position leading the project, the hiring of an outside contractor to track the project, and the assignment of more DOE staff to oversight tasks. He also ordered demotions and reassignments for an unspecified number of unidentified Livermore and DOE staff. At the same time, in an apparent reaction to NIF's troubles, the University of California has denied a routine pay raise to Livermore director Bruce Tarter, singling him out from among 26 senior managers at the three DOE labs it manages.

Richardson's announcement generated a terse reply from Tarter, who said he would "work cooperatively with DOE to ensure NIF's success and funding." Richardson told the House Appropriations Committee earlier this month that his goal is to wake NIF from its "management nightmare." And although critics say NIF faces formidable technical challenges, from growing ultrapure crystals to pouring extremely fine glass, Richardson says he's "convinced that the underlying science ... remains sound." –DAVID MALAKOFF

GENETICS

Chipping Away at the Causes of Aging

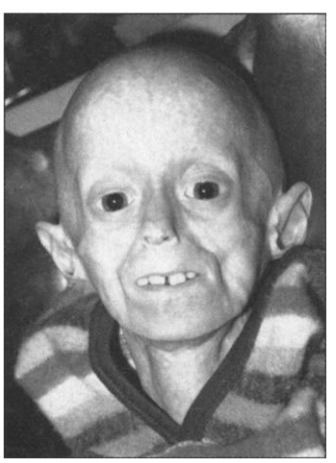
Aging is not kind. Our skin wrinkles, our hair may fall out, our bones and muscles weaken, and we become increasingly susceptible to a raft of fatal diseases. But despite ever-increasing interest as the baby boomers age—not to mention extensive research—relatively little is known about what causes this physical degeneration. Now, researchers are getting some clues from a hot new technology: DNA microarrays or chips, which enable them to perform wholesale analysis of gene expression patterns.

In one of a flurry of new studies, a team led by Richard Lerner and Peter Schultz of The Scripps Research Institute in La Jolla, California, has used microarrays to provide a snapshot of the gene changes that occur in aging fibroblasts, the cells that help form skin and connective tissue. As the researchers report on page 2486, some of the changes they found could produce such signs of old age as skin wrinkling. And they also found evidence for what may be a more global explanation of aging: an impairment of the machinery needed for normal separation of the chromosomes during cell division that could lead to genetic instability and a variety of disturbances in gene function.

"This is an extremely interesting piece of work," says aging researcher Leonard Guarente of the Massachusetts Institute of Technology. Still, he and others caution that it will be necessary to verify that the changes the Scripps group detected occur in living people and not just in the cultured cells they are working with.

The Scripps group compared gene expression in cells from healthy people of various ages and also from children with Hutchinson-Gilford progeria, a rare hereditary disorder that resembles an accelerated form of aging. In essence, microarray analysis involves putting snippets of DNA from known genes on a fingernail-sized chip and seeing which ones light up when the chip is exposed to fluorescently labeled DNA copies of the messenger RNAs from the cells under study. These are the active genes. The researchers found that the expression of just 61 genes—out of a total of some 6300 checked—changed with age. Many of these same changes also occurred in the fibroblasts from the progeria patients, a finding that indicates that these individuals, who often die in their early teens from such conditions as heart disease, are indeed experiencing an accelerated form of aging.

Although the changes the Scripps group found were intriguing, some were not surprising. For instance, several of the fibroblast genes whose expression patterns were altered are involved in forming and remodeling collagen and other proteins of the extracellular matrix, which provides support for the skin and other tissues. The researchers also observed up-regulation of genes involved in inflammation, which has been linked to a variety of the ills of old age, including heart disease and Alzheimer's. But perhaps the most intriguing change was the down-regulation of a set of some 15 genes that help control mitosis, the part of the cycle in which cells actually divide.



Aging too fast. This 10-year-old girl shows the typical features of progeria.

CREDIT: W. TED BROWN/INSTITUTE FOR BASIC RESEARCH, STATEN ISLAND

A common consequence of defects in the genes involved in mitosis is chromosome instability, a known contributor to cancer development, as it can lead to loss of genes that suppress tumor formation or activation of genes that promote it. Chromosome instability may also be a more general contributor to aging, by triggering the malfunction of genes other than those involved in cancer. From this, Lerner concludes, "aging is predominantly a disease of mismanagement of cell division checkpoints." Although other studies had pointed in that direction, the Scripps work "provides much more solid evidence for that idea, because the [microarray] screen picked up a lot of genes involved [in mitosis]," says aging researcher Judith Campisi of Lawrence Berkeley National Laboratory in California.

Still, Campisi and others would like to see the results confirmed. She notes that the Scripps team tested just 11 cell lines. Another concern is that the cells, which were obtained from commercial sources, might not be comparable in such features as the ability to divide, although Lerner says his team controlled for that possibility.

But if they're correct, the new findings would also suggest that different gene changes underlie aging in different tissues. In previous work, a team led by Richard Weindruch and Tomas Prolla of the University of Wisconsin, Madison, used microarrays to probe aging in mouse skeletal muscle (*Science*, 27 August 1999, p. 1390). Like the Scripps team, the Wisconsin team found that aging did not cause widespread alterations in gene expression.

Just 55 genes, or slightly less than 1% of those assayed, showed decreased activity in aged animals' muscles, while the activity of a comparable number went up. Many of the genes whose activities declined produce proteins needed for energy production and the synthesis of proteins, lipids, and other cell constituents—changes that could account for the muscle weakening that occurs with age. In contrast, many of the genes whose activities increased produce so-called stress proteins, which are needed to repair or eliminate damaged DNA or proteins. What's more, the Wisconsin team found that many of the changes they saw in aged animals fed a normal diet did not occur in mice on a calorie-restricted diet—a finding that provides a long-awaited explanation for how calorie restriction extends rodent life-spans.

But except for some stress-response genes, there was little overlap between the alterations the two groups saw. That suggests, Prolla says, that the fibroblasts, which are dividing cells, and the skeletal muscle cells, which have lost that ability, "probably undergo aging through two different mechanisms—a very important observation."

Whether the type of microarray studies being done by the two teams will help people live longer, or at least healthier, lives, is anyone's guess. Says Lerner: "Is the Fountain of Youth here, because of this paper? I don't think so." Still, the research is providing ideas to explore about the causes of aging—in other words, a fountain of knowledge, if not youth. –JEAN MARX