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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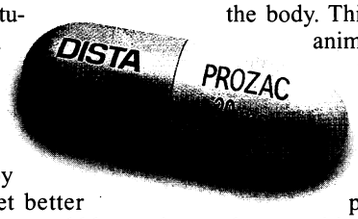
Response

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