Book Reviews, Notes and Comments

Edited by
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An appropriate epigraph for this outstanding work could be the well-known aphorism by Henri Louis Mencken: “For every complex problem there is an answer that is clear, simple, and wrong”. In fact, the terms “placebo effect” and “placebo response” are mostly used in a loose fashion to indicate any improvement following an inactive treatment. This inappropriate use has become increasingly frequent since the traditional term placebo, originally used to indicate the effects of an inactive treatment administered by the physician ut aliquid fieri videretur, has been extended to the protocols of various types of clinical trials; particularly (but not only), to double blind randomized trials – the golden standard of Evidence Based Medicine in the evaluation of a new treatment (pharmacological or other) or a new indication of a treatment already in use. The author warns the reader that improvements in these situations can be partly or entirely due to phenomena which have little to do with genuine placebo effects; e.g., spontaneous remission, fluctuation of symptoms, regression towards the mean, physicians’ or patients’ errors, etc. He also effectively argues that the elimination, or at least the reduction, of such confounding is difficult to achieve in clinical practice and in clinical research trials, which requires specific laboratory experiments.

The monograph, much more extensive than the previous “L’effetto placebo. Breve viaggio tra mente e corpo” (Placebo effect. A brief journey into the brain and body) by the same author reviewed in this journal (2013; vol. 49, p. 99-100), is subdivided in five parts. The first is devoted to general concepts and mechanisms of placebo effects; the second and the third to placebo and nocebo effects in a wide variety of different clinical conditions; the fourth to the resulting clinical, ethical and methodological implications; and the last one, to placebo and nocebo effects outside the therapeutic context.

The first section is a well organized meticulous analysis of the infinite variety of the mechanisms underlying placebo responses, ranging from classical (pavlovian) conditioning to the quality of the patient-physician relation and to a variety of social and cultural factors. Conditioning is particularly important in the case of non-conscious endpoints, like endocrine or immunological responses; while mechanisms involving the modulation of expectancies play a major role when the dependent variable is a conscious phenomenon, like pain or depression. The author provides ample and diversified evidence for an important role of subject factors (set), such as trait or state anxiety (e.g. in placebo subjects the latter, but not the former, influences tolerance to pain), and to environmental, social, and cultural factors (setting). For example, placebo responses are more pronounced when subjects are told that the cost of the therapy is high or when the media amplify the potential effectiveness of the treatment under study.

For most of these and related phenomena the author provides whatever evidence is available about neural changes, analyzed mainly by neuroimaging techniques, which may be specifically responsible for (or related to) one or the other type of placebo effect. Contrary to much literature in the neurobehavioral sciences, Benedetti – a neurophysiologist by training, a sophisticated behavioral scientist and a merciless logician – brilliantly succeeds in avoiding those all-too-frequent traps and pontifications by which brain events are assigned the status of dominant independent variables, whereas behavioral responses are reduced to ancillary dependent variables. His frequent digressions to possible evolutionary mechanisms which may account for the phylogenetic development of placebo responses, far from being “just so stories”, strengthen his well balanced analysis of brain-behavior relationships; in other words, his analysis has epistemological implications with an added value beyond the understanding of placebo and nocebo responses. The context of the physician-patient relations in which placebo effects occur is also effectively analyzed, starting with the illustration of the patient’s progress – from the initial “feeling ill” to the search for relief, to the encounter with the therapist, and to the reception of the therapy – and emphasizing the differences between phenomena like empathy and compassion. Empathy, “the feeling that you understand and share another person’s experiences and emotions” (Merriam-Webster), rather than compassion, “the sympathetic consciousness of others’ distress together with a desire to alleviate”, is what maximizes the effectiveness of the therapist’s action.

This review has so far dealt with less than a quarter of the book contents; necessarily, the reader must be left to discover by her- or himself the vast information in the following two sections: an information equally essential for the practitioner, for the clinical research scientist, and for the animal research scientist (yes, placebo effects have also been shown in animals). A large portion of this information deals with the modulation...
of pain, with neurological and mental diseases (witness the ample and controversial literature on the variable differences between the effects of active treatments and placebos in depression), and with endocrine and immunological diseases; by contrast, much less information is available for other fields of major relevance in the health and disease area, like cardiovascular and respiratory diseases.

After jumping over more than half of the book, however, some attention must be drawn to the significant messages in the last two sections. Section 4 addresses a series of thorny problems, starting with ethical questions raised by the use of placebos both in clinical practice, which inevitably involves cheating, and in clinical trials when a more or less effective treatment is already available. The author cautiously provides examples of situations in which such uses might be permissible or vice versa inadmissible – and this reviewer fully agrees with his suggestions; but, the conflict between different or even opposite opinions on these points is constantly escalating. Benedetti also makes some rational proposals aiming at increasing the sensitivity of clinical trials, e.g., by modulating placebo effects in ways suggested by specific experiments (too complex to be reported here), or by identifying the extent to which a placebo component contributes to the effect of an active treatment. Since a therapeutic act of any kind, be it by an active or an inactive treatment, be it by a shaman or by a top gun physician of the third millennium, triggers neural, hormonal and other changes which cause an unavoidable confounding, Benedetti shows that the problems he analyzes portray a situation not unlike that of Heisenberg's uncertainty or indeterminacy principle. Incidentally, the two versions – uncertainty and indeterminacy, the former prevailing in English and the latter in Italian – besides the subtle differences between the respective meanings, are poor equivalents of the original "Unschaerferelation" – imprecise, confused, blurred, out of focus relationship, rather than principle: a more appropriate definition of the confoundings illustrated by Benedetti.

Nevertheless, the author views these formidable obstacles as a strong stimulus for further sophistication of research strategies, rather than a push towards "learned helplessness" (the term used by psychologists to indicate the resigned surrender in the face of insoluble problems). In fact, the last chapter in this section is devoted to complex experiments using different types of active treatments (e.g., opioid and non-opioid analgesics) and different conditions (e.g., open vs hidden treatments and different types of verbal instructions), aimed at assessing either the nature of placebo effects (e.g., whether caused by classical conditioning, or by expectancies, or both) and the underlying neurobiological mechanisms (e.g., presence or absence of a role of endogenous opioids in the production of placebo analgesia). The author also provides some useful suggestions about which simplified forms of this complex experimental armamentarium could be transferred to clinical trials in order to improve the quality of the resulting information.

The last section, devoted to placebo and nocebo effects outside the treatment context, might look at first glance like a curio; but, besides providing some interesting or even startling data, it constitutes a powerful additional support to the significance and variety of mind-body and brain-behavior relations. Several experiments show that placebos can improve physical performance, and a couple of examples is in order here to show the nature of these effects and the resulting ethical problems. In a simulation of a sport competition, resistance to pain – an important asset in many sports – was increased by a placebo treatment. Moreover, treatment with morphine in the training phase before the competition, followed by replacement of the analgesic with a placebo on the day of the competition, produced a larger increase in resistance to pain – which makes that this effect can be obtained without producing abnormal results in doping tests. The effect is blocked by the opioid antagonist naloxone, showing that it is mediated by endogenous opioids. The author ends up in a question to which he prefers not to give an answer: is this to be equated to doping, or not?

In another non-pharmacological experiment, the dependent variables were the force exerted by the quadriceps (lifting a weight by extension of the muscle) and the rate of development of fatigue. Subjects received a placebo with the false instruction that the treatment was a substantial dose of caffeine, and the weight to be lifted was reduced to make them believe that the treatment had "ergogenic" properties. After restoring the original weight, the placebo produced an increase of muscular work and a reduction of fatigue. Combined with classical studies which show the role of peripheral factors in the development of fatigue (biochemical changes in muscles, etc.), these and other data show that muscular performance and fatigue are a joint function of peripheral (bottom up) and central (top down) influences, the latter from a "central governor" exerting a protective effect against potentially harmful extremes of exertion. Still other experiments show that negative expectancies result in a nocebo effect which reduces performance capabilities. And last but not least, various types of cognitive performances can also be enhanced or reduced by manipulation of expectancies.

A highly favorable reviewer must not forget the obligation to signal the imperfections in a work of an otherwise unique value. The vast amount of literature analyzed and quoted would undoubtedly have made the compilation of an author index a herculean (and costly) labor – but, the absence of such an index detracts from the consultation value of the book for a substantial portion of the readership. As concerns errors, typos are exceptionally scarce (at least by today's decreasing standards!); but, the box and figure p. 105-6, devoted to the famous Olds & Milner experiment on CNS self stimulation, indicates the mouse (topo), rather than the rat, as the experimental subject (and in fact, the corresponding reference p. 122 speaks of the rat brain).

Anyway, the perspectives opened by the various parts of this analysis are numerous and highly significant from both the theoretical and the practical viewpoints.
For example, a systematic confrontation between the placebo/nocebo literature and the socio-medical literature on differential effects of attribution processes in different pathological conditions (the patient’s beliefs about what made him sick and/or about what might facilitate recovery) could provide a useful independent cross-validation of data obtained by both approaches and open new research avenues. Susan Sontag’s “Illness as a metaphor”, challenging the “blame the victim” mentality and contradicting related misconceptions in the case of cancer, de facto illustrates an extreme case of absence of positive effects and prevalence of negative effects of attributions. But there are quite a few pathological conditions in which the patient’s beliefs and expectancies exert significant positive effects; and their understanding and exploitation should be an essential part of the therapist’s work. Equivalent considerations could be made for the ample animal and human data on stimulus functions of drugs and state dependence phenomena: considering, for example, that after an active and an inactive treatment have taken control of different responses in a discrimination test such a differential control can be maintained after the dosage of the active treatment has been gradually reduced to “homeopathic” levels.

Finally, one must acknowledge the way in which the author – notoriously the leader in the field covered by this monograph – systematically avoids any temptation to “play God”, in favor of an almost obsessive insistence on unsolved problems and new questions emerging from the data and models so far produced. Rara avis in terris nigroque simillima cygno, as Juvenal might have commented on such an exception to the aggressively competitive tendencies prevailing in today’s research world.

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In the latter years Jane Goodall recognises the fact that chimps and humans are just part of the picture. She founded the Jane Goodall Institutes and the “Roots and Shoots” program. These institutes are now present across the world, financing a myriad of projects, all dedicated to help children and people in need, through education and other efficient means (please, do visit www.janegoodall-italia.org/).

And she still goes around the world, giving a message of hope and dedication.

This little book is precious and inspiring, and is therefore highly recommended to any committed veterinary or to students of animal behaviour, to readers curious of moral issues when dealing with primates, ethologists, and technicians and general staff involved in caring for vertebrate animals in scientific and biomedical institutions. But, most of all, it is a must read for whoever is concerned with a better future, in harmony with the planet we inhabit.

This little and nice book resulted from the interaction between Goodal and Lisa Vozza, a well-known and expert Italian journalist who already successfully exploited the same format in which she served as a kind of enzymatic factor to trigger a scientific author’s capability to put in written words his or her thoughts.

Goodall definitely influenced the way in which scientists and average people interact with animals. It seems therefore useful to remember that the latest trends in the bioethics of animal experimentation showed that after a long and often contrasted period, in which different European countries treated and maintained animal under very different conditions, the European directive 86/609/CEE was issued in 1986; thereafter, in 2014, the maintenance styles and overall conditions for conducting animal experimentation were newly regulated, providing a substantially higher standard for both vertebrate and a few invertebrate species. As a result, the European bioethical landscape was changed, both introducing the 3Rs principle and putting under special protection Cephalopoda molluscs such as octopus, squid and cuttlefish [1].

European citizens are still in need of a more mature zoo-anthropological culture, having an increasingly attitude to appreciate regulations and norms minimizing animal suffering at many levels, including refinement procedures for farm animals. So presently, dogs, cats, monkeys and apes deserve a special treatment, when exploited as experimental species.

We are now involved in those types of bioethical research, by analysing, for instance, the behaviour of a lesser ape, the “White handed gibbon” (Hylobates lar) about procedures aimed at contrasting the effects of an unnaturally prolonged early isolation on the behaviour of a sub-adult subject. We are also beginning a new research line on cuttlefish, with the aim to measure their actual capabilities to display vertebrates-like, plastic behavioural patterns of predation.

This Goodall and Vozza essay is highly recommended to any committed veterinarian or students or animal bioethologist, including technicians and staff involved in caring of vertebrate animals in scientific and biomedical institutions.

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The behaviour of the adolescent exploring the environment around him has always been a source of concern for parents, and each generation seems to have to deal with completely new problems compared to previous generations. So it is commonly held that the today’s teenagers are particularly inclined to indulge the assumption of alcohol in intoxicating amounts. Probably they do not differ so much from previous generations, considering that the first Italian law on alcoholism, promulgated in 1913, was well aware of the scourge of childhood drinking, as surveys conducted in primary schools in the major towns of the Kingdom clearly demonstrated. But anyhow: Thomas theorem that “If men define situations as real, they are real in their consequences”, is probably also valid on this occasion considering the institutional alarm arisen from the issue.

The book by Alessandra Di Pietro dedicated to teenage drinking is therefore welcome. The author is a journalist who wanted to address the problem because she is the mother of two pre-teens and then personally curious to know exactly how to respond when the time comes. However, fortunately the book is not the product of the concerns of an anxious mother but rather the careful work of a reporter who poke her nose in the right places with detached curiosity. The author in fact went across Italy interviewing boys and girls, as well as privileged observers of the phenomenon selected within bartenders, marketing agents, law enforcement agents, school officials, and psychotherapists. Part of the book
information suitable for a rational and calm approach to the problem.

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Ebola disappeared from our screens and our newspapers. As other major epidemic emergencies, it came like a punch in our homes and invaded the media, spreading anxiety in the population and an incredible fear. With the same speed it is gone, vaporized: Ebola what? And the 27,000 cases of the past 12 months, with over 11,000 deaths?

Roberto Satolli felt himself unable to write on Ebola from its Milan office, and accepted the invitation of his old friend Gino Strada, diving in the worst epidemic site: the center of Lakka Ebola in Sierra Leone that Gino quickly set up to manage the outbreak.

He went there not only as a journalist reporter, but also as a doctor, carrying with him a smart protocol for an innovative therapy that could usefully deal with the virus. On the way back, after the necessary dangerous quarantine, he put pen to paper and Red Zone came out, published by Feltrinelli in the “White series”.

Satolli shared this task with Gino Strada and received a lively contribution from Fabrizio Pulvirenti, an infectious disease doctor, who was a volunteer in the Emergency center of Lakka, Sierra Leone and recovered from an Ebola infection acquired in the hospital.

Thousands of volunteer doctors, nurses, logisticians, etc. have helped to stop the most terrible infectious epidemic of this century, paying a very high contribution of life: 874 were infected by Ebola and 509 died.

The book is enjoyable and fast paced: the chronicle is compelling and keeps the reader on a blade of anxiety, as if he were experiencing first hand the tremendous steps of lives that flow into a high-speed framework where death and despair coexist with heroic efforts to fight a disease that proceeds inexorably through the frustration of those who try to defeat it.

But the book is not limited to a breathtaking chroni-
cle; it tackles with clarity the limits and errors that people and institutions have made; the local and international conflicts that Ebola has triggered, unfortunately already seen in many other large-scale international public health emergencies.

In the absence of a single strong local coordination, conflicts between humanitarian organizations present in the field were inevitable, but the worst is well described in the book: an approach away from the patient to protect the operator where the patient is seen, but not touched. In the center Emergency Lakka, unlike in other Ebola treatment centers, the patient was considered as a person to take care of, with the best possible treatment available, including measures of rehydration and saline reconstitution, which, as proved, reduce the lethality of the disease.

I cannot forget the charge that we received in the hospital in Lacor, Uganda, in the outbreak of Ebola in year 2000, when the death of 13 health workers was considered a result of the wrong strategy to take care of the seriously ill patients and not limited to remote viewing as practiced at a nearby government hospital.

The book touches the difficult issue of the compassionate treatment for those affected by Ebola: a generous attempt to introduce a rational use of a drug with a cardiac protocol stopped by the local bureaucracy and contrasted by international scientific community, not free from conflicts of interest with drug manufacturers.

Very interesting the story of Fabrizio Pulvirenti, infectious disease specialist from Sicily, volunteer in the Lakka Emergency center. He became infected with the virus despite the strict observance of safety rules: a breathtaking path to save the life of a generous man; a story with a happy ending thanks to the appropriate response of the structure of Emergency and of the Spallanzani Hospital in Rome.

The book addresses the inefficiency of some international organizations, in particular the WHO, slow to recognize the emergency and to act accordingly: together with local governments the problem was minimized and too much time passed before it was possible to use the IHR (International Health Regulations) tool, delaying the massive international mobilization needed to stop the epidemic. A delay only recently recognized by the Committee established (Ebola Interim Assessment Panel) which stated that “significant and unjustifiable delays occurred in the declaration of a Public Health Emergency of International Concern (PHEIC) by WHO”.

A book that is a must for any health care professional, but also, for once, a book with a positive truth: not only easy criticism from the window, but the chronicle of a life lived at high voltage described with professional coolness, but not without documented critical harbinger of substantial changes.

A tool of scientific potential of great impact for young people, but also an effective weapon to fight away from a scientific truth that now is a serious epidemic in our society.

Counter Ebola and the relentless continuous emergence of epidemic risk at international level cannot just be business of the specialists or of the emergency teams: the most effective prevention of these risks is undoubtedly an adequate systematic approach to the emergence of the society as a whole: a profound cultural change that will educate to live with these risks, the continuous sharing of best scientific evidence, in contrast to the myths and falsehoods that surround the epidemic.

Viruses and bacteria do not recognize borders: prevention is not the concern of some desperate places on the planet to offer solidarity, but is a global need, for each of us, each family in each country. So the publication of Red Zone is welcome as a useful tool and as a functional presence in the library of every family.

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