those containing the cystic fibrosis gene and the gene for Williams syndrome, to sequence in dog, cat, horse, cow, baboon, and five other vertebrates. Eric Lander's group at Whitehead is sequencing several fungi of known evolutionary distance from bakers' yeast to find out how evolutionary distance affects the comparisons. It turns out two closely related species can be too similar to reveal certain key conserved features.

In all likelihood, the big centers will tackle large genomes on their own in a few years. And that prospect is exciting not only to geneticists and biomedical researchers but also to a broad range of biologists. For instance, evolutionary and developmental biologists would like to decipher the genomes of some 100 species distributed across the evolutionary tree; they have already asked the National Science Foundation, which supported the first sequencing of a plant, for planning support. It won't be long, says Oklahoma's Bruce Roe, before "we have the technology to answer very broad-based questions on how organisms evolved."

21st century biology

As valuable as these genome sequences will be, the sequence by itself doesn't tell researchers what genes do—and that's rapidly becoming the focus of a number of centers, both large and small. National genome budgets are beginning to reflect this emphasis. Already, about 90% of Germany's human genome project budget goes toward functional genomics, says Jörg Wadzack, a molecular biologist for the German Human Genome Project. NHGRI is evaluating proposals for centers of excellence that will also push the U.S. human genome effort in a functional direction. Stanford, for example, is one of several centers helping to build the Mammalian Gene Collection, a set of 25,000 full-length complementary DNAs (cDNAs) for mouse and human. (cDNA includes all the coding regions of a gene.) Already, the Japanese have collected 20,000 full-length mouse cDNAs that are part of a mouse gene encyclopedia (*Science*, 9 February, p. 963). These cDNAs will "help annotate the genome and find genes," says Stanford's Myers. Adds Collins: "This [collection] will be one of the durable goods of the genome project."

At the Sanger Centre as well, "the big emphasis is going to be understanding how genes work," says bioinformaticist Richard Durbin. "We see ourselves expanding our biological programs." The Whitehead Institute is already well along that road: Since 1997 it has worked with Bristol-Myers Squibb Co., Affymetrix Inc., and Millennium Pharmaceuticals Inc. to develop microarrays for monitoring gene expression. Lander expects to increase his group's emphasis on the genetics of disease traits. "We got into the genome project 15 years ago because our interest was in studying complex traits," he says. "The genome was part of the necessary infrastructure [for] studying those traits."

While these researchers are expanding into functional and comparative genomics, they are also venturing into new territory. "We are sitting on a [sequencing] capacity that can really change our thinking," says Trevor Hawkins, director of JGI. Hawkins thinks it's now practical to sequence, say, the same coding region from 100 people to begin to understand the effect of variation on a particular disease or trait. Sanger's Bradley agrees: "A lot of sequencing capacity will be used for resequencing, looking at sequence variation, and looking for disease genes," he predicts.

As Collins, his predecessor James Watson, and others predicted at the outset, the sequence of the human genome is turning out to be a tool to enable an astounding new array of biological studies. And Sanger's Durbin agrees: "It's going to provide a kickoff for a whole lot of interesting science for a very broad set of scientists." Far from signaling the end of the genomic opera, this week's publication is merely the close of the first act.

–ELIZABETH PENNISI

With reporting by Dennis Normile and Robert Koenig.

NEW SCIENCE:

Hunting for Collaborators Of Killer Toxins

Many gene hunters track sequences that inevitably lead to disease. Environmental health researchers seek a different quarry: variations in genes that by themselves might be harmless, but, when a person is exposed to environmental toxins, can amplify that person's risk of illness. Studies of these genes, which often code for enzymes that metabolize toxins or repair DNA damage from carcinogens, could lead to a better understanding of how the genes make people vulnerable and which individuals are at risk.

The growing list of diseases linked to these environmental susceptibility genes includes asthma, diabetes, lead poisoning, and a lung disease caused by the metal beryllium. Many disorders involve more than one gene: Variants of two genes, for example, boost the risk of bladder cancer 10-fold in people who smoke, according to

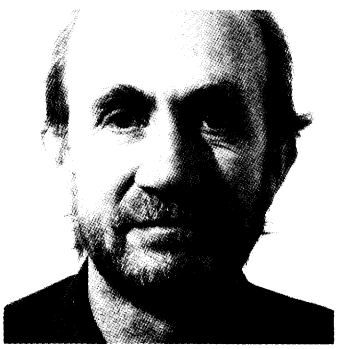
recent studies at the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina.

To help find these genes and explore how they operate, toxicologists are using DNA arrays—glass chips dotted with gene sequences (*Science*, 28 July 2000, p. 536). For instance, Leona Samson's team at Harvard University has found that DNA-damaging chemicals known as alkylating agents turn on or off at least 400 genes in yeast cells, including "totally unexpected" genes involved in novel repair pathways, says Samson. The complete sequence of the human genome will enable scientists to do such toxicogenomic studies with cells from various human organs, notes Michael Gallo of the University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School in Piscataway. "That's the real beauty of the genome. We can now start to dissect toxic responses at the molecular level," says Gallo.

–JOCELYN KAISER

UNSUNG HERO: ALAN COULSON

After developing sequencing technology with Fred Sanger and producing physical maps of *Caenorhabditis elegans*, Coulson headed up the sequencing effort with John Sulston at the Sanger Centre in Hinxton, U.K. As Sanger scaled up to tackle the human genome, Coulson "quietly rolled up his sleeves," says Sulston, to run the team that produced and selected clones for sequencing.



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