that the "radiation problem is very severe" and predicted it will be hard to overcome. But Goldin says both robots and humans ultimately will be needed for Mars exploration.

The working group has been asked to set near- and long-term goals for the kinds of technology and research infrastructure needed. A self-described "cheerleader" for the program, Baltimore says that the venture "is a real opportunity for thinking in novel ways about programs that cut across two agencies. ... Interdisciplinary science is on everyone's tongue. Today, it's a reality."

–ANDREW LAWLER

PSYCHIATRY

Are Placebo-Controlled Drug Trials Ethical?

HOUSTON—The psychiatric research community is increasingly polarized by a seemingly simple question: Is it ethical to use placebos in drug trials? Specifically, can you give some of your patients a dummy pill, if it means suspending their regular medication and possibly worsening their symptoms? Critics argue that doing so makes patients suffer unnecessarily and may drive some to suicide. But the Food and Drug Administration (FDA) has insisted that placebo-controlled trials are the only scientifically sound way to test the efficacy of most psychiatric drugs. Drug companies say they have no choice but to comply, and most researchers have gone along—some of them reluctantly.

> **"If the patient was your son or your mother, would you withdraw active treatment?"**
>
> —Karin Michels

Now, the FDA has two large meta-analyses to defend its policy. Both show that being in a placebo group does not increase the risk of suicide. But those studies—the most definitive to date—seem unlikely to quell the controversy. At a meeting* earlier this month where one of the studies was presented, critics lashed out again at placebo-controlled trials, calling them "unethical" and "immoral." Karin Michels, a clinical epidemiologist from Harvard University, asked: "If the patient was your son or your mother, would you withdraw active treatment from them for the sake of science?"

Instead of using fake pills, critics argue that new psychiatric drugs should be compared to one of the many drugs already on the market. Nobody would even consider using placebos for such treatable diseases as cancer and AIDS, Michels pointed out, adding that the practice violates the Declaration of Helsinki. Worse still, some psychiatric patients sign up for such trials without fully understanding what they're getting into, said Harold Vanderpool of the University of Texas (UT) Medical Branch in Galveston. For these reasons, Institutional Review Boards (IRBs), the panels at universities and hospitals that scrutinize trials for human risks, are increasingly loath to approve the use of placebos in psychiatric trials, says Paula Knudson, who administers an IRB at UT Houston.

But FDA maintains that psychiatric drugs—and some others, such as antihypertensives—are a special case because their effects are notoriously hard to prove. It's common in these trials for 30% to 50% of the patients in the placebo group to improve, thanks to a phenomenon called the placebo effect, while those on the real drug improve just a bit more. Indeed, even already-approved drugs regularly fail to beat placebos in later trials. If all FDA demanded was that a new drug perform as well as an old one, it would have no way of knowing how much of that improvement was caused by the placebo effect, officials say.

Because the placebo effect is so fickle, and nobody knows how to reduce it, FDA usually recommends that psychiatric drugs be tested in three-armed trials, in which a new drug is compared to a placebo and an existing treatment. If both drugs fail to beat the placebo, the whole trial is written off as a failure. Some people may be worse off from getting a placebo instead of an approved treatment, admits Thomas Laughren, team leader of FDA's Psychiatric Drug Products Group, but that's an acceptable risk as long as patients' lives are not at stake.

Laughren believes they are not. He and his colleagues conducted a meta-analysis of every recent trial submitted to FDA to win approval for eight new antidepressants (including blockbusters such as Prozac and Zoloft) and four antipsychotic drugs. More than 42,000 patients took part in these trials. In the antidepressant trials, 0.02% of the patients in the placebo group committed suicide during the trial, compared with 0.10% in the experimental drug groups and 0.13% in the groups that received an older drug. Laughren cautioned that those results must still be corrected for the amount of time patients spent in the trial, but he was confident that won't significantly alter the outcome. Trials with schizophrenic patients showed similar results. And the outcomes also match those from a smaller study led by psychiatrist Arif Khan from the Northwest Clinical Research Center in Bellevue, Washington, who looked at FDA data from seven antidepressant trials that together enrolled almost 20,000 people. The study, published in the April *Archives of General Psychiatry*, also failed to see an increased suicide risk.

But the critics are unimpressed. The Khan paper, for instance, is accompanied by six commentaries—three of them arguing that the study doesn't justify the use of placebo controls. Suicide is just one risk psychiatric patients face, says Michels. "Shouldn't we also think of the quality of life of the people we're withholding the active treatment from?" she asks. And Vera Hassner Sharav, president and founder of a New York City lobby group called Citizens for Responsible Care and Research, adds that suicide rates in all trial groups may have been increased; simply enrolling in a study that includes a placebo arm causes great stress and anxiety in some patients, she says. Michels and Hassner Sharav argue that trials that compare two active drugs could produce statistically relevant outcomes if they had more patients, time, and money.

Despite the arguments, participants at the Houston meeting did find common ground. Only patients fully capable of making a sound decision should be enrolled in trials, and they should be informed as fully as possible. Researchers can also reduce risks by screening out patients likely to harm themselves or others and by making sure there's a friend or family member on standby. IRBs should be especially vigilant, says Knudson. Her own panel has sometimes required that severely depressed or psychotic patients be hospitalized for the first 3 weeks of a trial to make sure they're okay. Pharmaceutical companies and researchers don't necessarily like these restrictions, she concedes, but they do provide a safeguard.

–MARTIN ENSERINK

PALEONTOLOGY

Revealing a Dinosaur's Heart of Stone

In the fall of 1998, Andrew Kuzmitz, a physician in Ashland, Oregon, invited seven cardiologists to a local hospital to view a computerized tomography (CT) scan. The experts all agreed on what they were seeing: two large, oval chambers or ventricles, divided by a septum. "Every one of them said, 'It's a heart,' " says Kuzmitz. But this was no ordinary heart: It belonged to a 66-million-year-old dinosaur. "As soon as I put the scan

* Placebo in mental health research: Science, ethics and the law, UT Houston, 7 to 8 April.

on the screen, the [cardiologists] were like little kids again," says Kuzmitz. "They couldn't believe what they were seeing."

The rare specimen—the first dinosaur heart known—was discovered inside the nearly complete skeleton of *Thescelosaurus*, a small, plant-eating dinosaur, as Kuzmitz and his co-authors report on page 503 of this issue. The heart's anatomy is more like that of birds and mammals than crocodiles or other reptiles, the team says. And a heart that beats like a bird's suggests that this dinosaur's metabolic rate would have been more like that of an endotherm (a warm-blooded animal) than an ectotherm (a cold-blooded animal), providing yet another feature shared by dinosaurs and their putative feathered relatives, the team asserts.

Heart of the matter. Stone concretion inside this dinosaur's ribcage turned out to be its heart.

CREDIT: JIM PAGE/NC STATE MUSEUM OF NATURAL SCIENCES

"I'm afraid that this little dinosaur would have had an 'unreasonably' high metabolic rate, one approaching that of birds," says co-author Dale Russell of the North Carolina State Museum of Natural Sciences and North Carolina State University in Raleigh. Until now, Russell has been skeptical about the evidence suggesting that dinosaurs' metabolic rates reached those of birds.

Some researchers want to inspect the evidence personally before accepting that the concretion is a heart, and others are already challenging the anatomical interpretations, but most are impressed. "It is a fantastic discovery," says Jack Horner, a dinosaur paleontologist at Montana State University's Museum of the Rockies in Bozeman. "It just shows you what you can find if you keep your eyes and mind open."

Michael Hammer, a professional fossil preparator from Jacksonville, Oregon, chanced on the skeleton in South Dakota's Hell's Creek Formation in 1993. Tucked beneath the dinosaur's upper ribcage in its thoracic cavity was a rust-colored concretion, the kind of annoying rocky material that paleontologists typically chisel away when cleaning a specimen. Hammer, however, knew that such concretions sometimes carry a surprise; he has unearthed similar concretions along the Pacific Northwest coast and carefully broken them open to find entire fossilized crabs or the heads of seals. "I think of them like little treasure boxes," he says. "You never know what's going to be in them." But Hammer also knew that soft tissue preservation is unlikely in such sandstone sediments.

"That's not where you normally find these kinds of things," agrees Paul Sereno, a paleontologist at the University of Chicago. "It's not an anoxic environment. ... That, and the absence of any other traces of nonskeletal tissues, raises a major red flag for me. I'd need to examine this before I'd agree that it's a heart."

But the paper's authors suggest that chemical reactions between the blood- and iron-rich heart and minerals in the groundwater preserved the shape of the once-beating organ. And they think their CT scans will convince skeptics. "The CT scans basically sliced the heart up like a loaf of bread," explains Paul Fisher, director of the Biomedical Imaging Facility at North Carolina State University and the study's lead author.

To study the heart, the team realigned the "slices" with a special software program, turning the two-dimensional images into several three-dimensional ones that could be rotated and manipulated on a computer screen. The images revealed the heart's ventricles and a single, large blood vessel—the systemic aorta—leading from the heart toward the back of the chest. One image of the rib cage and heart is so clear, says Kuzmitz, that it looks like a "carcass that should be hanging from a meat hook."

Despite the detail, the scan does not show all of the expected blood vessels. The pulmonary vessels, carotid arteries, and both atria are not visible; they may have collapsed at death or simply are not resolved in this scan, the team says. But other researchers say that the missing pieces leave the heart's anatomy and physiology open to other interpretations. "There's no apparent trace of other major vessels that we know would have been there in life," says John Ruben, a physiologist at Oregon State University in Corvallis. "So they can't say that there wasn't a second major systemic vessel leading from the right side of the heart"—as seen in cold-blooded, ectothermic crocodiles and alligators, but not in birds or mammals. "I think it's premature for them to say this is a heart of an endotherm."

The team plans a finer CT scan to address this question. In the meantime, they argue that their interpretation is the "most logical and parsimonious," says Russell.

The find is certain to propel paleontologists to look for similarly preserved internal organs. "It's going to open up a field of research about how things like this get preserved, especially in a sandstone environment," says Thomas Holtz, a paleontologist at the University of Maryland, College Park. "And it's certainly going to change the way we prepare fossils." Indeed, Horner has a nearly complete dinosaur skeleton that will be getting an entirely different examination than it would have a week ago, he says: "We're only just beginning to learn what things can be preserved. I don't think this is the last dinosaur heart we're going to find."

–VIRGINIA MORELL

Dinosaur heart can be viewed at www.dinoheart.org

HUMAN GENOME

DOE Team Sequences Three Chromosomes

Last week, the U.S. Department of Energy (DOE) elbowed its way into the spotlight with other groups that have been getting attention for sequencing the human genome. Although the Human Genome Project originated in part in DOE laboratories in the 1980s, DOE's contributions have been overshadowed in recent years by giant sequencing operations supported by the Wellcome Trust in the United Kingdom and the National Human Genome Research Institute in the United States, and the private sequencing venture pursued by Celera Genomics of Rockville, Maryland. But DOE is back: On 13 April, DOE Secretary Bill Richardson announced that it has finished the working drafts of human chromosomes 5, 16, and 19. These chromosomes are the first to reach this stage since Britain's Sanger Centre and its partners finished chromosome 22 to finer accuracy in December.

The DOE's dedicated program, the Joint Genome Institute (JGI), is part of a 16-member consortium that is scrambling to complete a draft of the human genome's 3 billion DNA bases by June and produce a 99.99% complete version by 2003. Like other members of the consortium, DOE releases sequence data to the public daily with no restrictions. Later this year, Celera plans to release its human genome data through its own Web site, strictly for noncommercial use.

DOE's chromosomes, sequenced at least