a loss of prefrontal control, we also witness a loss of placebo response.

FUTURE RESEARCH DIRECTIONS

Despite the recent explosion of neurobiological placebo research and the recent findings that help us better understand both human biology and clinical practice, several issues need further clarifications and many questions still remain unanswered. First of all we need to know where, when, and how placebos work across different diseases and therapeutic interventions. Second, a better understanding of the contribution of different mechanisms, such as expectation, anxiety, reward, learning, genetics, in different types of placebo responses is in order, and this would surely help identify the social, psychological and neurobiological determinants of the different placebo effects. Third, we need to understand why

some subjects respond to placebos, whereas other subjects do not, a critical point that is likely to be clarified by pursuing further research into both learning and genetic mechanisms. ▣

REFERENCES

AMANZIO M., BENEDETTI F. (1999). "Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems" in *J Neurosci* 19: 484-494.

BENEDETTI F. (2008a). "Mechanisms of placebo and placebo–related effects across diseases and treatments", in *Annu Rev Pharmacol Toxicol* 48: 33-60.

——, (2008b). *Placebo effects: Understanding the mechanisms in health and disease* (Oxford: Oxford University Press).

——, ARDUINO C., COSTA S., VIGHETTI S., TARENZI L., RAINERO I *et al* (2006a). "Loss of expectation-related mechanisms in Alzheimer's disease makes analgesic therapies less effective", in *Pain* 121: 133–144.

——, MAGGI G., LOPIANO L., COLLOCA L. (2007). "When words are painful – Unraveling the mechanisms of the nocebo effect", in *Neuroscience* 147: 260-271.

COLLOCA L., BENEDETTI F. (2009). "Placebo analgesia induced by social observational learning", in *Pain* 144: 28-34.

DE LA FUENTE-FERNANDEZ R., RUTH TJ., SOSSI V., SCHULZER M., CALNE DB., STOESSL AJ. (2001). "Expectation and dopamine release: mechanisms of the placebo effect in Parkinson's disease", in *Science* 293: 1164-1166.

EIPPERT F., BINGEL U., SCHOELL ED., YACUBIAN J., KLINGER R., LORENZ J., *et al* (2009). "Activation of the opioidergic descending pain control system underlies placebo analgesia" in *Neuron* 63: 533-43.

ENCK P., BENEDETTI F., SCHEDLOWSKI M. (2008). "New insights into the placebo and nocebo responses", in *Neuron* 59: 195-206.

FURMARK T., APPEL L., HENNINGSSON S., AHS F., FARIA V., LINNMAN C., *et al* (2008). "A link between serotonin-related gene polymorphisms, amygdala activity, and placebo-induced relief from social anxiety", in *J Neurosci* 28: 13066-13074.

GOEBEL MU., TREBST AE., STEINER J., XIE YF., EXTON MS., FREDE S., *et al* (2002). "Behavioural conditioning of immunosuppression is possible in humans", in *FASEB J* 16: 1869-1873.

KIRSCH I. (1999). *How expectancies shape experience*, American Psychological Association.

KRUMMENACHER P., CANDIA V., FOLKERS G., SCHEDLOWSKI M., SCHÖNBÄCHLER G. (2010). "Prefrontal cortex modulates placebo analgesia", in *Pain* 148: 368-374.

LEUCHTER AF., MCCRACKEN JT., HUNTER AM., COOK IA., ALPERT JE. (2009). "Monoamine oxidase a and catechol-o-methyltransferase functional polymorphisms and the placebo response in major depressive disorder", in *J Clin Psychopharmacol* 29: 372-377.

MAYBERG HS., SILVA JA., BRANNAN SK., TEKELL JL.. MAHURIN RK., MCGINNIS S., *et al* (2002). "The functional neuroanatomy of the placebo", in *Am J Psychiatry* 159: 728-737.

PETROVIC P., DIETRICH T., FRANSSON P., ANDERSSON J., CARLSSON K. (2005). "Placebo in emotional processing–induced expectations of anxiety relief activate a generalized modulatory network", in *Neuron* 46: 957-969.

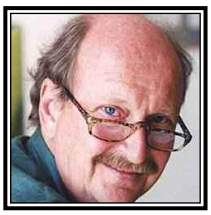
PRICE DD., FINNISS DG., BENEDETTI F. (2008). "A comprehensive review of the placebo effect: recent advances and current thought", in *Annu Rev Psychol* 59: 565-590.

SCOTT DJ., STOHLER CS., EGNATUK CM., WANG H., KOEPPE RA., ZUBIETA JK. (2007). "Individual differences in reward responding explain placebo–induced expectations and effects", in *Neuron* 55: 325-336.

TRACEY I. (2010). "Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans", in *Nature Med* 16: 1277-1283.

THE ETHICAL IMPLICATIONS
OF USING PLACEBO IN CLINICAL PRACTICE

EDZARD ERNST



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Ernst is the editor-in-chief of two medical journals, Perfusion and Focus on Alternative *and* Complementary Therapies. *Ernst once contributed a regular column to the* Guardian *newspaper, frequently reviewing news stories about complementary medicine from an evidence-based perspective.*

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→ | ALTERNATIVES

"It takes a wise doctor to know when not to prescribe."

GRACIÁN

1 ~ PREVALENCE OF USE

RECENT SURVEY DATA FROM SEVERAL COUNTRIES indicate that many clinicians use placebo in their clinical practice [1,2,3,4,5,6,7,8], often on a regular basis. Reasons for doing this include:

- to follow the wish of the patient;
- to avoid conflict;
- to calm the patient;
- to comply with patients' demand for receiving some sort of medications;
- to prevent the patient complaining.

According to these data, prescribing placebos is clearly considered to be ethically justifiable by a large proportion of clinicians.

The subject of placebo is notoriously complex, and discussions of this topic are often too abstract to provide practical guidance. It might therefore be helpful to focus on a concrete example: homeopathy. The best evidence available to date strongly suggests that highly dilute homeopathic remedies are pure placebos e.g.[9,10]. That is to say, they are devoid of specific therapeutic effects. Yet it is undeniable that many physicians and other healthcare professionals regularly use homeopathy. Many of them must be aware of the evidence and employ it as a "benign placebo" e.g.[11]. The question thus is whether this prevalent behaviour can be ethically justified.

2 ~ ARGUMENTS IN FAVOUR

Physicians using placebos, such as homeopathic medicines, in clinical practice might claim do so because they want to help their patients via a beneficial placebo effect[4-6]. Prescribing a highly diluted homeopathic remedy is, of course, unlikely to have direct adverse effects. Many patients expect to receive a prescription when consulting their doctor, and many believe in homeopathy, i.e. they are unaware of the evidence[9,10] and convinced that homeopathic remedies generate specific effects. Issuing a prescription for a homeopathic remedy should therefore be ethically commendable, particularly in cases where no drug therapy is indicated[12].

3 ~ ARGUMENTS AGAINST

At first glance this line of argument seems compelling. However, several counter-arguments emerge, once we scrutinize the issue in more depth.

3.1 ~ MERE CONVENIENCE

A critical analysis of the most frequent reasons for placebo-use (see above) is revealing. The desire of physicians to help their patients does not seem to be a prominent factor. On the contrary, the reasons provided demonstrate that placebo-use is not altruistically motivated but prompted mainly by convenience. It is

quite simply easier for a doctor to write a prescription for a placebo than to discuss with the patient that no such prescription is required or no effective treatment is available. The hope of avoiding conflict and the desire to prevent a complaint are, of course, understandable motives, but they have little to do with the physician's duty to help patients. Physicians' convenience, it would seem, is not a reason that is grounded in medical ethics.

3.2 ~ DECEIT AND INFORMD CONSENT

The prescription of placebos in clinical practice is usually based on what might be called paternalistic deception. Only a small proportion of clinicians

would tell their patients the true nature of this prescription[6]. Without pretending that the homeopathic placebo is effective beyond placebo, doctors cannot expect their patients to experience a clinically relevant placebo-effect. Truthfully telling a patient that the prescribed remedy contains no pharmacologically active ingredient would not generate expectation of benefit. Thus little or no placebo-response would result from telling the truth. However, doctors would "violate the principle of respect for patient autonomy and contravene the legal and ethical requirement to obtain informed consent"[13], if they decided to deceive patients, even if it were "for their own good".

3.3 ~ THERAPEUTIC RELATIONSHIP

Not telling the truth undermines trust which is an essential ingredient of any therapeutic relationship. A good therapeutic relationship can improve both the adherence to treatment and the clinical outcome[14-17]. Placebo-prescriptions cannot be used as substitutes for acknowledging uncertainty, exploring patients' concerns, beliefs and preferences, considering non-pharmacological therapies and inviting shared decision making[18,19]. These actions would be consistent with the physician's ethical responsibilities of non-maleficence, beneficence and respect for patients without, at the same time, depending on the deception of issuing a placebo.

3.4 ~ POTENTIAL FOR HARM

Clinicians using placebos in routine practice should consider at least two important risks of this approach. Firstly, the placebo might be administered instead of a treatment that has specific therapeutic effects. Secondly, the placebo might not be free of adverse effects. Homeopathic remedies, for instance are unlikely to cause adverse effects, but other types of placebos clearly do. For example, physicians often use impure placebos, i.e. treatments that are under-dosed or not indicated for a particular condition. A frequently prescribed impure placebo is an antibiotic for a non-bacterial infection[4,6]. Such impure placebos can cause serious, direct harm through their pharmacological actions. Antibiotics have a range of direct adverse effects and, can harm the population at large through the development of bacterial resistance.

3.5 ~ MEDICALIZATION

Prescribing placebos for the types of self-limiting complaint which placebos are most commonly

prescribed for will almost inevitably result in the medicalization of common states of reduced well-being. Such conditions are best treated by re-assurance and honesty. Prescribing a placebo in such situations would simply reinforce the belief that there is 'a pill for every ill'. This would be neither honest nor helpful. Braillon therefore stressed that "a placebo is a dangerous tool" because it encourages "disease-mongering"[20].

3.6 ~ PLACEBOS ARE NOT NEEDED FOR FOR GENERATING A PLACEBO-RESPONSE

In the vast majority of situations, effective treatments with proven effects beyond placebo are available – they may only be symptomatic rather than curative but they are helpful nevertheless. If, in such cases, we want to increase patient benefit through maximising placebo-effects, we should realize that the sympathetic and empathetic administration of any therapy would result in a placebo-effect, in addition to the specific effect of the prescribed therapy, particularly if expectancy is maximized[21]. Thus prescribing a homeopathic remedy to generate a placebo-effect is usually not only unnecessary, it would also deprive the patient of the specific effect of that treatment. This would clearly not be ethical.

4 ~ CONCLUSION

The prescription of placebos in clinical practice creates an ethical dilemma. On the one hand, clinicians might want to ease the suffering of their patients. On the other hand, this approach violates important ethical principles. The solution is to analyse this behaviour (self) critically. Once we do this, we are likely to find that much of such placebo-prescribing serves the convenience of clinicians rather than the welfare of the patient. Where possible, it should be avoided and replaced with more ethical and professional behaviour. ▣

REFERENCES

1 Berthelot JM., Maugars Y., Abgrall M., Prost A. (2001). "Interindividual variations in beliefs about the placebo effect: a study in 300 rheumatology inpatients and 100 nurses", in *Joint Bone Spine* 68(1): 65-70.

2 Norheim AJ., Fonnebo V. (2002). "Attitudes to the contribution of placebo in acupuncture - A survey", in *Complementar Ther Med*; 10(4): 202-209.

3 Lim EC., Seet RC. (2003). "Attitudes of medical students to placebo therapy", in *Intern Med J* 37(3): 156-160.

4 Hrobjartsson A., Norup M. (2003). "The use of placebo interventions in medical practice - a national questionnaire survey of Danish clinicians", in *Evaluation & the Health Professions* 26(2): 153-165.

5 Nitzan U., Lichtenberg P. (2004). "Questionnaire survey on use of placebo", in *BMJ* 329: 944-946.

6 Sherman R, Hickner J. (2008). "Academic physicians use placebos in clinical practice and believe in the mind-body connection", in *J Gen Intern Med* 23(1): 7-10.

7 Tilburt JC., Emanuel EJ., Kaptchuk TJ., Curlin FA., Miller FG., (2008). "Prescribing 'placebo treatments': results of national survey of US internists and rheumatologists", in *BMJ* 337: a1938.

8 Fässler M., Gnädinger M., Rosemann T., Biller-Andorno N. (2009). "Use of placebo interventions among Swiss primary care providers", in *BMC Health Services Research* 9: 144-152.

9 Ernst E. (2010). "Homeopathy: what does the 'best' evidence tell us?", in *MJA* 192: 458-460.

10 Shang A., Huwiler-Muntener K., Nartey L., Juni P., Dorig S., Sterne JA. et al., (2005). "Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy", in *Lancet* 366: 726-732.

11 Du Y., Knopf H. (2009). "Paediatric homeopathy in Germany: results of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS)", in *Pharmacoepidemiol and Drug Safety* 18: 370-379.

12 Jütte R., Hoppe J-D., Scirba P. (2010). "Stellungnahme des Wissenschaftlichen Beirats der Bundesärztekammer 'Placebo in der Medizin'", in *Deutsches Ärzteblatt* 107(28-29): 1417-1421.

13 Miller FG., Colloca L. (2009). "The legitimacy of placebo treatments in clinical practice: evidence and ethics", in *Am J Bioethics* 9(12): 39-47.

14 Stewart MA. (1995). "Effective physician-patient communication and health outcomes: A review", in *CMAJ* 152: 1423-1433.

15 Ong LM., De Haes JC., Hoos AM. (1995). "Doctor-patient communication: a review of the literature", in *Soc Sci Med* 40: 903-918.

16 DiMatteo MR. (2004). "'Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research", in *Med Care* 42: 200-209.

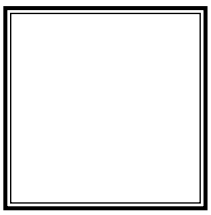
17 Haskard Zolnierek KB., Robin DiMatteo M. (2009). "Physician communication and patient adherence to treatment. A meta-analysis", in *Med Care* 47(8): 826-234.

18 Schenker Y., Fernandez A., Lo B. (2009). "Placebo prescriptions are missed opportunities for doctor-patient communication", in *Am J Bioethics* 9(12): 48-54.

19 Hrobjartsson A. (2008). "Clinical placebo interventions are unethical, unnecessary, and unprofessional", in *J Clin Ethics* 19: 66-69.

20 Braillon A. (2009). "Placebo is far from benign: it is disease-mongering", in *Am J Bioethics* 9(12): 36-38.

21 Crow R., Gage H., Hampson S., Hart J., Kimber A., Thomas H. (1999). "The role of expectancies in the placebo effect and their use in the delivery of health care: A systematic review", in *Health Technol Assess* 3(3): 1-97.

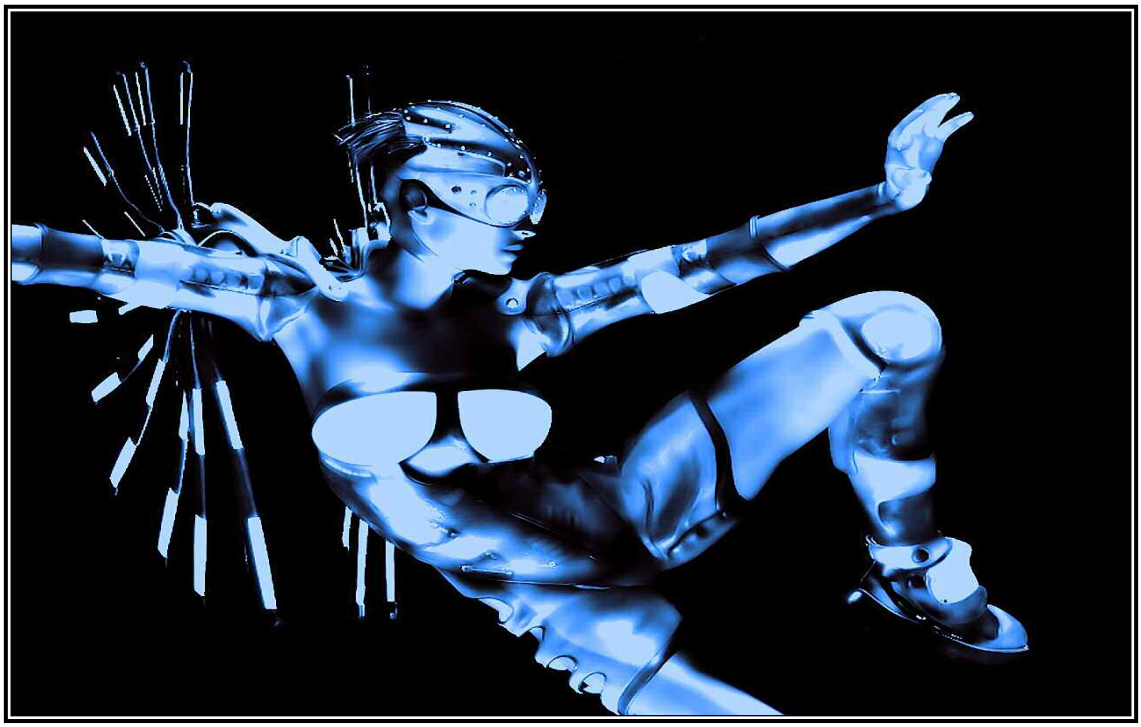


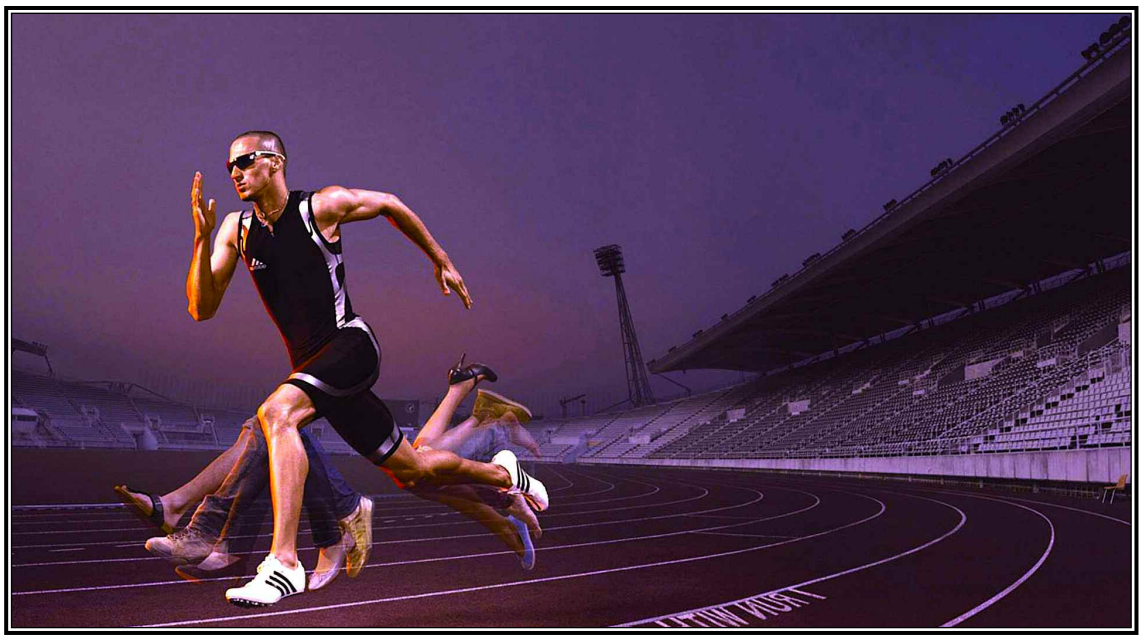
T

→| CHALLENGES

“A man who is ‘of sound mind’ is one who keeps the inner madman under lock and key.”

PAUL VALÉRY





Now, my tongue, the mistery telling
Of the glorious Body sing.

THOMAS AQUINAS, *Pange Lingua Gloriosi.*

THE STING OF POTENTIAL PAIN

KURT GRAY ~ DANIEL M. WEGNER

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Daniel M. Wegner is a social psychologist, John Lindsley Professor in Memory at William James Department of Psychology, Harvard University, US, and a fellow of the American Association for the Advancement of Science. He is known for his work on mental control (e.g., thought suppression) and conscious will, and for originating the study of transactive memory and action identification. His book, The Illusion of Conscious Will, *tackles the long-debated notion of free will through the scope of experimental psychology. Wegner's ideas have sparked interest among psychologists, neuroscientists, theologians, and philosopher interested in the nature of consciousness and freedom of action.*

→| PROPOSAL

"Old age is the most unexpected of all things that happen to man."

LEV TROTSKY

When someone steps on your toe on purpose, it seems to hurt more than when the person does the same thing unintentionally. The physical parameters of the harm may not differ – your toe is attened in both cases – but the psychological experience of pain is changed nonetheless. Intentional harms are premeditated by another person and have the specific purpose of causing pain. In a sense, intended harms are events initiated by one mind to communicate meaning (malice) to another, and this could shape the recipient's experience. This study examined whether self-reported pain is indeed higher when the events producing the pain are understood as intentionally (as opposed to unintentionally) caused by another person.

Although pain was traditionally conceived to be solely physical in nature (Aydede, 2005), its experience varies substantially with psychological context. The placebo analgesia effect, for example, is the reduction of pain without a change in physical stimulation when context, expectations, or sugar pills challenge the interpretation of a sensation as painful (e.g., Fields, 2008). The nocebo effect, in turn, is the experience of pain without any physical stimulation – as when participants report headaches when told that a (nonexistent) electric current is passing through their heads (Schweiger & Parducci, 1981). These variations in pain experience seem to depend on the meaning of the stimulus: A sugar pill is meant to decrease pain, whereas electric current is meant to increase pain. In an interpersonal context, the meaning of an action is derived from the perceiver's perceptions of the actor's intention (Clark, 1996), which means that intentional harms, unlike accidental harms, are meant to cause pain.

The possibility that the malicious intent of other people could be translated into additional physical pain is suggested by studies demonstrating that similar areas of cortex respond to both physical pain and social harms (Eisenberger, Lieberman, & Williams, 2003). Social harms, which are presumably laden with intention, have also been shown to be more painful to relive than simple physical harms (Chen, Williams, Fitness, & Newton, 2008). So, although a broken toe (or electric shock) may hurt, an intentionally broken toe (or electric shock) should hurt more.

METHOD

Forty-eight participants (68% female, 32% male) participated in a lab study of "psychophysical perception in pairs." Four participants were excluded for suspicion and one participant was excluded for failing to follow instructions, leaving a total of 43.

On arrival, participants met their study partner – a confederate – and were escorted to an individual room. They were then introduced to the psychophysical tasks of color matching, number estimation, pitch judgment, and discomfort assessment, each of which they completed. Discomfort assessment involved being administered an electric shock

and evaluating it on a 7-point scale ranging from not at all uncomfortable to extremely uncomfortable. Shocks of 1-ms duration were delivered to the wrist of the dominant hand through a stimulator (Biopac Systems, Goleta, CA), with voltage precalibrated for each participant to be "very uncomfortable." Voltages ranged from 40 to 75V between subjects. Participants evaluated two blocks of computer-administered electric shocks initially in an individual practice session as a baseline pain measure.

On each experimental trial, participants saw a computer screen with two potential tasks before completing one of them. When discomfort assessment was a potential task, the alternate task was evaluating the relative pitches of tones. On this and other trials, participants were told that the participant in the next room (the confederate) would select which task the participant would complete.

In the intentional condition, the confederate chose the discomfort-assessment task when it was an option, and participants received an electric shock. In the unintentional condition, the confederate selected the pitch-judgment task when discomfort assessment was an option. In this condition, however, participants were told that the mapping between the selection and administration of tasks was switched, unbeknownst to the confederate, so they would always receive the task opposite to the one selected by the confederate. Thus, when pitch judgment was selected for them, they completed discomfort assessment and received an electric shock.

On their computer screen, participants saw both the confederate choice and the actual task to be administered (in advance), which ensured that participants were not surprised when they received an electric shock and also reinforced the intentional or unintentional nature of the shock. Pilot testing confirmed that shocks were perceived (on a 7-point scale) as more intentional in the intentional conditional (M=5 5.64, SD=1.49) than in the unintentional condition (M=2.17, SD=0.83), $t(24)=7.13$, $p<.01$, $P_{rep}=.99$, and that the confederate was seen as more blameworthy (on a 5-point scale) in the intentional condition (M=2.43, SD=1.40) than in the unintentional condition (M=1.41, SD=0.67), $t(24)=2.29$, $p<.03$, $P_{rep}=.91$. In both conditions, participants completed three blocks of experimental trials after the two practice/baseline trials.

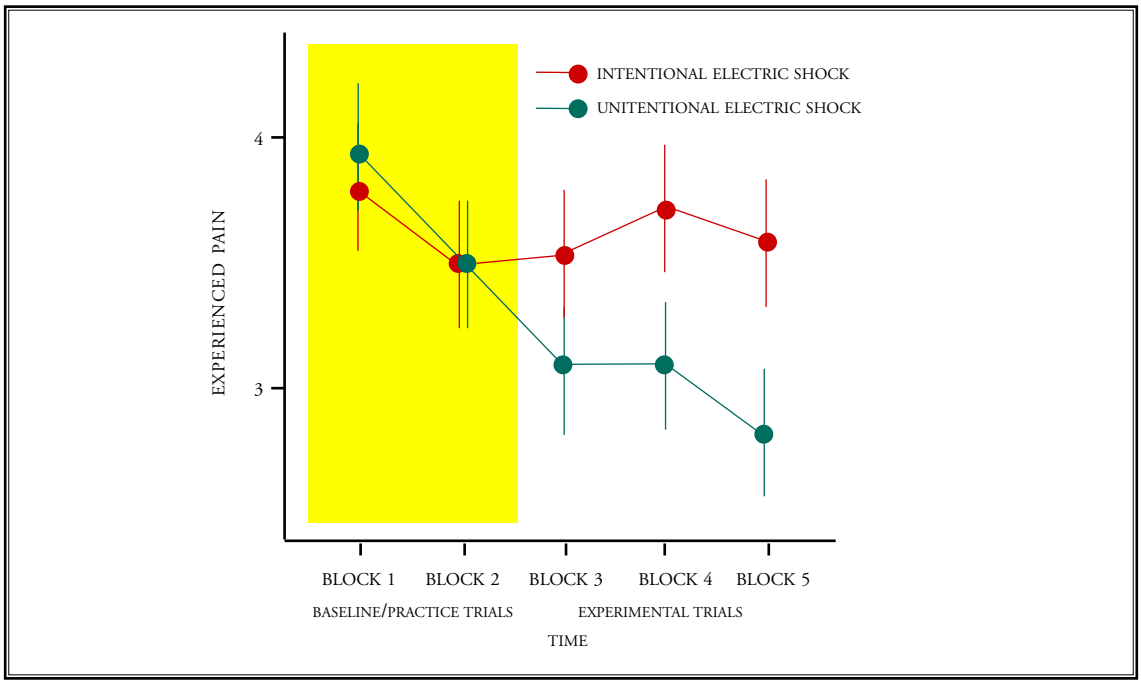


FIGURE 1 – Experienced pain as a function of whether electric shocks were perceived as intentional or unintentional.

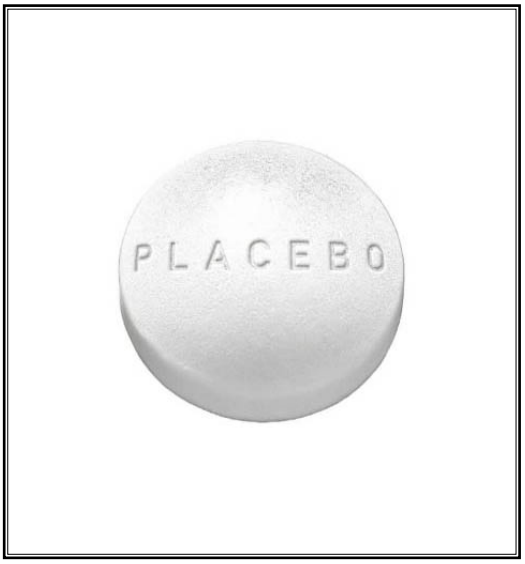
RESULTS AND DISCUSSION

Mean pain ratings from shocks in each of the 5 blocks (see FIGURE 1) were submitted to a 2 (condition: intentional; unintentional) x 5 (time: block number) between-within analysis of variance, which revealed the predicted interaction, $F(4, 164)=3.09$, $p=.02$, $P_{rep}=.93$, $\pi^2=.07$. A composite of the two practice blocks revealed no significant difference in experienced pain between conditions ($t<1$); however, an average of experienced pain in the three experimental blocks revealed that intended pain (M=3.62, SD=0.99) was experienced as more painful than unintended pain (M=3.00, SD=0.78), $t(41)=2.21$, $p=.03$, $P_{rep}=.91$.

Additionally, there was a significant decreasing linear trend of experienced pain in the unintentional condition, $F(1,17)=20.18$, $p=.001$, $P_{rep}=.99$, suggesting that participants in this condition exhibited the standard pattern of habituation to repeated painful stimulation (Greffrath, Baumgartner, & Treede, 2007). In contrast, there was no linear trend in the

intentional condition, F=0.08, suggesting that participants in this condition continued to feel the fresh pain of an intentional harm as time went on.

This study provides evidence that the experience of pain changes depending upon the psychological context in which people are harmed. Specifically, the meaning of a harm – whether it was intended – influences the amount of pain it causes. Although people can become accustomed to the pain of an unintentional harm, the malice behind an intentional pain keeps it stinging. ▣



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REFERENCES

AYDEDE, M. (2005). "Introduction: A Critical and Quasi-historical Essay on Theories of Pain", in M. Aydede (ed.), *Pain: New essays on its nature and the methodology of its study* (Cambridge, MA: MIT Press): 1-58.

CHEN, Z., WILLIAMS, K.D., FITNESS, J., & NEWTON, N. (2008). "When hurt will not heal: Exploring the capacity to relive social and physical pain", in *Psychological Science* 19, 789-795.

CLARK, HH. (1996). *Using language* (New York: Cambridge UP).

EISENBERGER, N.I., LIEBERMAN, M.D., & WILLIAMS, K.D. (2003). "Does rejection hurt? An MRI study of social exclusion". in *Science* 302: 290-292.

FIELDS, H.S. (2008). *Pain: Mechanisms and management* (2nd ed.) (New York: McGraw-Hill).

GREFFRATH, W., BAUMGARTNER, U., & TREEDE, R-D. (2007). "Peripheral and central components of habituation to heat pain perception and evoked potentials in humans", in *Pain* 132, 301-311.

SCHWEIGER, A., & PARDUCCI, A. (1981). "Nocebo: The psychologic induction of pain", in *Pavlovian Journal of Biological Science* 16, 140-143.

THE ETHICS OF PLACEBO-CONTROLLED

TRIALS IN DEVELOPING COUNTRIES TO PREVENT MOTHER-TO-CHILD TRANSMISSION OF HIV*

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→| REFLECTIONS

"Apart of the known and the unknown, what else is there?"

HAROLD PINTER

INTRODUCTION

PLACEBO-TRIALS ON HIV-INFECTED PREGNANT women in developing countries like Thailand and Uganda[1,2] have provoked recent controversy[3,4]. Such experiments aim to find a treatment that will cut the rate of vertical transmission more efficiently than existing 'gold standard' treatments like zidovudine. Is such an experiment morally justified? I think that the right question to ask is this: "Is it always, never or sometimes, morally justified to experiment on HIV-infected, pregnant women in developing countries (by means of placebo trials) in order to develop a new treatment X which will reduce the rate of mother-to-child HIV transmission more effectively than the existing ('gold standard') treatment Y?"

THREE ETHICAL PRINCIPLES AND HOW THEY CONFLICT

Put like this, the issue acquires a level of generality. For example, the specific country in which the experiment is carried out is not the issue. Unless there are clear differences from country to country which are morally relevant to the question above, our answer to it should be the same whatever the country in which such experiments are conducted.

Extracting a clear and consistent answer is not easy, given the emotional horror that surrounds even a suitably generalised question. The consequences of the disease are horrible and threaten to multiply through successive generations. The horror is accentuated by the innocence of the foetus as a recipient of those consequences, an innocence that remains regardless of the academic question of whether the foetus is a person or merely a potential person. Add to this the perplexing conundrum of placebo, with its levels of ignorance. Finally, we must contextualise the problem against the background of the horrors built into developing countries, such as unequal and inadequate resources, lack of education and poverty.

Where is a doctor or a researcher to look for guidance in such a case? 'Conscience', isn't any substantive answer, since differing consciences of doctors are just differing internalisations of some medical code. However, there is an authoritative code of medical practice, which provides guidance, namely the Belmont Report[5].

The Belmont Report provides an excellent sharpening of the principles laid down in the unmodified Helsinki Declaration[6]. In essence, it urges three principles: the Principle of Utility (there called Beneficence), the Principle of Autonomy (there called Respect for Persons) and the Principle of Justice.

The Principle of Utility has a negative and a positive form. Its negative form states that

> - PB neg) It is one's duty to refrain from doing harm while its positive states that
>
> - PB pos) It is one's duty to minimise harm and maximise benefit, *to society in general, including that of future patients*.

The Principle of Autonomy claims that individuals should be treated as autonomous agents, and that

persons with diminished autonomy are entitled to protection. In other words,

> ~ PA) It is one's duty to respect autonomous choices and to protect those with diminished autonomy.

The Principle of Justice states that 'research should not unduly involve persons *from groups unlikely to be among the beneficiaries* of subsequent applications of the research'. The spirit of this principle is that

> ~ PJ) It is one's duty to distribute benefits (of research) fairly

or at least, not worsen the imbalance of benefits and burdens of research among relevant groups.

These three voices of utility, autonomy and justice cannot, in themselves, provide clear guidance in all cases, since there are possible scenarios in which they give conflicting rulings. It seems reasonable to think that the negative voice of utility is not a total prohibition of any form of harm, such as a slightly painful injection. Rather it should be read as 'Do not cause more harm than benefit to a single individual', but this may still conflict with the positive voice of utility. Suppose that the general increase of good over harm to society in general (by means of a reduction of the number of children who will be born with HIV) can be purchased only at the cost of exposing the mothers in the experimental group to a risk of substantial harm that is greater than the chance of slight benefit. Since such exposure is itself a type of harm, the voice of utility is confused.

Now consider the cost to the mothers in the control group. Their babies are effectively condemned to HIV infection, the incidence of which could have been reduced by giving them the 'gold standard' standard treatment Y (for example, zidovudine) that is known to be effective in cutting the rate of vertical HIV transmission. In the name of both babies and their mothers, the negative voice of utility prohibits the experiment, while its positive voice demands it. Suppose further that HIV-infected mothers can only be recruited for the experiment by coercing them to participate or by withholding information about the risks involved (the absence of any effective treatment in the case of the control group and the risks-compared-to-benefits of treatment X in the case of the experimental group) relative to the benefits available to others (by means of the existing treatment Y). Here the voice of utility contradicts that of autonomy, since informed and free choice to participate has been ruled out. Or suppose that the treatment X, once available, will be restricted to a minority of HIV-infected pregnant women in countries wealthy enough to afford it, excluding those in the developing country in which they were originally developed. Even if we could be sure that the rate of vertical transmission would decrease worldwide, in line with the voice of utility, we would still hear the cry of injustice.

ONE HIERARCHY OF THE THREE ETHICAL PRINCIPLES

These examples show that the principle of utility will contradict those of autonomy and justice in cases that are at least possible. This means that we must decide in advance which voice has authority over which. As a matter of fact, most of us hear the least authority in the voice of utility. In examples such as those just considered, most will judge that maximising utility at the cost of injustice or at the cost of disrespecting the free choices of people (thus treating them as means to the end of increased health world-wide) is morally repugnant. Thus, one way to achieve consistency among the three principles that will fit the moral intuitions of many is to hold that *the voice of utility must be obeyed, but only after the voices of justice and autonomy have been obeyed*. Those who hear things that way will not be swayed in the least by the tinkering with the original wording of the Helsinki Declaration which was sent to the World Medical Association's member associations in advance of the World Medical Association Council Session in Santiago, Chile on April 15, 1999.

Working from the background of the question towards empirical specifics, the Principle of Justice is the most effective choice of principles to apply first. If the degree of poverty of most pregnant HIV-infected mothers in the developing country (such as Uganda) will prevent them from buying the improved cure, if found, for several generations of HIV-infected offspring to come, while most of the relatives of the researchers (such as Americans) will be able to buy it as soon as it hits the market, then surely this is injustice. As for other scenarios, surely enlarging the relative size of burdened group versus benefiting group proportionally worsens the injustice. Given that injustice will be done, there is something morally wrong with the experiment, quite regardless of whatever else is ruled wrong by the other principles. Taking the three principles as a guide to procedure, we must at least postpone such experiments until enough economic aid has been given to these countries as makes the chances of benefit more fairly distributed. Otherwise the researchers should experiment upon their own extended geo-political-economic kin. Given the commercial hegemony of the rich drug companies involved, their opposition to the production of cheaper 'generic' drugs and the huge disparity between levels of wealth in developing countries and developed countries, the chances of benefit to the burdened group were clearly *not* fairly available to them.

Let us now suppose (hypothetically but implausibly) that equality has been redressed or is not the issue. What does the voice of autonomy tell us? There are two groups for whom it could speak, the foetuses and their mothers. Clearly the foetus is incapable of making choices, informed or not, so whether or not we say that they are potential persons or already persons, there can be no autonomous choices made by

them which are respected or disrespected. In this respect, the voice of autonomy is neutral on the permissibility of the experiment. On the other hand, the principle of autonomy also commands us to 'protect those with diminished autonomy', which appears to include the foetus. If so, on balance, the voice of autonomy prohibits the experiment in the name of the foetus.

It might be objected that the class of those entitled to protection excludes non-persons such as the foetus. This objection clearly has little bite against those who hold that the foetus is to some degree a person at some stage in its development. Nor is it persuasive against those, including the mothers, who think that whether the foetus is an actual or potential person, it is still something valuable, which therefore needs protection.

How does autonomy speak for the mothers? It clearly prohibits the experiment unless the mother has made an autonomous choice to participate. Autonomous choices must be informed choices. In the case of a non-placebo experiment in which the new treatment X is to be tested, this means that the mother must understand the risks and probable benefits to herself and her foetus posed by the new treatment X, *as compared to risks and probable benefits conferred by the existing treatment Y*. Since the probability of risks and benefits of the new treatment may be precisely what the experiment is designed to discover, it may not be possible to give her precisely this information. In that case, the mother must be informed of *the degree of uncertainty* of the probability of possible harms and benefits of the new treatment X, *as compared to the degree of certainty already established* of the probabilities of harms and benefits of the existing treatment Y. Anything less would not be full information.

COMPLICATIONS ARISING FROM PLACEBO CONTROL

In the case of a placebo experiment, things are more complicated. Placebos aim to separate the causal powers of X from the causal powers of the belief in those causal powers. For example, they aim to filter out cases in which a patient feels better simply because that patient believes (correctly or incorrectly) that the treatment will work. The belief in question may be held by the mothers or the experimenters or both. Clearly no such belief can be held by the foetus. Assume a simple single-blind placebo control in which each mother has a fifty-fifty chance of being selected for the control group to receive sugar as opposed to the experimental group to receive the new treatment X, such that no mother will know which group she is in. Obviously, this design of experiment rules out informing the mothers which group they are in, but this does not mean they can be given no information at all. Autonomy demands that each mother understand that she has a half-chance of ending up in the control group, in which case her foetus will certainly be born with HIV and a half-chance of ending up in the experimental group, with possible risks and benefits to the foetus which are uncertain. *She must also understand that she faces these two outcomes in the teeth of the knowledge that treatment Y already exists, with its more certain risks and benefits to the foetus*.

It might be objected here that the lack of education among such mothers renders them incapable of understanding such information. If so, autonomy demands that education be a more pressing priority than medical research. The experiment must be postponed until the would-be participants are educated to a level that enables them to understand what choices are open to them. Since justice demands that the benefits of education be fairly distributed throughout the developing country in which the experiment is to take place, this means that the experiment must be postponed until any would-be sub-group of participants has a level of education that is representative of the whole population of that country.

This brings us back to the purpose of the placebo. Suppose that an HIV-infected pregnant woman believes that she is receiving a new miracle drug that carries an ironclad guarantee of protecting her foetus from infection. In fact her belief is mistaken, for the drug she has been given is just sugar. It seems unlikely that her belief could have any positive psychological effect upon her foetus. In terms of the mother, the placebo seems to serve no useful purpose. So far, there is no justification for the creation of the control group, in which the foetuses are condemned to HIV infection. Thus the only other purpose that the placebo can serve is to separate the causal powers of X in reducing vertical transmission from the causal powers of the beliefs of the experimenters. A double-blind trial, in which the experimenters do not know which mother is receiving sugar or receiving X, will ensure that they will not bias the development of one group of foetuses over the other, by giving different levels of care to the two groups of mothers. The question to ask now is whether the increased accuracy of the results of the efficiency of X is worth the price of allowing the mothers in the control group to go untreated. The voice of autonomy tells us that the price need not be paid. Since mothers in both groups are persons equally deserving of care and respect, the experimenters have a duty to provide both groups with the best possible level of care, *regardless* of their beliefs about whose foetuses are most likely to be protected from vertical transmission. Once this duty is discharged, there is no possible justification left for the inclusion of the placebo group.

Thus there appears to be no need for a placebo group at all. Surely the ethical procedure would be to *give the control group treatment Y instead*. After all, are we

not trying to measure the difference in effectiveness of the new treatment X *as compared to* the existing treatment Y? If the participants in both groups were fully informed of the experimental set-up, there would be no room for objection on grounds of autonomy, nor any room for objection on grounds of utility to the treatment of the participants in the control group, since this group is assured of the best known treatment available anyway.

Given my definition of a placebo as a control which aims to separate the causal powers of a treatment from the causal powers of belief (or faith) in that treatment, there is, strictly speaking, a conceptual difference between a placebo group and a 'no treatment' control group, which aims to help isolate possible unwanted side-effects of the treatment. In experiments to develop new treatments that are more effective in reducing the vertical transmission of HIV, a 'no treatment group' would help to isolate unwanted sideeffects of the new treatment on the foetus. I now turn to this issue.

'NO-TRATMENT GROUPS' WITHIN CONTROLLED STUDIES

Similar moral objections can be made to different kinds of experiments such as the Rakai project in Uganda[7], in which the experimenters studied the effect of other sexually transmitted diseases on the rate of heterosexual transmission of HIV and the natural risk factors that determine the heterosexual transmission of HIV-1 over periods of unprotected sex. Such experiments use a 'no-treatment' group within a controlled study. Such an experiment is ruled unethical on the grounds of autonomy, if those who were left untreated were not fully informed that this was precisely what would happen to them. By the experimenters' own admission, those in the 'no-treatment' group were not fully informed. Quinn *et al*[8] reported that 228 HIV-infected couples were left untreated for up to thirty months, and the decision to inform the uninfected persons that their partner was infected was left up to the infected persons themselves, although the experimenters regularly saw both. Surely this does not count as discharging a duty to give all parties concerned the full information. To so discharge it, the experimenters should have told each couple that one partner was infected *as well* as telling them that the infection would go untreated.

In the same project, the investigators treated half of the villagers for sexually transmitted diseases such as syphilis while leaving the other half untreated. Their aim was to determine the effect of concurrent sexually transmitted diseases on the heterosexual transmission rate of HIV. Assume for the sake of argument, that this information was obtained and that it helped to develop more effective ways of cutting the HIV transmission rate. In terms of maximising the utility to society in general, the investigators were morally justified. Moreover, anyone who maintains consistently that *the voice of utility always overrides the voices of autonomy and justice* can defend the investigators, but that is not the moral framework I have suggested. Given that utility is subordinate to autonomy and justice, we need to ask whether the investigators infringed the informed choices of the villagers who were left untreated. Deciding this is not easy. One way to look at it is to say that the untreated villagers were simply left alone by the investigators to carry on as before, so no interference took place. On the other hand, there is a clear sense in which the untreated villagers were *selected* by the investigators to form one half of the experiment. In this sense, they were intentionally included in the experiment by default. Therefore

the voice of autonomy demands that the experimenters give them an informed choice to continue to participate, which in turn means telling them that they would go untreated. Had the villagers heroically agreed to forgo treatment for the sake of future generations then there could be no objection in the name of autonomy. Otherwise, continuing to include them in the experiment would be morally wrong. Against this, it might be objected that the investigators were not doing anything extraordinary, since the villagers would not have been treated in the ordinary course of events anyway. However, it is not so clear that this means the investigators were not interfering. Given that the investigators selected this particular group of villagers for the control arm of the experiment, and then continued to withhold both treatment and information when they could easily have supplied both, were they not interfering? In *selecting* and then ignoring them, surely the investigators were actually *doing* something to them.

The scenario of the untreated villagers is no different in principle from that in which a group of pregnant HIV-infected mothers is left untreated as a control to a second group who are given a new treatment X, in order to help obtain information on (among other things) whether X will have unwanted side-effects on the foetus. Assume, for the sake of argument, that the information is obtained and that it is instrumental in reducing harmful side-effects to babies who are in general, less likely to be born with HIV (than when their mothers were treated with the original drug Y). Again, the voice of utility permits, even demands, the inclusion of the 'no-treatment group', but again, given that utility is subordinate to autonomy and justice, we need to ask whether the investigators infringed the informed choices of the mothers who were left untreated. If the investigators first selected them as a control arm and then withheld treatment and information (including the information that they were infected and that treatment was available), then the mothers' autonomy was violated.

THE UTILITARIAN 'NO LOSS' DEFENSE

Some commentators[9] in the debate have argued that most HIV-infected pregnant women in developing countries would not be able to afford any sort of treatment against vertical transmission anyway. Thus the women in the original experiment are in a no-loss situation. They have a half-chance of ending up in the placebo group, in which case they are no worse off than they would be anyway and a half-chance of ending up in the experimental group, in which case they have a secondary chance (the degree of which is yet unknown) of protecting their foetus.

This argument suffers from a number of flaws. Are the women in the placebo group really no worse off than they would have been had they never participated? If autonomy has been satisfied, then the women will know that they are in a kind of desperate lottery that holds out a chance for the well-being of their unborn. Since the chances of protection for the foetuses in the experimental group are less than certain, they should know that overall, the odds are against them. Nonetheless, some basis for hope exists, which may well be the very reason why they have agreed to participate. Yet the experimenters know in advance that for each mother in the placebo group, all hope will be dashed. This burden of false hope and its certain disappointment surely represents a significant cost to this group of mothers.

The no-loss argument gains its plausibility from the claim that the personal utility of the volunteers is not decreased. But it ignores the salient fact that the volunteers start from a position of inequality. Were justice done, the proven, if limited benefits of the existing treatment Y would be distributed fairly throughout the world to those in developing countries who need them most. Given that the inclusion of the placebo group is justified, the autonomous choice of the mothers would then be the more heroic one of taking a half-chance of no protection for their unborn and a half-chance of the uncertain degree of protection conferred by treatment X, *in preference to* the guarantee of the certain but limited degree of protection conferred by the existing treatment Y. Given, as I suggested above, that the inclusion of the placebo group is *not* justified, the autonomous choice of the mothers would then be the less heroic but still courageous one of *trading* the certain but limited degree of protection conferred by treatment Y for the possibly improved but uncertain degree of protection conferred by treatment X.

In the original experiment, even those mothers who end up in the experimental group are doubly wronged. Firstly, they are wronged both in the name of justice and in the name of autonomy by being unfairly denied the choice of treatment Y. Then the experimenters restrict their choices to the options of no treatment (by refusing to participate) or the option of a half-chance of the uncertain benefits of treatment X (by consenting to participate). The restriction is genuine, since it is always within the power of experimenters to offer treatment Y as well. Since this is a perpetuation of the original injustice and an erosion of autonomy, this is a further wrong. In this respect, the would-be participant resembles a workman who has been unfairly denied any payment. His employer offers to toss a coin. If the coin comes down heads, the workman will receive half his wages; if tails, nothing. If he refuses the bet, again he gets nothing. The workman is first wronged by being deprived any payment. When the bet is offered, he has nothing further to lose. Yet surely the offer of the bet is a second wrong since it perpetuates the original deprivation of full payment, one that the employer is in a position to put right.

EFFECTS OF MODIFYING THE DECLACARATION OF HELSINKI

Whereas the current Declaration assures research participants of 'the best proven diagnostic and therapeutic method,' the corresponding section in the modified Declaration adds the phrase 'that would otherwise be available to him or her.' This appears to vindicate the 'no loss' argument, since there is no treatment available to the would-be participants in the experiment should they not participate, given that they are too poor to afford any treatment, including treatment Y. But this vindication is an illusion. For one thing, there is an ambiguity in the phrase 'available'. On one reading, treatment Y is not available to the group in the sense that they would not have been able to obtain it, *had they never come in contact with the experimenters*. However, in that sense, since the best treatment available otherwise is none, this amendment is just another way of saying that the group in question is assured of no treatment. We should therefore reject this amendment to the Declaration, in the name of both justice and utility as originally voiced by it. Utility demands that the benefit to society be maximised and justice demands that this benefit be fairly distributed. In other words, the group in question must be given a fair chance of treatment Y. The other, more sensible, reading of 'available' is that treatment Y is not available to the group *as would-be participants who are now in contact with the experimenters*. However, in this sense, treatment Y *is* available to them even if they now choose not to participate, since it is fully within the experimenters' power to provide it. Thus even the modified declaration tells us that the experiment is morally wrong.

CONCLUSION

Given plausible assumptions about the level of poverty and education in the developing country targeted, the placebo-controlled trials of the type discussed are unethical violations of both justice and autonomy. In any case, no moral justification can be found for the inclusion of a placebo group. By contrast, the inclusion of a 'no control' group may be justified, but only when the experimenters have not interfered with the autonomy of its members. Experiments such as the Rakai project in Uganda are such unethical violations of autonomy. The development of third-world countries, in the form of economic development and education, must be priorities that come before such experiments. ▣

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REFERENCES

1 CONNOR E. M., SPERLING R. S., GELBER R., KISELEV P., SCOTT G., O'SULLIVAN MJ. *et al* (1994). "Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment", in *N Engl J Med* 331: 1173-80.

2 SHAFFER N., CHUACHOOWONG R., MOCK P.A., BHADRAKOM C., SIRIWASIN W., YOUNG NL., *et al* (1999). "Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: A Randomised Controlled Trial", in *Lancet* 353: 773-80.

3 LURIE P., WOLFE S. M. (1997). "Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries", in *N Engl J Med* 337: 853-6.

4 ANGELL M. (1998). "The Ethics of Clinical Research in the Third World", in *N Engl J Med* 337: 847-9 [see also correspondence in *N Engl J Med* 1998; 338: 836-44].

5 *NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH*. The Belmont Report. April 18, 1979.

6 *DECLARATION OF HELSINKI IV*, 41st World Medical Assembly, Hong Kong, September 1989. In: Annas GJ., Grodin MA. (ed.) *The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation* (New York: Oxford UP, 1992: 339-42.

7 WAWER MJ., SEWANKAMBO NK., SERWADDA D., QUINN TC., PAXTON LA., KIWANUKA N. *et al* (1999). "Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial" in *Lancet* 353: 525-35.

8 QUINN TC., WAWER MJ., SEWANKAMBO N., SERWADDA D., LI C., WABWIRE-MANGEN F. *et al* (2000). "Viral load and heterosexual transmission of human immunodeficiency virus type 1", in *N Engl J Med* 342: 921-9.

9 PHANUPHAK P. (1998). "Ethical issues in studies in Thailand of the vertical transmission of HIV" in *N Engl J Med* 338: 834-5.

The limits of my language
mean the limits of my world.

LUDWIG WITTGENSTEIN, *Tractactus Logico-Philosophicus.*

FABRIZIO BENEDETTI

THE MANY PLACEBO EFFECTS

Due to the involvement of many mechanisms, the study of the placebo effect can be viewed as a melting pot of concepts and ideas for neuroscience. Indeed, there exist not a single placebo effect, but many, with different mechanisms and in different medical conditions and therapeutic interventions. In fact, expectation, anxiety and reward are all involved, as well as a variety of learning phenomena. There is also some experimental evidence of different genetic variants in placebo responsiveness. Pain and Parkinson's disease are today the most productive models to better understand the neurobiology of the placebo effect, and the neural networks that are involved have been identified, such as an opioidergic-cholecystokinergic-dopaminergic modulatory network in pain and part of the basal ganglia circuitry in Parkinson's disease. Important implications emerge from these recent advances in placebo research, such as the impact of the psychosocial context on the patient's brain.

EDZARD ERNST

THE ETHICAL IMPLICATIONS OF USING PLACEBO IN CLINICAL PRACTICE

By using the concrete example of homeopathy, this paper considers whether placebo use can be ethically justified. On one hand, clinicians may want to help patients through a beneficial placebo effect, and highly diluted homeopathic remedies are unlikely to have adverse effects. Also, many patients expect to receive a prescription when visiting the doctor and believe in the effectiveness of homeopathy. However, the author presents several reasons the use of placebos may not be considered ethical. Recent survey data shows that the most frequent reasons for prescribing placebos are mainly for the physicians' convenience rather than for altruistic motives. To obtain the placebo effect, physicians cannot tell the patient they are receiving a placebo, which goes against the ethical requirement for a doctor to obtain informed consent from a patient. This deception can undermine trust, which is necessary for good therapeutic relationships. Placebos, especially impure ones, also present the risk of producing adverse effects and may cause people to believe there is a medical cure for every state of reduced well-being. This paper suggests that an effective treatment that treats a patient's symptom(s) will be more useful than a homeopathic remedy because the patient will get relief from his/her symptom(s) while also receiving the placebo effect. The author recommends that clinicians analyse their own behaviour to determine whether placebo use is in the best interest of the patient or for their own convenience.

CHRISTOPHER J. BEEDIE

ALL IN THE MIND? PAIN, PLACEBO EFFECT, AND ERGOGENIC EFFECT OF CAFFEINE IN SPORTSS PERFORMANCE

The ergogenic effects of caffeine on performance are well documented. These effects are more evident in endurance and short-duration, sustained-effort events than in interactive or stop-go sports. Experimentally-induced placebo effects of caffeine on sports performance have also been observed in a number of recent studies. In the present paper it is argued that, given the nature of the sports in which caffeine effects are observed, the well documented hypoalgesic effects of caffeine, and the fact that pain is highly placebo-responsive, a reduction in perceived pain might be the common factor in both the biologic and placebo ergogenic effects of caffeine on sports performance. This idea is supported by evidence from medicine that suggests placebo effects are often associated with mechanisms similar or identical to those of the substance the subject believes they have ingested. Research findings from both biomedicine and sports medicine that attest to the interaction of biologic and psychologic factors in caffeine and pain responses are briefly reviewed. In conclusion, it is recommended that researchers investigate the pain hypothesis. Furthermore, researchers should consider psychosocial factors that might modulate the pain response as variables of interest in future caffeine and performance research.

KURT GRAY ~ DANIEL M. WEGNER

THE STING OF INTENTIONAL PAIN

This study tests whether the psychological context of pain affects the amount of pain an individual feels, namely whether intentional harm causes more perceived pain than unintentional harm. The researchers used an experiment in which the subjects were instructed to perform a series of tasks with a partner in a separate room, who was actually an accomplice. One task, discomfort assessment, involved the subject receiving an electric shock and rating his/her level of discomfort. One group was led to believe their partner intentionally chose for them to receive the shock rather than choosing for them to complete another task, while the other group was told the partner unintentionally chose for them to get the electric shock. The results show that intended pain was experienced as more painful than unintended pain. In addition, intended pain appeared to be felt fresh every time, rather than lessening as the subject became habituated to repeated painful stimulation.

JOHN NICHOLAS WILLIAMS

THE ETHICS OF PLACEBO-CONTROLLED TRIALS IN DEVELOPING COUNTRIES TO PREVENT MOTHER-TOCHILD TRANSMISSION OF HIV

Placebo-trials on HIV-infected pregnant women in developing countries like Thailand and Uganda have provoked controversy. Such experiments aim to find a treatment that will cut the rate of vertical transmission more efficiently than existing treatments like zidovudine. This scenario is first stated as generally as possible, before three ethical principles found in the Belmont Report, itself a sharpening of the Helsinki Declaration, are stated. These three principles are the Principle of Utility, the Principle of Autonomy and the Principle of Justice. These are taken as voices of moral imperative. But although each has intuitive appeal, it can be shown that

there are possible scenarios in which they give conflicting prescriptions. To achieve consistency, one must be subordinate to the others. The voice of utility is taken as subordinate to those of justice and autonomy and it is shown that given plausible assumptions about the level of poverty and education in the developing country targeted, the experiment is ruled morally wrong in the name of both justice and autonomy.

Moreover, it is argued that no justification can be found for the inclusion of a placebo group, when strictly defined. By contrast, a 'notreatment' control arm might be justified, but only when the demands of autonomy are satisfied, demands that are more stringent than they might appear. A utilitarian defense of the experiment is examined, namely that the would-be participants are in a no-loss situation, and it is shown that this defense is seriously flawed. Finally, it is concluded that there is no justification for amending the Declaration of Helsinki. ▣

Some circumstantial evidence is very strong, as when you find a trout in the milk.

HENRY DAVID THOREAU, *Journal,* 11 November 1850.

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