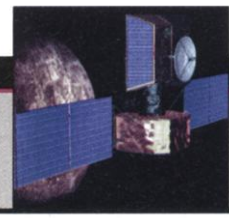
PAGE 421
How a plant invader thrives



423
Europe's space science choices

BIOETHICS

Helsinki's New Clinical Rules: Fewer Placebos, More Disclosure

After 3 years of intense debate, medical researchers and ethicists have agreed on international standards that would dramatically tighten the rules for clinical research and put new limitations on the risks to which patients may be exposed. Meeting in Edinburgh, U.K., on 7 October, the general assembly of the World Medical Association (WMA) gave a clear victory to patient-advocacy groups seeking a change in the way experimentation on humans is conducted. The WMA voted to approve a revised version of the 1964 Declaration of Helsinki, the cornerstone of clinical research ethics, that reduces ambiguity in existing guidelines and could force changes in the design of future drug trials.

Already, critics are warning that the newly proposed restrictions on the use of placebos, or dummy treatments, are at odds with common practice and clash with policies of the U.S. Food and Drug Administration (FDA). Indeed, researchers and drug companies may soon find themselves in an ethical conundrum: In order to test a drug for approval on the U.S. market, they would have to use research protocols that the declaration specifically rejects. Journal editors would be affected as well: Those wishing to abide by the Helsinki rules would have to turn away articles based on methods that are widely used today.

Global view. "Our objective is to protect our patients," says Delon Human of the World Medical Association.

The controversy centers on the use of placebos to get quick and clear-cut results in clinical trials. According to the new declaration, placebos may be used only when there are no other therapies available for comparison with a test procedure. If there's an appropriate drug already on the market, then a trial should compare any new treatment to the existing product, the declaration says. That way, patients volunteering to participate in a trial wouldn't run the risk of getting a fake treatment and being worse off as a consequence of participating. "Our main objective is to protect our patients," says WMA secretary-general Delon Human.

Patient groups are jubilant. "It's a major improvement," says Peter Lurie of Public Citizen, a group in Washington, D.C., that lobbied heavily to influence the outcome of the revision process. But FDA officials Robert Temple and Susan Ellenberg, who pleaded in favor of placebo-controlled trials in a paper in last month's *Annals of Internal Medicine*, disagree strongly. The declaration's paragraph on placebos "doesn't make sense to me," says Temple.

"The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods."

—New Declaration of Helsinki, approved October 2000

Placebo use has led to major controversies over the past few years—for instance, in trials in Africa and Asia to find out whether short-term use of an antiviral drug could prevent the transmission of HIV from a mother to her newborn baby. Public Citizen decried those trials, arguing that by using a placebo, the researchers allowed some babies to become infected, although they had the means to prevent it. But researchers argued that the trials had to be designed this way to get credible information. Besides, they said, their approach was ethical, because the mothers wouldn't have received the drugs if they hadn't been included in the trial (*Science*, 27 February 1998, p. 1299).

Researchers and activists have also faulted the use of placebo control groups in testing drugs for non–life-threatening ailments in the Western world, such as depression, chronic pain, and arthritis. Stopping treatment for the sake of a trial, they argue, causes unnecessary suffering and, in the case of mental illness, may cause patients to become violent to themselves or others. But Temple argues that comparing new drugs to a placebo is often the only way to establish efficacy, especially in treating diseases like depression, where success rates vary widely from trial to trial (*Science*, 21 April, p. 416).

The Declaration of Helsinki—prompted originally by the gruesome medical experiments of the Nazi era—contained a phrase suggesting that placebo use should be restricted, but the wording wasn't explicit. To end the ambiguity, expert groups, including the American Medical Association, pushed for a revision in 1997. Several early drafts drew strong criticism from opponents of placebo-controlled studies, like Lurie. They rejected one draft, for example, from a panel chaired by prominent Yale bioethicist Robert Levine. Levine's group proposed relaxing the Helsinki rules considerably in 1999 to allow the use of placebos if they don't cause death or disability. This version also implied that research subjects in the developing world should get the best care normally available to them. But Levine's attempt proved "totally unacceptable" to the medical community, says WMA's Human. "It was very useful," says Human, "because it defined exactly what we didn't want."

The final version, drawn up by a four-member committee that included Human, does exactly the opposite, stating that new drugs should be tested against the best current treatments—period. This standard would rule out the controversial placebo-controlled perinatal HIV trials, says Human. He also

CREDIT: WORLD MEDICAL ASSOCIATION

suggests that the use of placebo control groups in the developed world should end. "We're very pleased," says Harvard University epidemiologist Karin Michels, who, along with her colleague Kenneth Rothman, has long argued against the widespread use of placebos in clinical trials. "We really see this as a big success."

The FDA says it's studying the revised document and doesn't have an official reaction yet. But Temple, associate director for medical policy in the agency's Center for Drug Evaluation and Research, says it will be hard to live by the letter of the declaration and carry out trials that meet the FDA's demands for scientific rigor. "The answer is not clear," he says. Human agrees: Adhering to FDA guidelines could mean violating the new Helsinki document. But the FDA isn't always right, Human suggests: "Bob Temple and the FDA are one voice. But we are a global organization, and this was a consultation from one side of the world to the other."

The new document contains several other provisions aimed at strengthening the patient's position. For instance, it asks researchers to divulge to participants how the trial is funded and whether they have any conflicts of interest. Such disclosures are rarely required now.

Another surprising provision, some say, is that the new document asks that all study results, "negative as well as positive, should be published or publicly available." "That is really wonderful news," says Kay Dickersin, who directs the Center for Clinical Trials and Evidence-Based Healthcare at Brown University in Providence, Rhode Island. Currently, trials showing that a drug has no efficacy are often buried, says Dickersin. Researchers don't get around to writing them up, journal editors don't want to waste space on them, and pharmaceutical companies don't want to publicize their failures. The result of this so-called "publication bias" is often an unrealistically rosy picture of a drug's efficacy, which the new declaration may help prevent, says Dickersin.

It isn't clear that any of these new principles will be widely accepted, however, because the declaration doesn't have the power of law. "But you have to start somewhere," says Human. "This is an ethical document. What we hope is that it will be adopted in many national regulations and legislation."

–MARTIN ENSERINK

ARCHAEOLOGY

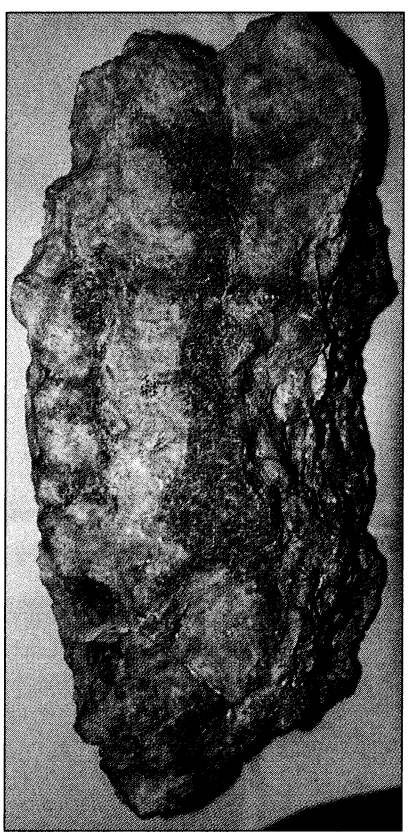
Paintings in Italian Cave May Be Oldest Yet

Traces of what could be the world's oldest known cave paintings have been found in northern Italy. Stone slabs bearing images of an animal and a half-human, half-beast figure were uncovered during excavations by an Italian team at the Fumane Cave northwest of Verona. The slabs, painted with red ochre, had apparently fallen from the cave roof and become embedded in floor sediments previously dated to between 32,000 and 36,500 years ago. That would make the images at least as ancient as some found in the Grotte Chauvet in southern France—the current record holder at 32,000 years—and possibly even older (*Science*, 12 February 1999, p. 920). More important, cave art experts say, the new paintings bolster other evidence that humans engaged in sophisticated symbolic expression much earlier than once thought.

"This is an extremely exciting discovery," says archaeologist Randall White of New York University. Cave art expert Michel Lorblanchet of the University of Toulouse in France agrees. "The Grotte Chauvet has shown that we already had a very elaborated art" by 32,000 years ago. With Fumane, Lorblanchet says, "we now have confirmation."

Moreover, White and Lorblanchet say that there is little reason to doubt that the paintings are as old as the Italian team claims. "The [radiocarbon] dating is even better" than at Chauvet, Lorblanchet says. At Chauvet, very small samples of charcoal drawings were taken directly from the cave walls—a tricky technique that is prone to error. Although the inorganic red ochre paintings at Fumane cannot be dated by similar techniques, radiocarbon dates from plant and animal remains buried in the cave floor sediments where the art was found "are practically sure," Lorblanchet says.

Fumane Cave, which has been under excavation since 1988, had already revealed rich evidence of occupation by early humans, including stone tools. The painted slabs were discovered last year but kept a closely guarded secret until this week. Paleontologist Alberto Broglio of the University of Ferrara, who co-directs the dig with geologist Mauro Cremaschi at the University of Milan, told *Science* that the paintings were covered with a thin layer of calcite that made them difficult to see. This summer an Italian art restorer removed much of the calcite. Although the team has not yet figured out what the images on three of the slabs represent, the other two appear to depict some sort of four-legged beast and an 18-centimeter-tall human figure with the head of an animal—which Broglio says is similar to images often seen in more recent caves and called "sorcerers" by cave art experts.



Symbolic find. Red ochre drawing (18 cm long) resembles figures found in France and Germany from the same period.

CREDIT: A. BROGLIO

Lorblanchet says that the finding of a sorcerer at Fumane "does not surprise me," because a similar motif—a strange hybrid of rhinoceros and human—has also been found at Chauvet. Another spectacular example, a statuette of a human with a lion's head dated to at least 30,000 years ago, was uncovered in southern Germany in 1939. With the discovery at Fumane, White says, "we now have this image in three different places during this early time period."

This concurrence has cave art experts re-