(continued from page 369)

pancreatic tissue had no counterparts in the gene databases. Using the SAGE tags, the Kinzler-Vogelstein team identified the clones for those genes in a pancreatic gene library, sequenced the clones, and added the sequences to the database.

Brown and his colleagues reach the same endpoint as the Johns Hopkins team—a detailed description of gene activities in a given tissue or cell—but they get there not by sequencing gene fragments, but by using a miniaturized system that makes use of the fact that similar DNA strands bind or hybridize to complementary sequences. "Suppose you're [from] one of those many labs that have been madly sequencing cDNAs," says Brown. "You have sequences of tens of thousands of cDNAs, but little information about where they are expressed, and you want to find out very quickly." With their new "microarray" assay, he says, it's feasible to monitor the activity of thousands of genes per day.

For its proof-of-principle experiment, the Brown team turned to a weed called *Arabidopsis thaliana*, the fruit fly of plant genetics. Using a tiny computer-controlled two-pronged fork that they had designed specifically for the task, the researchers dropped onto a microscope slide spots of solutions, each containing a different double-stranded cDNA from an *Arabidopsis* gene library. After fixing this array of spots to the slide with heat and chemicals, the Brown team added pooled cDNA prepared from the protein-coding mRNA extracted from *Arabidopsis* leaves and labeled with a dye that glows red, and cDNA prepared from the protein-coding mRNA extracted from *Arabidopsis* roots and labeled with a dye that glows green. The spots where cDNA from the plant leaves or roots bound to the corresponding cDNA in the microarray fluoresce red and green.

The fluorescence patterns, measured by a computerized scanner, indicate the relative levels of expression of the genes in the two tissues, and the absolute activity of each gene can be determined by comparing its fluorescence to standards of known amounts of cDNA. Expression of some of the genes was 100-fold or greater in one tissue than the other, Brown says, "and when we sequenced them, it was exactly what you would have expected." For example, he says, the genes for photosynthetic enzymes were turned on in the leaves, but not the roots. In this initial test case, the microarray contained only 45 cDNAs, but since then the team has created microarrays with 1800 yeast DNA sequences, increasing the information gleaned from each experiment 40-fold.

Currently, both of the new techniques are in the prototype stage, and "it remains to be seen which technique will be more amenable to widespread use," says Trent. Nonetheless, he says, either technique—or one of the similar techniques coming down the pipeline—will be instrumental to the success of efforts to study how coordinated changes in the activity of batteries of genes convert undifferentiated cells into cells with specific tasks and attributes, trigger the responses of differentiated cells to radiation, hormones, or other outside stimuli, and drive healthy cells through the abnormal changes that end in disease. Other teams are making progress in developing techniques that allow them to assess directly what proteins are present in cells, although this work is not quite as far along (see p. 369).

Indeed, the two gene-expression techniques are already being put through their paces in real-life research situations. Both groups are trying to use them to spot the differences between normal and cancer cells. "As soon as we knew that SAGE worked," says Kinzler, the Hopkins team started a project to compare the activity patterns of genes in normal cells lining the colon with those in colon cancers. Kinzler expects definitive results within 6 months. Meanwhile, Trent and his colleagues, in collaboration with the Brown team, are using the microarray technique to search for the tumor-suppressor genes that may prevent abnormal, but not yet cancerous, skin cells from taking the final steps to malignancy.

Brown and team member Ronald Davis, also of Stanford University, have even bigger plans afoot. Sometime in 1996, when the sequence of the whole genome of the yeast *Saccharomyces cerevisiae* is complete, they intend to mass-produce microarrays containing the organism's entire suite of about 6500 genes. By studying changes in gene expression under different conditions—for example, when the nutrient-starved yeast produces spores, says Brown, "we will be able to see when the cells call different genes into action, and from that information generate new hypotheses about what the genes do."

Although the potential of having all this new information at their fingertips promises to make a geneticist's life more interesting, it is likely to generate another information glut, warns Kinzler. "Instead of the Krebs cycle," he says, referring to the complicated graphic depiction of the cell's major energy-generating system that adorns many laboratory walls, "we are now going to have expression maps of 100,000 different genes. Good luck figuring that out!"

–Rachel Nowak

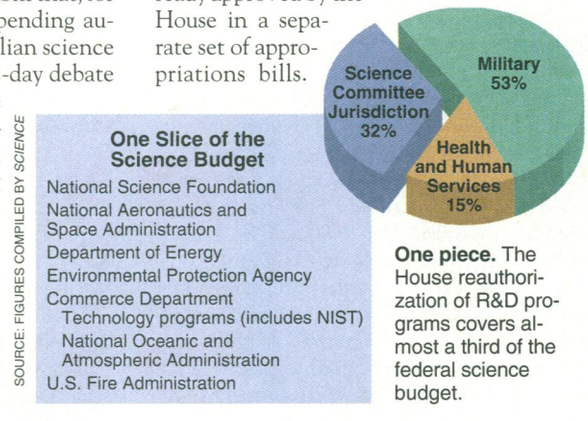
POLITICS

House Bundles 7 R&D Programs

The Senate is largely indifferent to it, the Administration is hostile, and it is unlikely to have any real effect on the 1996 budget. But last week the House passed a bill that, for the first time, lumps together spending authority for most nonmedical civilian science and technology programs. The 2-day debate leading up to the 248 to 161 vote provided a rare—and heated—discussion of federally sponsored research. In addition to putting science on center stage, it highlighted the widening gulf between the two parties on priorities for federal R&D.

Congressional action on civilian science and technology programs typically is scattered through the legislative calendar. This year, however, House Science Committee Chair Robert Walker (R–PA) championed a single bill that authorizes $21.5 billion—$3 billion less than current levels—for seven R&D agencies. "It's the first time we've focused attention on government R&D on the House floor," Walker told *Science*. "It makes more sense to look at science in a coordinated way." Congressional aides say the measure also demonstrates Walker's influence with the Republican leadership and advances his long-shot plan for a single Department of Science (*Science*, 31 March, p. 1900).

The funding figures in the omnibus authorization largely match the levels already approved by the House in a separate set of appropriations bills.



One piece. The House reauthorization of R&D programs covers almost a third of the federal science budget.

Those bills determine 1996 budgets for agencies including the National Science Foundation, the National Aeronautics and Space Administration (NASA), the Environmental Protection Agency (EPA), the Department of Energy (DOE), and parts of the Commerce Department. High-ranking Democrats including Vice President Al Gore and Representative George Brown (CA) used the debate to lambaste Republican plans to cancel industrial research programs like the Commerce Department's Advanced Technology

Program and to restrict global change and anti-pollution research conducted by EPA and the National Oceanic and Atmospheric Administration (NOAA).

The bill, Gore said, "would hurt American workers, jobs, and living standards now and well into the future." The Office of Management and Budget warned that agency heads would recommend Clinton veto the bill "because of its unacceptably deep reductions" in a host of programs. Brown complained that Republicans were targeting nonmedical civilian programs and favoring defense and medical research, calling the bill "a first step toward the most significant postwar reduction in science funding ever proposed."

Walker disputes Brown's analysis, saying that the GOP bill preserves basic research and cuts what he calls corporate welfare—joint industry-government research programs aimed at developing technologies likely to be critical for high-tech industry. He also dismisses the threat of a Clinton veto. "The White House is saying it will veto everything," he says. "I can't take these veto threats seriously."

Democrats had little success in altering Walker's plan on the House floor. Brown's alternative, which would have boosted spending for the seven agencies to $25 billion, slightly above the president's 1996 request, was defeated, 229 to 177. "It's tough sledding," admits one Democratic staffer. At the same time, fiscally conservative Democrats, led by Representatives Tim Roemer (IN) and Bill Richardson (NM), failed to win support for cuts of up to 30% in DOE laboratory staffs. Freshmen Republicans fared no better with a proposal by Representative Scott Klug (R–WI) that would have forced Energy Secretary Hazel O'Leary to sell the department's civilian laboratories and consider privatizing Lawrence Livermore National Laboratory in California.

In the Senate, there is little support for an omnibus bill, and even individual authorizations are facing an uphill battle, with NASA's the most likely to succeed. But Senate passage of even one could lead to a conference between the House and Senate, giving Republicans a chance to send at least one science-related authorization to the president.

The real impact of the omnibus House bill may be the heightened visibility for federally funded research. And even though the Administration opposes the details, it sees merit in taking a broad look across federal science. "It's clearly a good thing," says one White House official, "because it allows you to make trades, to compare and contrast priorities." And at a time when issues like Medicare, welfare reform, and the budget deficit dominate political conversations, science advocates from both parties say they need all the publicity they can get.

–Andrew Lawler

NUCLEAR DISARMAMENT

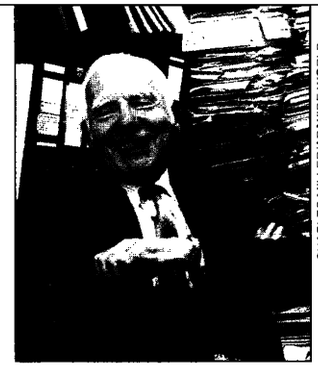
Physicist Wins Nobel Peace Prize

A British physicist, campaigner for arms control, and the only person to quit the Manhattan Project on principle has been awarded the 1995 Nobel Peace Prize. Joseph Rotblat shares the honor with an anti-weapons group he founded 38 years ago, the Pugwash Conferences on Science and World Affairs. (For news of the scientific Nobelists, see p. 380.)

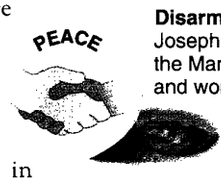
In awarding the $1 million prize last week, the Norwegian Nobel Committee praised Rotblat and Pugwash for working to "diminish the part played by nuclear arms in international politics" and trying to eliminate such weapons. It also wanted to deliver a pointed protest against recent testing of nuclear weapons by China and France, said Nobel committee chair Francis Sejersted, professor of economic and social history at the University of Oslo in Norway. Although one French politician declared himself "scandalized," the French government sent Rotblat its congratulations.

Rotblat began protesting the atom bomb even before the public knew it existed, according to a memoir he published of the event (*Bulletin of the Atomic Scientists*, August 1985, p. 16). In 1939, Rotblat, who had been studying the energy distribution of fission neutrons, was recruited to work on the Manhattan Project in Los Alamos, New Mexico. He says he participated only to deter the Germans, who had their own bomb project, from ever using such a weapon. In hindsight, he recognized that it was "folly" to imagine that this would have stopped Hitler.

One evening in 1944, according to Rotblat, the Manhattan Project's military commander, General Leslie Groves, casually mentioned that "the real purpose in making the bomb was to subdue the Soviets." This remark, and evidence that Germany had abandoned its own bomb effort, persuaded Rotblat in late 1944 that "the whole purpose of my being in Los Alamos [had] ceased to be." Rotblat asked for permission to quit, and immediately found himself accused of spying for the Soviets. The allegations, he wrote, were "rubbish," although he had broken security during the project by meeting and helping—without Army approval—a disabled friend in Santa Fe, New Mexico. According to Rotblat, the U.S. military used this protocol violation to pressure him into silence. His colleagues didn't learn for decades that he had left the Manhattan Project in protest.



CHARLES MILLER/AP/WIDE WORLD



Disarming winner. Joseph Rotblat quit the Manhattan Project and won a Nobel.

The experience "radically changed my scientific career," Rotblat wrote, for he realized that even the most esoteric research will find practical applications. In 1955, Rotblat drafted an appeal for peace addressed to all the world's scientists, signed by Albert Einstein, Bertrand Russell, and other intellectuals. It warned of the threat posed by thermonuclear weapons and urged scientists to find a way to prevent catastrophe.

This manifesto solidified into an institution after Rotblat organized a meeting of scientists and others in 1957 at the summer home of industrialist Cyrus Eaton, in Pugwash, Nova Scotia. "We tried to change the name," recalls William Epstein, a 30-year member of the Pugwash Conferences who later served as the United Nation's adviser on disarmament. "But people liked the sound of 'Pugwash,' and it stuck." In its Cold War heyday, Pugwash served as an unofficial channel for communication among weapons scientists and negotiators both in the Soviet Union and United States. In doing so, Pugwashers and Rotblat drew the ire of conservatives; the organization looked like a "vehicle for Soviet propaganda," as a Reagan Administration official said last week. Nonetheless, the organization supported technical talks that smoothed the way for a series of arms-control treaties, including most recently the 1992 Chemical Weapons Convention.

After quitting his job as a bomb designer, Rotblat conducted research in nuclear medicine. Colleagues cite his studies on autoradiography, the use of radioactive iodine as a diagnostic tool, and his debunking of a theory in the 1950s that nuclear fallout was responsible for rising infant mortality. But his greatest achievement, says physicist John Holdren, chair of Pugwash's executive council, has been "making it respectable" to believe that nuclear weapons can be abolished.

Now 86, Rotblat was "totally overwhelmed" by the announcement, says an aide, Thomas Milne of Pugwash's London headquarters, and Rotblat soon lost his voice from giving interviews. But he was able to communicate his intentions for the prize money: It will go into the Pugwash "peace chest" to further disarmament.

–Eliot Marshall