facing an uncertain future this fall. The National Aeronautics and Space Administration (NASA) is finding that many of its programs are about to run into a fiscal wall, too. Congress approved a total budget for NASA of $14.3 billion—"virtually a hard freeze," according to Senator Mikulski. This is just $26,000 more than NASA got last year, and $677 million less than the Administration wanted.

BIG SCIENCE PROJECTS

Project	1992	1993 req.	1993 approp.	change %
	($ millions)			
Space Station	2029	2250	2100	3
Superconducting Super Collider	484	650	517	7
Human Genome Project (NIH only)	105	110	106	1
Strategic Defense Initiative	3916	5312	3800	-3

One NASA program that Congress protected—the space station—will get $2.1 billion, a small increase over 1992 and about $150 million less than NASA requested. The Office of Space Science and Applications, which runs NASA's basic research, will receive $2.86 billion, 5% more than last year. However, in order to make room for the station's growth, many programs will have to reduce their ambitions. Congress killed NASA's 1993 request for the national aerospace plane and scuttled a $32 million darling of the White House Space Council called the "space exploration initiative," an attempt to plan trips to the moon and Mars. Congress also trimmed NASA's search for extraterrestrial intelligence and cut back a new rocket development program called the "national launch system." The three largest science programs, the big x-ray satellite (AXAF), the Earth Observing System, and the Cassini probe to Saturn, will all continue at a steady pace, however.

Budgetary supercollision. The Department of Energy (DOE) has taken substantial hits in all of its science programs, with one exception—the controversial $8.25 billion Superconducting Super Collider (SSC). Congress whacked $15 million out of the high-energy physics base program budget and then another $15 million from a proposed $30 million for a new injector at Fermilab's Tevatron accelerator. DOE's "small science" programs in materials, chemistry, and computing also suffered a $7 million cut from last year's level. And despite DOE promises to increase the fusion budget by 5% a year for the next 5 years, Congress cut $20 million from last year's appropriation.

In striking contrast to this bloodbath, the SSC was handily rescued from political oblivion with an appropriation of $517 million. This is $133 million less than the Administration requested, but substantially more than the $33.7 million the House offered last June, when it voted to cancel the project. Congress also gave the endangered Los Alamos Meson Physics Facility (LAMPF) a new lease on life by transferring the $64.5 million program to DOE's military budget. But DOE's contribution to the Human Genome Project is still in doubt, thanks to a last-minute, $28 million "general reduction" ordered for DOE's biological sciences budget (which still managed to eke out a slim 1%, $3.4 million increase). The agency has not yet apportioned the pain among its various projects.

Funding at other research agencies followed a similar pattern: None received big increases and many took small hits. Congress was working on the defense budget as *Science* went to press, but appeared ready to cut the Strategic Defense Initiative 3% while giving both in-house and extramural research a small boost. Funding of extramural science at the Environmental Protection Agency remained flat, as did the total approved for both internal and cooperative research at the U.S. Department of Agriculture. There will be a modest increase in funding for the National Oceanographic and Atmospheric Administration (5%) but a slight decline at the U.S. Geological Survey (-1%).

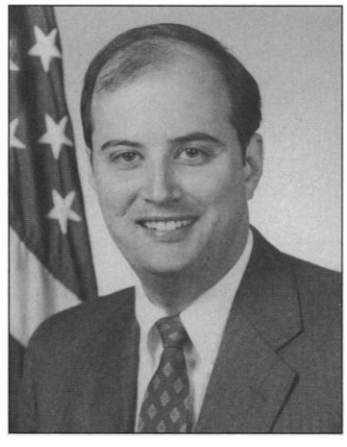
As bad as this picture may seem, things could be worse next time around. Much of this year's pain resulted from the tight spending caps on domestic discretionary programs in the 1990 budget agreement, which led legislators like Harkin to push as much spending as possible into the defense budget. Next year, the "fire wall" that separates defense and domestic spending will come down. But so will the spending caps, forcing additional cuts of up to $70 bil-lion. None of the champions of fiscal reform seems willing to take that entire amount out of the military budget alone. So, absent a new budget agreement, pressure on domestic programs—including civilian research—is likely to grow.

–Eliot Marshall and David P. Hamilton

GENE PATENTING

Top HHS Lawyer Seeks to Block NIH

A civil war that has been going on in the Department of Health and Human Services (HHS) over attempts by the National Institutes of Health to patent gene fragments of unknown function erupted into the open last week. HHS general counsel Michael Astrue told *Science* that he will force the National Institutes of Health (NIH) to abandon its patent application, but NIH Director Bernadine Healy promptly responded that she has no intention of dropping the matter. Although Astrue is the department's top legal official, it's not clear who will prevail. For one thing, Astrue is leaving HHS on 6 November to go into private practice, and for another, his boss, HHS Secretary Louis Sullivan, has not yet signed off on the issue.



Saying no. HHS's Michael Astrue is trying to stop the patent.

This power struggle between Healy and Astrue further complicates an already confused situation surrounding NIH's patent application. On 20 August, the U.S. Patent and Trademark Office issued a preliminary rejection of NIH's patent claim, a rejection that Healy has characterized as routine and easily overcome. (NIH has 6 months to respond.) But Astrue and others have described it as a devastating blow. Independent observers have been unable to determine who is correct, because NIH has declined to make the patent office's report public. *Science* has obtained a copy, however (see box on next page), and the handful of patent attorneys who agreed to read it on short notice tended to come down in the middle, saying the decision is slightly more than routine—but definitely short of devastating. The ultimate outcome is of broad concern, as several patent attorneys told *Science*, that NIH's is not the only gene fragment application before the patent office.

Astrue argues that the patent office's rejection confirms what he has long argued within the department: That the application never should have been filed in the first place. Sequencing of the gene fragments, done by former NIH researcher Craig Venter, does not constitute an invention, he insists, but is basic science "that does not meet the threshold requirements for a patent." And Astrue insists that he has the authority to block NIH from responding to the patent office's rejection. "I have to approve it, and I won't because I don't think they have a legitimate base for

What the Patent Office Report Says

■ Claims 1-24 are rejected under 35 U.S.C. § 101 because the claims lack patentable utility.... Given what is disclosed in the instant application, it would be necessary for one to do further work in order to establish a utility for any of the nucleotides embraced by the claims.... Although the oligonucleotides embraced by the claims may be hybridized to a variety of different preparations of other nucleic acids, one of skill in the art has no clue as to the significance of any result of such a hybridization because the instant application fails to provide any basis for the interpretation of any putative results.

■ The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention. The instant application indicates that errors are present in the sequences disclosed...thus, one of ordinary skill in the art cannot know what the invention is.

■ The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure. Each of claims 4-17 and 19-24 requires some knowledge about the coding regions of the DNAs disclosed in the instant application.... The application gives no information in connection with actual coding regions of any of the DNAs disclosed.... An inspection of Tables 6-9 shows that nearly 80% of the ESTs of the instant application have a poor probability of coding for any protein at all.

■ Claims 1-18, 20, and 22-24 are rejected under 35 U.S.C. § 102 (a) as being anticipated as the claimed invention was known or used by others in this country before the invention thereof by applicant for patent. The claims are broad enough and vague and indefinite enough...so that they embrace the cDNA libraries that were used to determine the nucleotide sequences disclosed in the instant application (Stratagene Catalog Numbers 936206, 936205, and 935205). Applicants acknowledge that the cDNA libraries used to obtain the sequence data of the instant application were purchased from Stratagene in California.

■ Claims 1-4, 7, 10, 11, 16-19, 23, and 24 are rejected under 35 U.S.C. § 103 as being unpatentable over Travis *et al.* in view of either one of Suggs *et al.* or Marcus-Sekura. Travis *et al.* discloses a DNA sequence from the gene responsible for retinal degeneration slow (rds), which sequence (Figure 3) contains a 15-mer that is contained in SEQ ID NO 9 (positions 12-26 inclusive). Each of Suggs *et al.* and Marcus-Sekura *et al.* teaches the use of oligonucleotides as short as 15 nucleotides in length as probes in processes of nucleic acid molecular hybridization. It would have been obvious for one of ordinary skill in the art to use the sequence data disclosed in [Travis] as a basis for constructing an oligonucleotide that would hybridize to the DNA of [Travis] in the manner and of the length suggested by either one of [Suggs *et al.* or Marcus-Sekura].

the application," asserts Astrue. Indeed, it turns out that Astrue—with Sullivan's backing, he says—already tried to block the application back in June by filing a petition with the patent office asking them to suspend action on it—which they obviously didn't do. This time, however, the secretary's support is clearly in question. "To say the secretary has made any policy decisions is flatly wrong," said Healy, challenging Astrue's authority. Similarly, a top spokesman for Sullivan said: "Mike Astrue is not Secretary Sullivan. A decision has not been made." And when it is, he adds, "Secretary Sullivan will speak for himself."

If Sullivan comes down on Astrue's side, the decision will be welcomed by the Europeans, who have criticized the NIH decision from the start. While the United Kingdom's Medical Research Council (MRC) has filed for patents of its own, that was largely a defensive move to protect the MRC's own interests should the NIH patent be granted. On being told that NIH is under pressure to drop the matter, MRC Secretary Dai Rees responded: "We would very much like to get to a position where we all felt safe in terms of not patenting." If the NIH application is dropped, Rees favors dropping the MRC applications as well but says the final decision would depend on discussions with Bill Stewart, head of the Office of Science and Technology, and UK science minister William Waldegrave.

If, on the other hand, Sullivan rules for Healy and NIH, they will clearly face an uphill battle in obtaining the patent. While describing the rejection as "typical" and "nothing dramatic," several patent attorneys noted that it is longer and more thorough than usual, covering all the bases. Even so, says Jorges Goldstein of Sterne, Kessler, Goldstein & Fox, "It does not impress me as an open-and-shut case. There is lots of room to maneuver."

One strongly worded rejection was on the grounds of "utility"—an issue that has plagued the application since NIH first announced it. The problem is that Venter does not know the function of the genes he has partially sequenced and is seeking to protect. Even so, he and NIH assert that the partial sequences (called ESTs for expressed sequence tags) are useful in several ways, as forensic markers for personal identification, for instance, or diagnostic markers for disease. The patent office was not impressed by these claims. But since this short section of the report does not take up NIH's claims one by one, patent attorney Henry Wixum of Hale & Dorr in Washington, D.C. sees it as simply "the opening shot across the applicant's bow on the utility question."

The patent office also rejected the claims on the grounds that they are "vague, indefinite, misdescriptive, inaccurate, and incomprehensible,"—standard boilerplate language, says Steve Bent of Foley & Lardner, though it is a bit unusual for the examiner to use all the adjectives at once. The patent office's bottom-line assessment is that Venter and NIH did not adequately define the invention or provide enough information to enable someone else to repeat what they have done. Indeed, in what Bent at least views as a serious challenge, the patent office attacks an underlying premise of the application—that the 300 to 500 base fragments Venter sequenced are sufficient to pull out entire genes. In the patent office's words, the claim "fails to teach one of skill in the art how to obtain complete genes."

The patent office saves most of its ammunition to challenge the application on the grounds that Venter's ESTs are obvious. This conclusion is based on a computer search that looked to see if any short 15-base stretches of Venter's new ESTs had already been published in the sequence databases. It found a number of matches. For example, one 500 base pair EST had 15 bases in common with the previously published sequence of the interleukin-2 gene. Venter dismisses this argument as "absolutely ridiculous." These are simply random matches, he says, that any good scientist would dismiss as meaningless. Another attorney puts the blame squarely on NIH, however, for attempting to claim sequences as short as 15 bases.

None of the experts *Science* spoke with saw the rejection as insurmountable. Wixum, for one, thinks it could be overcome—in a normal case. The problem is that this case isn't normal. Because the issue is "so hot," he predicts that the patent office will reject the patent, no matter what the merits of the response, and kick it upstairs, to the Board of Patent Appeals and Interference. "And I would not be surprised if the board thinks it is too hot and kicks it upstairs to the next level, to the Court of Appeals for the Federal Circuit." But all of that depends on NIH getting approval to respond, which at this point is in question.

–Leslie Roberts