amniotic cavity of early chick embryos, she and her colleagues found progeny of the mouse cells in the liver, spinal cord, stomach, and kidneys of about one-quarter of the surviving embryos.

Both sets of experiments produced a puzzling result, however: Neural-derived cells did not appear in the blood systems of either the mouse or chick embryos. In light of last year's results, that is a "glaring, interesting conundrum," says neuroscientist Fred Gage of the Salk Institute for Biological Studies in La Jolla, California. The cells' absence in the bloodstream "doesn't mean they can't" become blood, he says, "but it leaves open the possibility that they don't."

Even more important, several researchers say, is the question of exactly what type of cell formed the various other tissues. Frisén and his team cannot tell whether the cells that contributed to the various embryonic tissues are some sort of rare, undifferentiated cell or whether something in the embryonic environment actually reprograms a cell that had already begun to differentiate. Scientists would dearly love to know the answer to that question, as it would help them understand what molecular factors allow stem cells to change their fates.

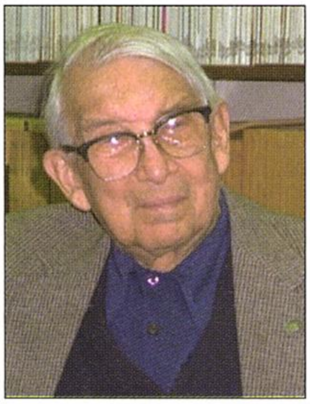
Rossant notes that it would also be nice to know whether the neural-cell chimeras would continue to develop into normal adults as ES-cell chimeras can, and especially whether the neural cells could become mature sperm and eggs. Nevertheless, she says, the work "is another demonstration that adult stem cells have more potential than we thought. Now we have to figure out how to harness that potential."

–GRETCHEN VOGEL

MATHEMATICS

Statistical Physicists Phase Out a Dream

For decades, the Holy Grail of statistical mechanics has been a mathematical problem known as the Ising model. Introduced in the 1920s by German physicist Ernst Ising, the Ising model is a powerful tool for studying phase transitions: the abrupt changes of state that occur, for instance, when ice melts or cooling iron becomes magnetic. Although they've learned much from approximate solutions and computer simulations, physicists have long sought an exact mathematical solution to the Ising model, which would provide much more information about such still-mysterious transitions.



Ernst Ising. His phase-change model is doomed to be inexact.

CREDITS (LEFT TO RIGHT): S. KOBE; C. THOMAS/NASA

Unfortunately, it looks as if that's not in the cards. Sorin Istrail, a theoretical computer scientist at Celera Genomics in Rockville, Maryland, has proved that the Ising model —at least in its most general, three-dimensional (3D) form—belongs to a class of problems that theorists believe will remain unsolved forever. "People have always thought the 3D solution was just around the corner," says Alan Ferrenberg, a computational physicist at the University of Georgia, Athens. "It really means now that numerical analysis is the only way we've got to approach [the Ising model]."

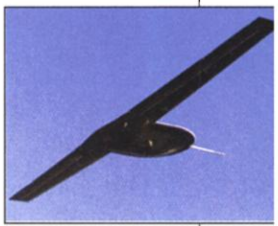
The Ising model deals with objects—say, atoms—laid out in a regular array, such as a rectangular grid or a honeycomb arrangement. The array can be 1D (think of beads on a string), a 2D grid, or a 3D lattice. What makes the model so useful is that it helps physicists understand how a large system of objects, each interacting only with its nearest neighbors, can combine to create a large-scale order. In a ferromagnet, for example, each atom has a magnetic moment that points either up or down. Pairs of neighbors with opposing moments raise the total energy of the system, while those with parallel moments lower it.

Solving the model means counting the number of arrangements that add up to each given energy level. Some versions of the Ising model can be solved exactly. Ising himself solved the 1D ferromagnetic model—and found it had no phase transition. In 1944, the Norwegian chemist Lars Onsager discovered an exact formula for the 2D model, which does possess a phase transition. But scientists have never been able to extend Ising's and Onsager's solutions to the physically realistic realm of three dimensions. "We now know why," says Istrail. "What these brilliant mathematicians and physicists failed to do, indeed cannot be done."

While working at Sandia National Laboratories, Istrail proved that computing the energy states for the general 3D Ising model is what computer scientists call an NP-complete problem—one of a class of recalcitrant calculations that theorists believe can be solved only by arduous brute-force computations. In effect, an exact solution to the Ising model would provide the key to efficient algorithms for solving thousands of other computational problems, ranging from factoring large numbers to the notorious traveling salesman problem, in which the salesman must find the most efficient route through a given number of cities. Al-

ScienceScope

Defenses Raised In February, President Clinton alarmed academic researchers in math, engineering, and computing—fields that get major military funding—by proposing to slash the Department of Defense's (DOD's) applied research spending by 8%, while boosting basic funding by 4% (*Science*, 11 February, p. 952). But leaders of the House and Senate panels that oversee DOD's budget promised to do more to keep innovative ideas flowing (such as drone aircraft, right)—and last week they followed through.



On 25 May, the House Appropriations Committee approved a bill providing $3.4 billion to applied studies, about 2% below this year's level, while giving basic research a 12% increase to $1.3 billion. Earlier, a Senate panel approved even rosier numbers, giving applied and basic science increases of 5% and 10%, respectively.

"We are pleased that Congress has recognized the importance of basic research, but we will continue to push for overall increases," says Caroline Trupp Gil of the American Chemical Society and the Coalition for National Security Research, a lobbying alliance. Computer researchers, for instance, will be pushing to raise some program budgets to requested levels when the full House and Senate vote on the bills later this month.

Hair of the Bear DNA samples taken from grizzly bear hair may help resolve a bitter dispute over the size of the bear population in and around Wyoming's Yellowstone National Park. Last month, federal scientists released a preliminary count of bears in Yellowstone's Lake area based on hairs found on barbed wire fur catchers. The figure—84 individuals, compared to 44 estimated in the 1980s from bear tracks—benefits from "a much more sophisticated technology" for tracking bear numbers, says Chuck Schwartz, head of the Interagency Grizzly Bear Study Team.

Schwartz now wants to do a Yellowstone-wide hair study to help pin down grizzly population trends—information that could prove pivotal in the debate over whether the animals should be removed from the U.S. endangered species list (*Science*, 23 April 1999, p. 568). A similar new study in Montana's Glacier National Park proved useful, but it's "not an inexpensive proposition," Schwartz says. A baseline bear count could cost $1 million, with more surveys needed to establish trends.

though no one has proved that such a sweeping solution is impossible, theorists are fairly certain the NP-complete problems really are as hard as they seem to be. If so, the 3D Ising model is intractable, too.

To reach that dismaying conclusion, Istrail started by translating the Ising model into terms of graph theory. A mathematical graph is just a collection of points called "vertices," pairs of which are connected by "edges"—just as in the Ising model pairs of neighboring atoms are linked by the interactions between them. The edges may be weighted with numerical values. In the traveling salesman problem, for example, the weights are the distances between pairs of cities. For the Ising model, the weights describe the amount by which parallel or opposing magnetic moments of neighboring atoms increase or decrease the energy.

Computing the lowest energy state for the Ising model, it turns out, is equivalent to cutting the corresponding graph in two by plucking off the edges whose weights add up to the smallest possible number. For planar graphs—that is, graphs that can be drawn on a piece of paper without any of the edges crossing—that calculation is a relative breeze. But 3D lattices are inherently nonplanar, and that, Istrail recognized, is the key. He has shown that any nonplanar graph throws up a barrier of computational intractability.

It might still be possible to find exact answers for some special cases of the Ising model, Istrail notes. In particular, the ferromagnetic case of the 3D Ising model may turn out to be simple enough to solve. Nevertheless, the overall message is clear. "We need a paradigm shift," Istrail says. "Instead of waiting for the mathematics to advance, we have to accept this impossibility." And the computational complexity of the Ising model could be just the tip of the iceberg. "There is something about this world that doesn't allow us to understand it." –BARRY CIPRA

WOMEN'S HEALTH

Reports See Progress, Problems, in Trials

Ten years after its scathing report on the National Institutes of Health's failure to include women in clinical research, the General Accounting Office (GAO) has concluded that the NIH is doing much better. Women are clearly taking part in clinical studies—in even greater numbers than men. And the amount of money devoted to diseases, such as breast cancer and depression, that disproportionately afflict women has risen steadily, outpacing increases in the NIH's overall budget. But NIH-supported researchers aren't always putting their data on women subjects to use.

The 2 May GAO report, amplified by a study in the June *Journal of Women's Health & Gender-Based Medicine*, shows that only a small fraction of publications based on NIH-funded research report a sex analysis of the data. "It's important to have women in clinical trials," says Phyllis Greenberger, head of the Society for Women's Health Research (SWHR) in Washington, D.C., "but not for the hell of it. The point is to do the gender analysis."

Such analyses are crucial, she and others note, because women respond differently to some drugs, carry a higher risk of certain diseases, and can present with disease symptoms different from men's. Without a comparison of the sexes, both men and women miss out on sensitive diagnostics and tailored treatments. The director of NIH's Office of Research on Women's Health, Vivian Pinn, acknowledges the importance of gender-based analyses but points out that NIH has no control over whether grantees carry out and report them. "We don't dictate editorial policies for journals," Pinn says.

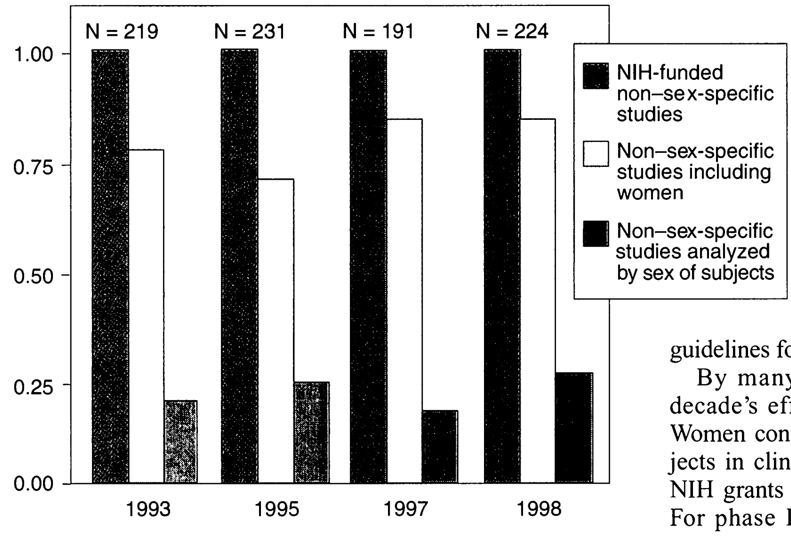
Researchers had historically been reluctant to include women subjects, says molecular biologist Regina Vidaver of the SWHR, because they didn't want to deal with potential birth defects or variability in responses due to hormonal changes during the menstrual cycle. The problem was exacerbated in 1977 after the Food and Drug Administration barred women of childbearing age from participating in early clinical trials because of fear of birth defects. In 1985 the U.S. Public Health Service pointed out the obvious repercussion: The lack of information could seriously compromise health care for women. The NIH, in response, urged researchers to include women in their clinical studies.

Not much had changed by 1990, according to a GAO study, which along with outrage over studies showing the benefits of exercise and of aspirin for preventing stroke—conducted in men only—prompted NIH to act. By the end of the year, the NIH began to require the inclusion of women and minorities in research. In 1993, Congress passed the NIH Revitalization Act that established guidelines for accomplishing that.

By many measures, the past decade's efforts have succeeded. Women constitute 62% of all subjects in clinical studies funded by NIH grants to outside researchers. For phase III protocols, the last stage of clinical trials before a treatment is approved for widespread use, 75% of subjects are women. Even when sex-specific studies, such as those focusing on ovarian or prostate cancer, are excluded from the analysis, more than half the remaining subjects are women.

The GAO report cautions that NIH bookkeeping methods preclude a detailed analysis of funding for women's health research. But funding for some conditions that disproportionately affect women grew steadily between 1993 and 1999. Research expenditures went up 78% for osteoarthritis, 59% for breast cancer, and 73% for depression and mood disorders. For comparison, the overall NIH budget rose by 29% during that time. The NIH also collaborates with other federal agencies in the Women's Health Initiative, a study of 164,000 postmenopausal women that is examining the effects of hormone replacement therapy, diet, and vitamins on cardiovascular disease, breast cancer, and the bone-thinning disorder osteoporosis.

The problem, Vidaver points out, is that NIH-funded researchers still aren't breaking down their data by sex. Her team examined hundreds of NIH-funded, non–sex-specific studies published in *The New England Journal of Medicine*, *The Journal of the American Medical Association*, the *Journal of the National Cancer Institute*, and *Circulation* between 1993 and 1998. Of those, 80% included women. But only 25% to 30% of the studies with women subjects reported a gen-



Room for improvement. Most publications in four major medical journals still don't report an analysis of the data by sex.

SOURCE: JOURNAL OF WOMEN'S HEALTH & GENDER-BASED MEDICINE