# Paradox of placebo effect

SIR — When testing for the effectiveness of a drug in ameliorating a disease, it is common practice to compare the treated group to a control population, matched in all essential respects, to whom is administered a placebo containing substances that are presumed to be inert. The placebo-controlled trial is an integral part of evidence-based medicine. Although the nonspecific effects of placebos are widely studied, the possibility that the chemicals used as placebos may have specific effects has received virtually no attention.

The US Food and Drug Administration sets no regulations on the constituents of placebos, and any guidelines are at best informal. Astonishingly, no systematic efforts are made to ensure the inertness of placebos: there is nothing validating the placebo standard against which other agents are measured. Further, the drug companies funding the trials control the placebo ingredients.

The identity of the placebo and fillers used with the experimental drug are rarely stated in scientific studies. In one exception to this practice, several early papers exploring the use of cholesterol-lowering agents to curb heart disease did in fact name the placebos used: olive oil in one case[1], and corn oil in another[2]. Mono- and poly-unsaturates such as olive oil and corn oil are now widely known to decrease low-density lipoproteins[3], so that with hindsight these agents may not have been inert with respect to the outcome studied. Indeed, it was noted in one such study[2] that the rate of cardiac mortality was lower in the placebo group than expected.

How can we be sure that placebos are free of specific effects? Few if any agents are truly inert, and placebos are given systematically over prolonged periods. Even substances that are not absorbed, such as methylcellulose (which reduces cholesterol), can have significant effects.

Placebos used across trials may differ: such differences are among many factors that may underlie outcome differences in otherwise similar trials. Placebos used across trials may, on the other hand, be similar, or have similar effects: thus we cannot rely on meta-analyses to cancel differing specific effects of placebos. In addition, it is felt by many that the correct solution to the thorny problem of irreconcilable smaller studies is a single very large trial rather than a meta-analysis. Indeed, in some fields the evidential basis of a population-based treatment regimen rests on the outcome of a single significant trial. The Scandinavian Simvastatin Survival Study[4] is the lone cholesterol-lowering trial, among many, that showed improved overall mortality with cholesterol reduction during the time of treatment, even in the secondary prevention population; it is cited as proof of the benefits of cholesterol reduction therapy. Clearly, small effects by a placebo may be pivotal when clinical practice is determined by the results of a single very large trial, whose large size is necessitated by small effect size of the treatment.

Until recently the possibility of small effects of placebos accruing over long periods may not have been of serious concern because most trials sought large effects in small subject populations studied over relatively short times. Large-scale trials (or aggregate analyses of trials) involving thousands of individuals studied over many years and seeking small effects (see, for example, ref. 5) are a modern phenomenon. It is in this setting that small beneficial or harmful effects of placebos could be significant. An apparent positive, negative or null effect of a drug may instead be the consequence of a negative, positive or same-direction effect of the placebo.

What should be done? First, it is essential that all studies should state the composition of the placebos as well as all fillers included with the drugs. Studies should be carried out to test for possible specific effects of placebo agents, even though this process will be fraught with difficulty. Meanwhile, in interpreting the results of prior trials, we should be aware that possible specific effects of placebos represent a potential confounding factor that may be vital to interpreting the study results.

The foundation of evidence-based medicine is undermined by the absence of evidence that placebos are inert. It is paradoxical that there is no standard of evidence to support the standard of evidence.

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# Vatican confusion

SIR — Recent correspondence (*Nature* **372**, 124; 1994 & **373**, 278; 1995) demonstrates the confusion that the BC/AD baseline of the calendar can generate. Now it appears that even the Pope is confused. In his Apostolic Letter *Tertio Millennio Adveniente* (Libreria Editrice Vaticana, 1994), he proclaims (p. 16) that *Anno bismillesimo Magnum idcirco erit Iubilaeum* ("The Great Jubilee will be therefore on the 2000th year"), and refers (p. 25) to the *Magnum Iubilaeum exeunte altero millennio* ("The Great Jubilee at the end of the second millennium") and (p. 40) to the *Magnum Iubilaeum quod annum bismillesimum concludet* ("The Great Jubilee which closes the 2000th year"); but then he states (p. 41) that the *Christiani invitantur ut se tertii millennii Magni Iubilaei ab initium incohandum expediant* ("The Christians are invited to prepare themselves for the Great Jubilee beginning at the start of the third millennium") and concludes (p. 50) by asking the Virgin Mary to be like a guiding star *Christianis procedentibus tertii millennii in Magnum Iubilaeum* ("for the Christians proceeding toward the Great Jubilee of the third millennium").

Until p. 40 the Pope correctly assigns the year 2000 to the second millennium; but after p. 40 he assigns it incorrectly to the third millennium. Following a procedure initiated by Pope Alexander VI in AD 1500, the Great Jubilee proclaimed by John Paul II will start on Christmas Eve of the year 1999 and terminate on Christmas Eve of the year 2000, seven days before the beginning of the third millennium.

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# Side by side

SIR — The juxtaposition of two leading articles in a recent issue of *Nature* (**374**, 392; 1995) was mildly entertaining, and mightily scaring.

In the left-hand column ("Equity and addiction") is was suggested that perhaps, in order to "save some people's lives", "users of [marijuana, tobacco and alcohol] should require a medical licence to do so".

In the right-hand column ("Murder and the metro") it was stated that "[t]he outlook for strictly technical control of the ingredients of the gas [sarin] are [*sic*] not bright, given the damage inflicted upon liberal societies by protective regulations that are themselves *intrusive and thus illiberal*". (My italics.)

Should one infer that, in your view, regulations are less "illiberal and intrusive" when they strictly regulate the private lives of individuals than when they strictly regulate corporations?

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