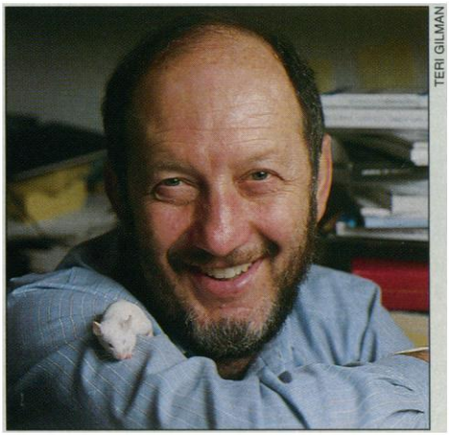
Hughes' Tough Stand on Industry Ties

Irving Weissman got rich, but conflict concerns cost him his plum position as a Hughes investigator. Other elite Hughes researchers are now wondering: Could it happen to me?

It's every scientist's secret fantasy: Start a small company around your research, watch the world beat a path to your door, sell shares in the company for hundreds of millions of dollars, and live happily ever after. For Stanford immunologist Irving Weissman, it came true—almost. In 1991, Weissman's company, SyStemix Inc., turned into one of the hottest biotech properties on Wall Street, but that sweet financial success soon acquired a bitter aftertaste. Weissman's employer, the Howard Hughes Medical Institute, decided that his ties to SyStemix constituted a potential conflict of interest and last October he resigned his envied position as a Hughes investigator.

Just what did Weissman do wrong? As far as Stanford is concerned, nothing. Stanford, which has retained Weissman as a faculty member, also looked into Weissman's relationship with SyStemix and decided that it did not contravene any university rules. (Hughes provides salary and research expenses for its investigators, who are on the faculty of universities and nonprofit institutions.) Moreover, Weissman claims that Hughes raised no objections to his company affiliation when he was hired as a Hughes investigator in 1989. Hughes officials contend, however, that they knew nothing of Weissman's involvement in SyStemix until they read about it in *The Wall Street Journal*.



TERI GILMAN

Cash mouse. Weissman's company extended his stem cell work from mice to humans.

As news of the Weissman case spread among other Hughes investigators in recent weeks, it has led some Hughes investigators to wonder if what happened to Weissman could happen to them. And the uncertainty may soon deepen: *Science* has learned that at least one other Hughes investigator, cell biologist Lewis "Rusty" Williams of the University of California, San Francisco (UCSF), may soon be forced to sever his relationship with Hughes because of his anticipated involvement with a research institute a major drug company is planning to establish at UCSF. Like Weissman, Williams contends Hughes officials initially gave their approval but later changed their minds. Again, Hughes says it never approved the arrangement.

You might think Hughes officials would be eager to broadcast their reasons for taking such a tough stand against Weissman and Williams, so that the institute's other elite investigators wouldn't find themselves in similar predicaments. But Hughes officials said nothing publicly about the cases until pressed by *Science* for comment. The institute then released a brief statement contesting some aspects of Weissman's and Williams' versions of the events, but declined to explain just how their activities may contravene Hughes' conflict-of-interest policies.

All this leaves considerable uncertainty about just what commercial ties Hughes considers permissible, and some Hughes researchers say they are now being cautious about

Conflict Confusion: Five Views on Equity

Should a scientist hold equity in a company for which he or she is consulting? The answer depends on whom you ask:

■ **National Institutes of Health (NIH).** Draft rules circulating in Washington last year (see page 885) are designed to help institutions themselves determine whether specific cases constitute a financial conflict of interest. George Galasso, NIH associate director for extramural affairs, says NIH intends to discourage researchers from holding equity in large companies with which they have a scientific affiliation, but not in startups, which often have little cash and nothing but equity to give. NIH would only explicitly forbid a researcher from holding equity in any company whose products he or she is evaluating under an NIH grant.

■ **Johns Hopkins University.** Last June, Johns Hopkins reversed a long-standing prohibition on researchers holding equity in companies they work with. Researchers may now hold stock, but they may not sell it until typically 2 years after the product on which they worked hits the market. For diagnostics the freeze could be only 1 year, but some drugs might require a 3-year wait. Other universities are said to be considering adopting similar rules.

■ **Howard Hughes Medical Institute.** Hughes does not allow any "significant" equity holding on the part of its investigators. Although it has no set rule on just what constitutes "significant," Hughes president Purnell Choppin says 5% is the rule of thumb. The greater the value of the company, he says, the less equity Hughes would allow. Decisions are made on a case-by-case basis.

■ **National Science Foundation (NSF).** Proposed regulations require a scientist to disclose all significant industry ties to his or her institution. It would be up to the institution to decide whether there's any conflict of interest, but the institution must pass the information on to NSF when the researcher applies for an NSF grant. NSF will then evaluate each case individually, says associate general counsel Micki Leder, but it hasn't decided how to treat equity. "Right now we don't know what to expect, and we want to allow for variation [in conflict policies] among universities" she says.

■ **Department of Energy (DOE).** Researchers at DOE's national laboratories work for the contractors that run the labs, not DOE. Those contractors (such as the University of California system and several university consortia) have varying rules, but Associated Universities Inc., which runs Brookhaven National Laboratory, is one example: Brookhaven researchers are allowed to own equity in companies as long as "the work they do for the company is decoupled from the work they do for the lab," says Mark Sakitt, the lab's assistant director for planning and policy.

their connections with industry. "It's a constraining influence," says cell biologist Robert Lufkowitz, a Hughes investigator at Duke University. "There's no doubt that it's restrictive." Hughes' rules, adds Williams, "have been a moving target for all of us. This kind of approach certainly doesn't encourage transfer of technology."

The Hughes statement does note, however, that the institute "encourages scientifically important collaborations with commercial enterprises," provided researchers clear them with the institute in advance. And Hughes president Purnell Choppin, in an earlier interview with *Science*, made the same point, noting that the institute has broad conflict-of-interest guidelines designed "to ensure that the fruits of the research [go] to the public good and not the good of a particular researcher or company. Our primary interest is that a scientist's work is science driven." Rather than providing its investigators with extensive written guidelines, Hughes instructs them to call before entering any deals. Hughes officials then evaluate each case individually.

Hughes is hardly alone in having vague conflict-of-interest policies. More than a decade after the biotechnology revolution, most institutions are finally drawing up rules, but no two are alike, and on issues such as scientists owning equity in companies, university policies now span the full spectrum from outright prohibition to qualified endorsement. On top of this, Congress is encouraging researchers to transfer technology to the private sector, but the National Institutes of Health (NIH) has yet to issue conflict-of-interest guidelines spelling out what is permissible (see box on this page).

But Hughes convulsions on the issue carry extra weight for the biotechnology industry and its links to academia. After all, as one Hughes investigator who requested anonymity puts it: "Hughes is the major funder of the top 200 labs in the world. Any decision it makes on this issue can have a profound impact."

Federal Conflict Rules Nearing Completion

After several false starts, the National Institutes of Health (NIH) and the National Science Foundation (NSF) are finally getting ready to issue guidelines on what constitutes conflict of interest among their grantees. With a final shove from Congress, the rules should be in place by summer.

NIH, in particular, has had a tough time drafting acceptable guidelines. Its first attempt, unveiled more than 3 years ago, was buried under an avalanche of some 800 angry letters from researchers and scientific organizations, complaining that the rules were too tough (*Science*, 12 January 1990, p. 247). NIH's legal office came up with another version—now configured as a full-blown regulation—in mid-1991, only to be sent back to the drawing board by NIH Director Bernadine Healy, who thought the revised rules on equity holdings were too weak. Late last year, NIH officials finished yet another draft, but this time eight different offices in the Department of Health and Human Services objected for various reasons and back it came for more work. Finally, just as the agencies reached agreement, the administration changed and the rules are again in limbo, waiting for the new administration to get around to them.

Congress, however, is about to step in. The Senate version of the NIH reauthorization bill (see page 889) directs NIH to release final conflict regulations within 180 days after the bill becomes law. Given that the bill is on a fast track and could be passed by the full Congress as early as this month, that language may force NIH into overdrive. If the language becomes law, the agency would have to release a notice of proposed rulemaking, receive and evaluate comments, and issue a final rule, all within 6 months—warp speed for a federal agency.

The 3-year delay, concedes Claudia Blair, an NIH official who worked on the rules, "is appalling." But on the other hand, she says, "it's preferable in an area this complicated and evolving to consider many perspectives. It's better to do it slowly and right."

At NSF, the transition to a new administration has also slowed progress on conflict rules. NSF published proposed guidelines in July last year and received some 70 letters before the comment period closed in October. Like NIH's rules, they are now awaiting review by the new administration. That means at least a 4-month delay before NSF could come up with final rules, says Micki Leder, the agency's assistant general counsel. And NSF director Walter Massey's impending departure won't help matters. NSF officials say the rules will probably have to await approval by the new director.

–C.A.

Divorce proceedings

If the Weissman and Williams cases are any guide, the message Hughes is sending its investigators would seem to be that Hughes is prepared to take a tougher stand on conflict of interest than universities are. Nobody is contesting the fact that both researchers' activities fall within the rules of their own institutions. But the issue is more than just one of differing policies. Investigators know that Hughes takes a hard line; what they're not so sure about is just where that line is drawn. And the Weissman case, born in confusion, has left even more confusion in its wake.

Weissman's commercial connections began in 1988, when he cofounded SyStemix, along with a Stanford colleague and a New York venture capitalist, to develop immunotherapeutics. The company was then valued at just $10 million. Over the next few years, Weissman and company researchers took his Stanford work on separating stem cells—immune system precursors—from mice bone marrow, and started parallel work at SyStemix on the technique in humans, for which they applied for a patent. The technology, which could lead to new treatments for cancer and immune disorders, quickly captured the attention of Wall Street types. Indeed, when the company went public in mid-1991, its value had grown to $49 million. Just months later, after the patent issued, the price went through the roof. Sandoz bought up 60% of the stock for $392 million, raising the company's paper value to $650 million, and the value of Weissman's share (which was diluted to 5.3% by the public offering and then cut again to 1.7% by the Sandoz purchase) to an estimated $16 million, including profits and stock.

Hughes entered the picture in 1989, when the institute bestowed on Weissman one of its coveted investigator awards. Weissman says Hughes approved his arrangement with SyStemix at that time. But Hughes' statement maintains that Weissman did not inform the institute of his relationship with the company, and the institute first learned of it in December 1991.

Hughes says lengthy discussions ensued aimed at bringing Weissman's relationship with SyStemix into line with institute policies, though the statement does not say what the problem was. According to Weissman, Hughes officials told him that the institute's policies forbid consultative relationships with companies in which a scientist owns a "significant" equity position. And, indeed, the one thing Hughes' Choppin would say about the case is that, in general, 5% is usually the threshold for "significant." But, Choppin says, the bigger the company, the smaller the equity holding should be, and even 1% of a $650 million enterprise can be too much. "If you're consulting for a company in which you're a major [financial] player, there is a potential, if not a real danger, that your research will be governed by the company's priorities," he says.

Whatever the cause of the dispute, the effect was a divorce, complete with lawyers, that came last October. Weissman's 13-per-

son Hughes-funded laboratory was transferred back to Stanford when Hughes phased out the funding it was giving Stanford for the lab. A Stanford statement prepared at the time (but never released until requested by *Science*) stoutly supported Weissman: Hughes and Weissman were severing their relationship "to resolve concerns arising out of differences between Stanford and [Hughes] Institute policies relating to consulting activity and intellectual property," the statement read. It concluded: "Dr. Weissman's activities have at all times been consistent with the university's policies on these subjects."

Confusion at UCSF

In the wake of the Weissman case, could some of Hughes' scientific giants conclude that corporate ties just aren't worth the trouble—or that Hughes' own munificence comes with too many strings? Take UCSF cell biologist Williams: "Hughes is on the side of being extra careful about interactions with for-profit companies, to the extent that it is not worth it for us to do it."

And he's not just sounding off. For the last year and a half, the Hughes investigator has been negotiating with a large pharmaceutical company that wants to set up an independent research center at the university. Williams would be the chairman of the institute's scientific advisory board, but no company funds would go to his Hughes lab. It seemed to all parties like a sound deal, and Williams says his initial check with Hughes last year indicated no problems.

Yet as the arrangements neared completion earlier this year, Hughes refused to allow Williams to participate in that capacity. "Their concern is that I'm working for the pharmaceutical company," says Williams. "That couldn't be further from the truth." The company's money, he says, will go straight to the university to distribute to the institute as it sees fit.

"I told them about [the deal] a year ago," says Williams, "but I didn't know it was going to be a problem until we got to the final stages of discussion," with the pharmaceutical company. By that time, he felt he was already in too far to back out. So Williams, like Weissman, may have to give up his enviable Hughes connection. "There's a good possibility I'll have to resign," he says.

Dingell on the warpath

Hughes' tough stance in these two cases may not be too surprising in view of the political climate surrounding conflict-of-interest issues. Congressional watchdog John Dingell (D–MI) is just one of several legislators sniffing around this issue, for example, and Dingell is asking two federal offices—the inspector general of the Department of Health and Human Services and the Defense Contract Audit Agency—to launch investigations of "profiteering" by academic researchers. He is planning a hearing this summer that will focus on several specific cases.

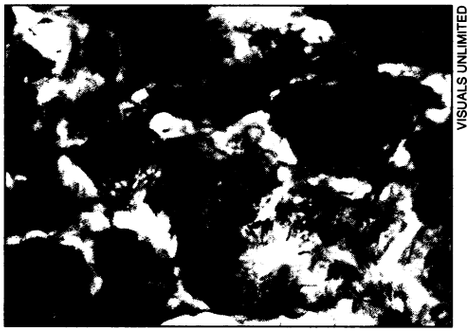
The last thing Hughes needs is a scandal involving one of its researchers. Yet Hughes' caution in the face of that threat imposes some of the nation's toughest conflict policies on its investigators. "Hughes has the best and brightest scientists in the country. It's got to expect them to be entrepreneurial," says Karl Hittelman, associate vice chancellor for academic affairs at UCSF. Many Hughes investigators are willing to accept the rules, as long as they know what exactly they are and that they won't change. But at the moment, that's not the case. And with the Weissman affair a reminder of how things can go wrong, Hittelman says, that's something Hughes will have to think about soon.

–Christopher Anderson

BIOMEDICAL FUNDING

A Shot in the Arm for TB Research

Almost 10 years after tuberculosis (TB) began making a comeback in American lungs, the disease is also regaining its place on the government's list of high-priority research topics. In one measure of concern, National Institutes of Health (NIH) Director Bernadine Healy plans to give the disease a quick funding boost by exercising for the first time her authority to reallocate money among the NIH institutes. In a letter to the Clinton transition team last December, Healy wrote that in 1993 she will devote $12.5 million more than planned to research on the TB mycobacterium and on new diagnostic techniques and therapies, obtaining $9.2 million of it by trimming other NIH tesearch programs.



VISUALS UNLIMITED

A mycobacterium rises again. And so does TB funding—at least for now.

That will raise NIH's total spending on the disease to $37 million in 1993—still too little, Healy thinks. To supplement that relatively small sum and help lure more researchers into studying TB, Healy also hopes to lobby Congress for millions of dollars in emergency funds to be spent this year. But congressional staffers say that will be a tough sell at a time when Congress is likely to be facing numerous budget-busting measures in President Clinton's upcoming economic stimulus package. And TB researchers, while grateful for any windfalls, say that the emergency funds won't address a need for sustained funding.

Healy's willingness to press the issue reflects health officials' increasing alarm over the disease, which is rising not only in incidence—the number of TB cases in the nation grew 18% from 1985 to 1991—but also in potency as new, drug-resistant strains appear. NIH officials are also feeling political pressure to devote more money to TB: Over the past year, several members of Congress have called for increased spending. At a congressional hearing last week, for example, Representative J. Roy Rowland (D–GA), a physician, tacitly accused Healy of neglecting the disease after it had become a public health emergency.

Healy's reallocation authority allowed her to take unilateral action. This power, which Congress granted to the NIH director 2 years ago, allows her to skim up to 1% of the budget from each of NIH's constituent organizations and direct it to other programs. In this case, the $9.2 million will come from across the board; the TB programs it will support are concentrated in the National Institute of Allergy and Infectious Diseases.

After years of receiving skimpy funding, TB researchers were quick to praise the increase. But many told *Science* that they are dismayed that at least some of the money will come at the expense of research in other areas.

Researchers would have fewer reservations about the still-undetermined sum that Healy hopes to get from Congress. But even if Congress responds to her plea, the emergency funds, like the transfer money, would apply only to 1993. Researchers worry that TB programs would be left high and dry after the emergency funds are depleted. "One hundred million or $1 billion is not going to turn this problem around," warns Barry Bloom of the Albert Einstein College of Medicine. TB researchers, he says, need "funding continuity and not some political fix." In light of this widely echoed view, Healy's efforts to win TB funding in 1993 may mark the beginning of a yearly struggle to fund research on a disease that, 10 years ago, seemed a quaint illness whose day had passed.

–Traci Watson