A reader objects to the apparent method of killing infected pigs in Malaysia. Considerable discussion is sparked by a News article about the role of the placebo effect in testing drugs for the treatment of depression. One reader comments that "Clearly, traditional views of drug action need to be revised." Another says, "[Antidepressant treatments] are better...than placebos in reducing the symptoms of depression." The dialog about physician-scientists continues. And cave art from France and Africa is compared.

Inhumane Death?

Martin Enserink (News of the Week, 16 Apr., p. 406) reports the isolation and characterization of a new virus in Malaysia, transmitted to humans by pigs. Accompanying this article are two pictures (p. 407), one of the scientists who isolated the virus and another of workers killing possibly infected pigs. To my surprise, the pigs, seen being thrown into a large pit, look very much alive. It appears that measures were not taken to ensure a painless termination of life, and the pigs were sent to a cruel death by suffocation.

As ethical demands, such as laboratory animal care and use guidelines, are strictly enforced by scientific journals worldwide, I believe that the apparently cruel way in which these pigs were put to death should have been mentioned and criticized.

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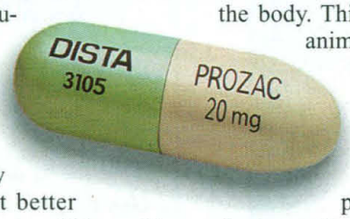
Response

We, too, were surprised to discover when we examined the printed version of the picture that the pigs appear to be alive. The caption material supplied by the photo agency made no mention of the fact, nor was it clear from the draft pages we reviewed.—**News Editors**

Pills or Placebos?

In his article about the placebo effect problem in psychopharmacology (News Focus, 9 Apr., p. 238), Martin Enserink does not discuss one feature of clinical trial design that makes interpretation of results even more problematic. To maximize the chance of demonstrating efficacy, it is common for subjects in trials of antidepressants initially to be given a placebo. Only those who do not improve are then randomized to the study drug or a placebo. This "enriched" design is not described in the labels of such drugs, and in actual clinical practice the population using these drugs is not limited to the subgroup for which efficacy was demonstrated in clinical trials: those initially displaying no placebo effect. A similar design is used in trials of other drugs where all subjects are initially simply observed. Only those who do not improve during this "run-in" period are randomized to the study drug or placebo. Run-in trials are less problematic than enriched trials because actual clinical practice can at least incorporate a run-in observation period. One final comment: A true placebo effect as described by Enserink—patients get better because they believe they could be getting a real drug—can be distinguished from a natural history effect only if there is a third arm in a trial in which subjects receive neither the study drug nor a placebo. And any natural history effect observed in such a trial cannot be distinguished from the Hawthorne effect (the effect of being observed or monitored).



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Enserink's article emphasizes the methodological and ethical issues fostered by the use of placebos in research. The scientific issues, namely, identifying the underlying mechanisms of placebo effects, are also critical. Placebo effects provide enormous opportunities to identify the interplay of the interpersonal environment, cognitions, and brain processes that in turn affect changes in other biological and psychological spheres. How can placebo responses be evoked and optimized? Can these processes be mobilized or invoked in other ways (for example, biochemical or psychosocial) that equally influence health, well-being, and psychiatric symptoms? What are the parameters along which dose-response relations might be demonstrated? Are there psychokinetics that reveal the processes and how environmental input, cognitions, and brain processes promote change?

There is rarely a question about whether placebo effects are real—that is, whether they produce change. The history of medicine is strewn with examples of the ameliorative and curative effects of suggestion, belief, and expectations, as punctuated by such familiar figures as Anton Mesmer in the late 1700s. It is difficult to find such a reliable phenomenon that has lacked scientific attention.

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The News article "Can the placebo be the cure?" reminds us of 20 years of research by this and other laboratories. This work shows that the effects of drugs, antidepressants included, grow with the passage of time after even a single treatment, and continue to do so after the drug is out of the body. This has been demonstrated in animals and humans for so many types of drugs and end points that it likely represents a general principle of biological functioning. The raison d'être for this phenomenon—"time dependent sensitization" (TDS)—relates to the nonspecific, "foreign,/stressful" aspect of drugs (rather than their pharmacology), perceived by the organism seeing them for the first time or after a hiatus. One would therefore expect—and we have shown many times in animals (*1*)—that TDS induced by drugs is mimicked by drug vehicles (that is, placebos) as well as by numerous types of nondrug stressors. In other words, placebos do the same thing as drugs when they are also perceived as stressors. Regarding TDS, drugs and placebos differ only in that placebos are stressors of lesser intensity. TDS undoubtedly reflects a primitive nonspecific surveillance system by which cells monitor and remember stressful stimuli—such as drugs or their vehicles—which are too small and structurally simple to be perceived as antigens and trigger an immune response.

Clinical examples of TDS after antidepressant treatment are seen in studies using clomipramine (*2*) and electroconvulsive therapy (ECT) (*3*). Although the antidepressant treatment—drug or ECT—was given only once, clinical effects grew with time, so that 3 weeks later, the TDS regime produced the same degree of improvement seen when these agents were given over a period of time. Clearly, traditional views of drug action need to be revised. Neither shooting the

messenger nor denial is the answer.

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Enserink's article describes Irving Kirsch's meta-analysis of the effects of antidepressant drugs, as well as his analysis of data submitted to the Food and Drug Administration from 30 trials of five antidepressants. Kirsch's analyses showed that at least three-quarters of the drugs' effectiveness was due to the placebo effect. It also pointed out the resistance of drug companies and psychiatrists to accepting his findings.

The recognition of the centrality of expectancies to both making people miserable and helping them to change has long been a minority view in the mental health field (*1*). The placebo effect is psychological, so it is easy to argue that it lies behind the effectiveness of multiple psychological therapies with differing (and even contradictory) rationales for treating depression, anxiety, and other forms of distress. Furthermore, Kirsch's demonstration, that therapeutic effectiveness is substantially increased by hypnotizing a client before intervening (for example, with a cognitive or behavioral treatment) (*2*), provides a psychological counterpart to the active placebo. That is, individuals who feel drug side effects, or who experience the novelty of closing their eyes and relaxing while being talked to by a therapist in a situation labeled as hypnosis, are more likely to have the sense that something important is happening. This leads to a greater expectancy that they will feel better.

Over the years, therapists have been resistant to recognizing that most of their effectiveness can be understood in terms of the placebo effect. The same economic self-interest and professional identity maintenance that explain the resistance of drug companies and psychiatrists to Kirsch's findings explain therapists' resistance as well. As a result, the mental health treatment community continues in its attempt to control for the placebo effect rather than learn how to maximize it.

The best predictor of future behavior is past behavior. Placebo disparagement has

been going on for decades. I see no reason to believe that mere data should cause it to change.

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Citing the disappointing results of tests of the novel Merck compound and the recent Agency for Health Care Policy (AHCPR) meta-analysis which indicated the similar efficacy of the new selective serotonin reuptake inhibitors (SSRIs) and the older tricyclic antidepressants (TCAs), Enserink suggests that there may be no value in active treatment for depression. There are several problems with this presentation.

The full AHCPR report is not yet widely available. News reports have emphasized the similarity of TCAs and SSRIs in efficacy, with both classes of drugs said to be better than placebos. They have not discussed the differences in the side-effect profile. The newer drugs are less sedating, do not produce weight gain, and have less potential for lethality with overdose.

There are several clinical trials showing the efficacy of psychotherapies developed specifically for depression that are more efficacious than controls or placebos, or both (*1*). Psychotherapies are important alternatives to medication. Women of childbearing years are the highest risk group for depression and often can not take medications during pregnancy and lactation (*2*).

Patients in any clinical trial receiving placebos are not receiving "no treatment." They receive a full psychiatric evaluation, a chance to talk about their problems, and regularly timed assessments of clinical status with a mental health professional. Even brief psychological attention can have an impact on the course of an illness (*3*). Some portion of the psychological attention effect is captured in the placebo control group. The dismissive slant of Enserink's article, if accepted, could lead to further undertreatment of depression.

The answer to "Can the placebo be the cure?" is "not very well." There are a range of new drugs and psychotherapies for depression whose efficacy has been established through controlled clinical trials. They are better than no treatment and even better than placebos in reducing the symptoms of depression.

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When my colleagues and I researched psychopharmacologic agents in the 1950s, it was abundantly clear that this was an enormously complicated area requiring the development of research methodology to clarify the issues and to tease out the many elements at work. We concluded that it is best to think of a range of nonspecific factors to account for the response to a medication (which can be both positive and negative), rather than speaking of a placebo reaction or a placebo reactor as an explanation. There has been an enormous amount of research on nonspecific factors in drug research, particularly in psychopharmacology. It is worth noting, also, that depression is a fatal disease in the 15% or more of its sufferers who commit suicide.

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The Physician-Scientist Template

In a letter by David A. Hume ((*Science*'s Compass, 2 Apr., p. 49), it is alleged that physician-scientists are no worse off than "harried university professors trying to balance research with increasing teaching and administrative responsibilities," and it is further questioned whether there is in fact evidence for a decline in disease-oriented research. Additionally, the point is raised that disease-oriented research is increasingly being done by "full-time professional scientists" and that this effort not only should offset any decline in such research done by physician-scientists but that the "professional scientist" template is the most desirable one with which to carry out disease-oriented research. All told, the implication of the letter is that there should be little concern about the decline in physician-scientists.

But perhaps we should back up. First