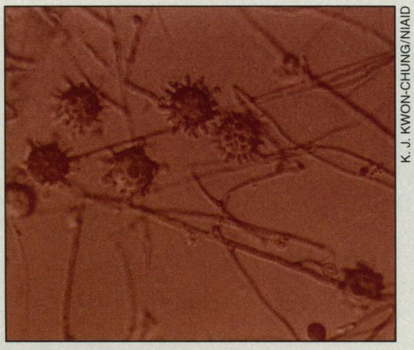
mended only in severe cases.

But Amphotericin B remains the most effective anti-fungal drug on the market, and several companies are experimenting with liposomal formulations of this and other polyenes, which researchers hope will reduce the drugs' toxicity and perhaps even improve their efficacy, says NCI's Walsh. Fujisawa-USA Inc. of Chicago and Vestar Inc. of San Dimas, California (in a collaboration); the Liposome Co. of Princeton, New Jersey; and Liposome Technology Inc. of Menlo Park, California, are working with Amphotericin B; Argus Pharmaceuticals of Houston is working with nystatin.



K. J. KWON-CHUNG/NIAID

Dirty business. Spores and hyphae of the soil fungus *Histoplasma capsulatum*.

The other two classes of anti-fungals are less toxic than amphotericin B, but they have their own drawbacks. The azole derivatives, including ketoconazole, fluconazole, and itraconazole, are synthetic compounds that interrupt synthesis of ergosterol. Although not as difficult to tolerate as the polyenes, they do have side effects. The third class are the allylamines-thiocarbamates, used mostly for treating skin infections.

The growing market for these drugs, as illustrated by the success of fluconazole, which suppresses *Candida* and has found a large market among AIDS patients, has prompted drug companies to begin making up for lost time. One approach is to target a fungal-cell structure that human cells don't share: the cell wall. Two types of potent experimental agents that attack cell walls—the echinocandins and the pneumocandins—appear particularly promising, according to Walsh; these drugs, which are being developed by Eli Lilly and Co. and Merck & Co., Inc., are almost ready for clinical trials.

Such efforts are coming none too soon, because new approaches are urgently needed to outpace drug resistance (which is now cropping up against some azole derivatives) and to keep pace with once-benign fungi that are being seen in clinics. "Microbial resistance has become a particular problem in AIDS patients who've been treated repeatedly for thrush [oral candidiasis] with small doses of the azoles, usually fluconazole, itraconazole, and ketoconazole," says UCLA's Edwards. "It is common in most centers where AIDS patients are being treated deep into the course of their disease."

The pattern of new, or newly resistant, species emerging in response to widespread and prolonged drug treatment, particularly with the azoles, is not limited to AIDS patients, adds Gaynes of CDC. Several new species of *Candida* have emerged as tormentors in the last decade, he says. Among them are *Candida krusei*, which generally afflicts patients with solid tumors or leukemias; *Candida lusitanae*, a new cause of infection in people who have had cytotoxic or long-term anti-microbial treatment and who have had in-dwelling catheters; and *Candida lypolytica*, a mildly virulent organism that has so far been isolated from just six patients.

While *Candida* has long been known as a pathogen, some other species of yeasts that were once considered benign are now being seen in destructive form in immunocompromised patients. According to a report by Bertrand Dupont of the Institut Pasteur in Paris, *Trichosporon*, *Rhodotorula*, *Malassezia*, and even *Saccharomyces cerevisiae* (baker's yeast) have been observed as causes of systemic infection. "As we suppress susceptible species," says Nafsika Georgopapadakou of the Roche Research Center in Nutley, New Jersey, "others begin to take over."

If the new drugs aren't sufficient to address these emerging killers, there is another hope: vaccines. John Robbins of the National Institute of Child Health and Human Development and John Bennett of the National Institute of Allergy and Infectious Diseases are conducting clinical trials of a vaccine designed to prevent *Cryptococcus* infection in AIDS patients. Several groups of investigators have begun looking at candidate vaccines against *Coccidioides* and *Histoplasma*. The antifungal vaccine effort is "gaining momentum" and has "much promise," says Walsh.

The recent CDC report on the outbreak in California says a vaccine is probably the best hope for preventing future epidemics in endemic areas. But the report comes to stark conclusions about the nation's defenses against fungal infections. CDC acknowledges that surveillance of fungal infections is "generally inadequate" and that vast gaps remain in medicine's understanding of the "environmental, behavioral, and host risk factors for acquiring infection and developing [fungal] disease." As researchers search for ways to fill those gaps, medicine may begin to catch up with the opportunistic and once-benign fungi, in spite of the running start those organisms have on science.

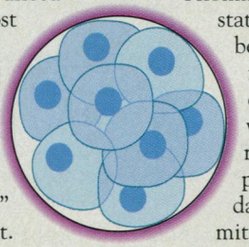
–Steve Sternberg

Steve Sternberg is a science writer who is a Kaiser Media Fellow for 1994–95.

HUMAN EMBRYO RESEARCH

Clinton Rules Out Some Studies

On 2 December, a top-level advisory committee at the National Institutes of Health (NIH) unanimously endorsed a set of guidelines for research on human embryos, crafted over the past year by a commission of researchers, ethicists, and lawyers. Eight hours later, President Bill Clinton announced that he couldn't accept the most controversial of the proposed guidelines. "I do not believe that federal funds should be used to support the creation of human embryos for research purposes, and I have directed that NIH not allocate any resources for such research," Clinton said in a public statement.



Clinton's announcement—widely perceived as an attempt to fend off conservative critics—represents "the president's position" on "a very controversial subject," says M.R.C. Greenwood, associate director for science at the White House Office of Science and Technology Policy. Greenwood noted, however, that the statement should be "very narrowly construed." It explicitly forbids only the use of NIH funds for the creation of embryos for research, such as the study of processes of egg maturation and fertilization. The president presumably has not ruled out other areas of human embryo research covered by the guidelines, which would end a 13-year ban on such research.

Among those apparently surprised by Clinton's announcement was NIH Director Harold Varmus. NIH spokesperson Anne Thomas says Varmus saw the text of the statement just half an hour before it became public. Varmus didn't mention the impending presidential announcement last week when the NIH Director's Advisory Committee considered the proposed new guidelines during a 2-day meeting. The advisory committee accepted the guidelines, which will pave the way for Varmus to implement those not covered by Clinton's statement. The guidelines permit studies on in vitro fertilization (IVF) techniques and basic biological research on "spare embryos" from IVF clinics up to the 14th day of development (*Science*, 19 August, p. 1024).

The president's edict banning the creation of embryos for research purposes leaves some questions hanging, however. For example, it's not clear whether NIH will be allowed to fund research on human parthenotes (eggs that have been artificially stimu-

lated to divide and grow). Nor is it clear how NIH will draw the line between the permitted creation of extra embryos for clinical use (which may be donated to research) and the forbidden creation of embryos for research. And exactly how the field will be regulated is still up in the air. Several senior members of Varmus's advisory committee urged him to create a panel to review individual proposals and to model it on an existing committee that monitors recombinant DNA and gene therapy protocols. Varmus seemed agreeable to this idea.

Although many researchers welcome the expected resumption of some areas of embryo research, Clinton's statement has been greeted with disappointment. One important area that's likely to suffer, says Brigid Hogan, the Vanderbilt University biologist who chaired the science subpanel of the commission that drafted the guidelines, is research on human egg maturation, which requires that eggs be fertilized to test their viability. These studies—if they were allowed to proceed—would help improve the efficiency of in vitro fertilization, making the process safer and less expensive. Michael McClure, a reproductive scientist at the National Institute of Child Health and Human Development, adds that a ban on creating embryos for research will have a "substantial impact on basic science" aimed at understanding how sperm and egg interact. McClure adds that, while researchers hope they will soon be permitted to use "spare" embryos, these are "very scarce."

Not all researchers were disappointed by Clinton's stance, however. Patricia King, the Georgetown University law professor who served as co-chair of the commission that drafted the guidelines, was relieved to see that the president shared her own qualms and had acted on them. She felt that his decision was in tune with the public mood and said that in retrospect she wished she had been more forceful in arguing this point of view while on the NIH advisory panel.

David Challoner, vice president for health research at the University of Florida, Gainesville, and a senior member of Varmus's advisory panel, urged a philosophical perspective. "Clearly this is a political decision," says Challoner. "A good deal of heat has already been generated and will continue to be generated for the NIH, the Department [of Health and Human Services], and the White House" by those who oppose research on embryos. He thinks Clinton couldn't afford to "deal with" the most controversial of the proposed guidelines at this time. The result, says Challoner, is that Clinton has asked NIH to defer a socially important area of research, but at the same time, he has tried to quiet a furor that might have engulfed NIH in broader controversy.

–Eliot Marshall

FREEDOM OF INFORMATION

Washington Law Forces Grant Disclosure

The Washington State Supreme Court recently sent a tremor through Washington's research community. On 22 November, the court ruled that a 21-year-old state law requires institutions in Washington to make public on request grant proposals that would involve government money—even if the proposals haven't been funded.

The ruling will have a chilling effect on research, predicts Alvin L. Kwiram, vice provost for research at the University of Washington, because it means anyone can now gain access to ideas long before publication. And the impact could extend well beyond Washington's borders. "This ruling will mean that many investigators in other states who are not subject to our kind of problem will be loath to collaborate with our faculty if they were forced to reveal their ideas prematurely," says Kwiram. "And the same is true of any effort to collaborate with industry." The ruling, moreover, could make research involving animals more vulnerable to attack by animal-rights groups.

"Many investigators in other states ... will be loath to collaborate with our faculty."

—Alvin L. Kwiram

Indeed, the state supreme court ruling is the result of a suit brought by an animal-rights group—the Progressive Animal Welfare Society (PAWS)—in an effort to force the University of Washington to release details of an unfunded research proposal involving monkeys. The proposal, by primatologist Gene Sackett of the University of Washington Primate Center in Seattle and neuropathologist Linda Cork of Johns Hopkins University in Baltimore, was designed to study mildly self-abusive behavior in monkeys in search of clues to similar behavior in autistic children. The project, which would have involved isolating some monkeys at birth, didn't get a good enough priority score to be funded by the National Institutes of Health, however, and it has never taken place.

PAWS' lawyer, John T. Costo of Bellevue, Washington, said that in January 1991, his client sought the names of the researchers involved with the proposed study, the kinds of animals that would be used, budget details, and the researchers' bibliographies. The organization planned to circulate the information in its newsletter, he said. When the university refused to turn over the information, PAWS filed suit, arguing that Washington's Public Records Act requires release of the information. The act stems from a citizen initiative, approved by Washington voters in 1973, that mandates "full access to information concerning the conduct of government at every level."

The university lost the first round in 1992, when a judge in King County Superior Court in Seattle ruled that the law required release of much of the information in Sackett's proposal. The university took the case to the state supreme court, where its appeal was supported by a bevy of learned societies and industry groups, including the American Psychological Association, the Association of American Medical Colleges, the American Council on Education, and the Washington State Biotechnology Association.

The university argued that unfunded research proposals are protected from disclosure by a variety of laws, including the federal Freedom of Information Act, copyright and patent statutes, and the Uniform Trade Secret Act. Sackett, in an interview with *Science*, added that PAWS was "asking me to give up my intellectual property." He argued that proposals that have not been funded are the property of the individual researcher. Moreover, he noted that in his case, the implications of making unfunded research proposals public aren't merely theoretical: During his 30 years of animal research, he says, he has experienced death threats, has had his house trashed three times, and has received harassing telephone calls from animal-rights activists. "I'm getting a little gun-shy."

The supreme court, however, says the mandates of the Public Records Act are so strong that disclosure is required. The court even awarded attorneys' fees to PAWS and noted that the lower court can penalize the university $100 for each day PAWS was denied access to the information. Costa says the penalties could amount to $146,000 on top of $20,000 in attorneys' fees.

The university is now planning to ask the legislature to amend the law. "Most other state laws exempt research proposals and intellectual property in its broadest sense from disclosure," Kwiram notes. "But the laws in the State of Washington ... are far more sweeping in what they encompass." In the meantime, the university is reviewing its immediate options.

–Victoria Slind-Flor

Victoria Slind-Flor is in the San Francisco bureau of The National Law Journal.