will make a profit. Already, BioMed Central has recruited an impressive board, including Varmus, now president of the Memorial Sloan-Kettering Cancer Center in New York City, Steven Hyman, director of the National Institute of Mental Health in Bethesda, Maryland, Philippe Kourilsky, director of the Pasteur Institute in Paris, and Mitsuhiro Yanagida, a molecular biologist at Kyoto University in Japan.

At the New York meeting, the contrarian role fell to Pieter Bolman, president of Academic Press of San Diego, California. In a brief talk, he dismissed the free publication schemes as utopian, joking that they looked like the work of "academics on the loose" or "a communist plot." To put all biomedical research data into a single open archive is "asking for trouble," Bolman said, because it asks "existing publishers to give up their files" and "commit economic suicide." The journals won't do it, Bolman predicted, unless forced by the government.

The PubMed Central experiment, Bolman argued, is plagued by "a mainframe mentality"—meaning centralized management. Bolman touted an alternative, a publisher-initiated venture called CrossRef, launched in June. Later this year, it will house an electronic index with links to 3 million articles in 4000 journals. But unlike users of PubMed Central, users of CrossRef will have to pay a fee in most cases to get the full text. PubMed Central "has served its purpose," Bolman asserted: "I invite you to join CrossRef and get it all over with."

The experiment in electronic publishing has begun, and "we are tacking to a distant port."

—Harold Varmus

Infuriated, Brown rose to give the final talk and fired a broadside at "parasites" who get the work of scientists for free, take forever to publish it, and charge readers a high price for a product they often make worse by editing. Instead of joining CrossRef, Brown urged scientists to lend support instead to free alternatives like PubMed Central. Brown's comment to the publishers: "We'll call you if we need you, but don't sit by the phone." But right now, Brown himself is calling the publishers, because he wants them to donate their back issues to PubMed Central—"so that people can see the value" of having a free electronic archive.

Although participants in the meeting diverged sharply on how the Internet will affect publishing, all seemed to agree with Varmus's comment that the experiment in electronic publishing has begun, and that "we are tacking to a distant port" with winds that sometimes favor and sometimes hinder progress.

–ELIOT MARSHALL

ARTHRITIS

A Gene for Smooth-Running Joints

At first glance, tartar control toothpaste and water softeners seem to have little in common with the crippling joint erosion that haunts tens of millions of arthritis sufferers worldwide. But a new study on page 265 of this issue suggests that a genetic defect in mice causes the joint's cartilage cells to pump insufficient amounts of pyrophosphate—a natural water softener—into the joint cleft, and this in turn leads to the formation of bony spurs that eventually stiffen the joints completely. Because humans have an almost identical gene, and disorders such as osteoarthritis also feature an abnormal outgrowth of bones, some arthritis researchers are hopeful that these new findings may point the way toward a new class of pyrophosphate-based drugs similar to the antiscaling chemicals in washing powders and toothpaste. But, as many of the researchers point out, the numerous roads that lead to human joint degradation make a single cure-all unlikely.

Arthritis and other rheumatic afflictions dwarf cancer and heart disease in terms of the disability they cause. The World Health Organization estimates that arthritis-related diseases—of which there are more than 100 different forms—afflict half the world's population over 65. Although sports injuries, age, and obesity are among the most common risk factors, about half of all arthritis cases also have a strong hereditary component.

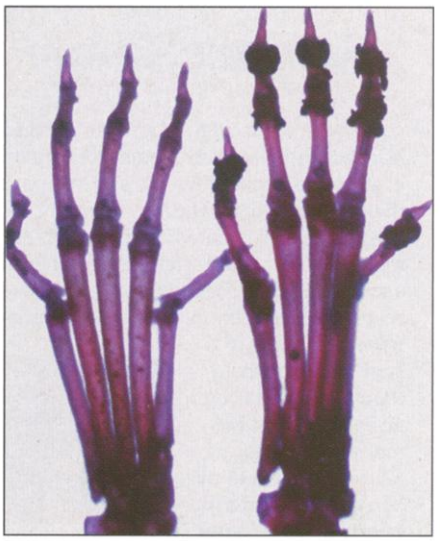
To pinpoint genes that contribute to a specific disease, researchers often turn to animal models that mimic the ailment. Developmental geneticists David Kingsley, Andrew Ho, and Michelle Johnson of the Stanford University School of Medicine have been trying to unravel the genetic mutation at work in a strain of mice called *ank*, which has progressive ankylosis, or fusion of the bones. The disease starts by stiffening the digits and paws, then spreads to virtually every joint in the body, including the spine. By about 6 months of age the animals are completely immobilized and eventually die. Despite its unparalleled severity, the mouse disease and various forms of human arthritis share several hall-

ScienceScope

Castle Revolt Scientists at the Smithsonian Institution in Washington, D.C., are up in arms about what they see as a raid on their research funds. The new secretary, Lawrence Small, ordered his managers last month to freeze all discretionary money in a special account used to pay for small research projects, new initiatives, and special travel, according to a staff letter to Small that was obtained by *Science*. Most of this money—between $3 million and $16 million, according to a museum official—comes from researchers themselves, who solicit gifts and donate honoraria, consulting fees, and royalty payments. Staff scientists asked the secretary to reconsider. When he didn't respond, the Council of the Senate of Scientists at the National Museum of Natural History protested in a 22 June letter, warning that the move would be a "devastating blow to morale." Small's failure to offer any explanation for the move, the memo states, "gives the impression of an arbitrary, ill-informed decision-making process." Small, a former banking manager, is just trying to sort out the Smithsonian's finances, explains spokesperson David Umansky. "No money is being taken," Umansky says. The secretary is merely "asking what these funds are used for." Another spokesperson says Small likely will decide what to do in the next 2 weeks.

CREDIT: SMITHSONIAN

Larger Pie Japanese R&D boosters are optimistic that the government will back an ambitious plan to raise science and technology spending to 1% of the country's gross domestic product (GDP) within 5 years, with a special emphasis on funding information technology and life sciences. The 1998 level—the last for which complete figures are available—was $39 billion or 0.7% of Japan's GDP. (U.S. government spending that year was about 0.76% of GDP.) The goal may be included in a 5-year science and technology plan being drawn up now by the advisory Council for Science and Technology for the 2001 budget, which begins next April. Hiroo Imura, former president of Kyoto University and a key member of the council, says that because R&D spending has already grown rapidly the group initially had modest expectations. But backing for a more aggressive approach found "many supporters among the [ruling] Liberal Democratic Party," Imura says. He warns, however, that the plan ultimately will have to win the backing of the powerful Ministry of Finance.



Foot fault. Mineral deposits and bone formation around toe joints of mouse with mutation in the *ank* gene (mutant foot shown on right, normal skeleton on left).

marks, including deposition of calcium phosphate crystals in the joints and degradation of cartilage, the smooth, gel-like cushions at the tips of the bones. "The *ank* mouse immediately attracted a lot of interest from arthritis specialists," says Kingsley. But the genetic defect remained elusive.

Other researchers had linked the *ank* mutation to mouse chromosome 15. To narrow the search further, Kingsley and his colleagues engaged in a brute-force breeding effort, crossing *ank* mice with another strain and then picking those with the *ank* mutation from more than 4000 offspring. They finally homed in on a 150,000–base pair stretch of DNA containing 11 candidate genes—"none of which had any obvious link to arthritis" at first, recalls Kingsley.

When the team compared the sequences of the 11 genes between normal and mutant mice, letter by letter, they found a single typo in one of the genes that led to a protein about 10% shorter than the normal version. The gene is highly conserved among vertebrates—the human counterpart is about 98% identical—but strikingly absent in invertebrates, which lack skeletons and, hence, bones, joints, and arthritis. Further strengthening the case, in mouse embryos the *ank* gene is most active in developing cartilage.

Kingsley's team had no idea what the normal gene does, but an intriguing clue came from Yusuke Nakamura and his colleagues at the University of Tokyo, who had recently identified the genetic defect behind a similar mouse disease—and determined that its protein product normally generates pyrophosphate on the outside of joint cells to keep the joints scale-free. When the Stanford team measured pyrophosphate levels in cultured cells derived from *ank* and normal mice, they found that the chemical accumulated in cells from the *ank* mice but decreased in the culture medium. Kingsley speculates that in its normal form, the ank protein may be "a pyrophosphate channel that allows pyrophosphate levels to remain high in cartilage throughout life" to prevent calcium phosphate crystal formation in the joint cleft. When that protein is defective, however, pyrophosphate is sequestered inside the cells and crystals can build up in the joint fluid, leading to inflammation and joint destruction.

Rheumatologist Michael Doherty of the City Hospital in Nottingham, United Kingdom, notes that the *ank* mouse "most closely resembles familial chondrocalcinosis," a genetic disease that leads to crystal deposition in numerous joints and shows a similarly imbalanced pyrophosphate distribution in the joints. In several afflicted families, moreover, the genetic defect has been mapped to the same chromosomal region that harbors the human *ank* gene. "It's a really hot candidate for [human] chondrocalcinosis," says Matthew Brown, a skeletal geneticist at the University of Oxford.

The role of pyrophosphate in osteoarthritis is unclear, however. Doherty points out that some osteoarthritis sufferers have too much instead of too little pyrophosphate in their knee fluid, suggesting a different disease mechanism. "I'd say the likelihood that this leads to some interventions [for osteoarthritis] in the near future is pretty low," he says. Nonetheless, "David's study is fascinating, because it sheds light on the molecular mechanism of what's happening in the *ank* mouse." –MICHAEL HAGMANN

U.K. FUNDING

New Program Supports Facilities, Stipends

CAMBRIDGE, U.K.—British scientists are celebrating a $1.7 billion windfall, announced last week by the U.K. government, to shore up deteriorating facilities and raise stipends for Ph.D. students. The 2-year spending boost is intended to keep the pool of British science well stocked, both by attracting more talented students into the field and stemming the flow of scientists out of the country. But the benefits are not spread evenly across the research spectrum.

The extra money, to begin in 2002, surpasses the wishes of the scientific community to extend the popular Joint Infrastructure Fund (JIF) beyond next year. Both are bankrolled by the government and The Wellcome Trust charity, but the new Science Research Investment Fund will spend at an annual rate almost double the 3-year, $1.2 billion JIF. The largesse amounts to a roughly 20% increase in the overall science budget, says Peter Cotgreave, director of the Save British Science Society. U.K. Chancellor Gordon Brown said that "the scale of this investment is unprecedented, ensuring world-class facilities for world-class science."

JIF has been doling out competitive grants of at least $1 million to universities for everything from purchasing pricey instruments to building world-class facilities. The latter include a tropical medicine research center at the University of Oxford and a human genetics institute at the University of Newcastle upon Tyne. Success rates have been running at about 20%, and the last call for grants is slated for October. Last week's announcement in essence extends JIF for 2 years (see table).

Government officials said they hope the new fund will ensure that the country's most productive institutions don't lose their edge. A cost-sharing provision aimed at making the money go farther also favors well-endowed universities by making mandatory a practice, begun under JIF, that institutions contribute 25% to a project's overall cost. Major universities such as Oxford and Cambridge "will find it relatively easy to unlock the money," Cotgreave predicts. On the other hand, he says, the country's dozens of former polytechnics are likely to flounder in the hunt for matching funds.

To bolster the quantity and quality of future scientists, the government will also boost annual science and engineering Ph.D. stipends from $10,000 to $14,000 by 2004. That hike, which analysts estimate will cost $80 million, follows a January plea from the U.K. Life Sciences Committee, an umbrella

A WINDFALL FOR BRITISH SCIENCE

Source	Purpose	Amount (in millions $)
Department of Trade and Industry; Higher Education Funding Council	New facilities and equipment; renovations; all fields	1080
Wellcome Trust	New facilities and renovation; limited to biomedical sciences	360
Office of Science and Technology	Modernize research council institutes; national projects	160
Research councils	Higher doctoral stipends	80

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