Labstyles of the Famous and Well Funded

Small labs have their partisans; so do big ones. The key, however, is not size alone but the style of the lab's chief—his talent for organizing, inspiring, and communicating

AS THE COMPETITION FOR FUNDING AND fame becomes ever fiercer among molecular biology laboratories, conversation among colleagues often turns to questions of style: What manner of lab is best for producing good science and staying competitive? In such discussions, the first topic is often size, in part because lab headcounts are creeping up, and facilities of 20 to 30 researchers are more common than they used to be. This trend sparks other questions: Must large labs sacrifice creativity for efficiency? How many people and research projects can one investigator effectively manage? Under what conditions might a lab director lose track of the papers to which he is signing his name—risking becoming party to fraud, misconduct...or just plain embarrassment?

While questions such as these have long been asked in private, events in recent years have made them public quandaries: Could many of Robert Gallo's miseries have been avoided had he been forced to employ a tough day-to-day manager for his sprawling lab? Did the recent announcement of two investigations into possible frauds in Leroy Hood's huge operation at Caltech indicate a major down-side of bigness?

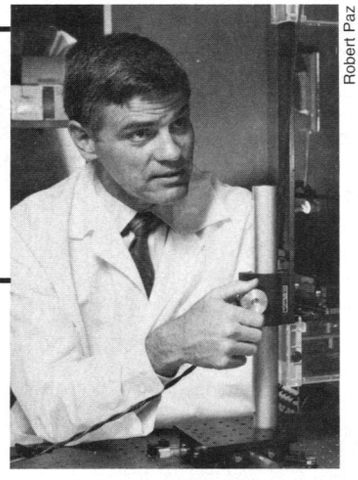
To many, of course, such matters have nothing to do with large size, and indeed there is the less publicly debated question of whether small labs are handicapped by their scarcer resources in competitive projects such as the race to identify important disease genes.

As engaging as the debate over size may be, however, it barely brushes the surface of the rich and complex subject of lab management. "It's like asking whether parents of only children are better parents than those with 10 kids," says geneticist Gerald Rubin, who runs a lab of about 20 people at the University of California, Berkeley. "There are some parents that do a good job with 10 kids, and there are parents who do a lousy job with one."

Rubin and others point to many qualities that define a lab chief's style and determine whether a lab environment—small or large—will be productive or flawed. While any list of qualities is bound to be incomplete, a survey by *Science* of several dozen top investigators turned up the following overarching themes: the capacity to inspire others, the sense of how to choose quality people and give them independence and direction, the ability to stay on top of fast-moving technology, and the knack for doing administration while finding the time to be available for the people in your lab.

Lee Hood

Lab size: 65
"Could I go [to the lab bench] tomorrow and do a perfect northern [blot]? No."



Robert Paz

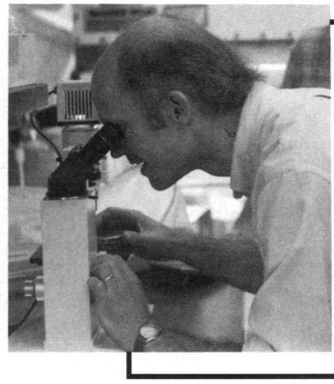
And—whether researchers resist the idea or not—lab size is intertwined with almost every other dimension of performance: how involved a lab chief wants to be in the hands-on work, how many different projects he or she can keep moving at once, and the degree of personal contact between lab head and staff. Therefore, the subject of size serves as a point of departure for any inquiry into the pluses and minuses of the lab styles of the well funded and famous.

In the teeth of the trend toward large labs, some prominent researchers, such as Steven McKnight of the Carnegie Institution in Baltimore, believe having a small lab has been crucial to their success. McKnight works in the competitive field of transcription regulation, and has made key discoveries concerning the nature of proteins called transcription factors that turn genes on and off. His success has made him popular among postdoc applicants, but lab size at the Carnegie is strictly limited, and his lab of eight can grow no larger.

That limit is a blessing, says McKnight, because it forces scientists to make hard decisions and pursue only their most creative ideas. In his own work, McKnight says he is less interested in "purifying seven more transcription factors" than in learning how such proteins interact with each other and with DNA. Continuously advancing to the next level of inquiry, he says, relies more on innovation than on manpower.

Examples that support McKnight's view are the UC San Francisco labs of David Cox and Richard Myers, both smallish operations of about 10 people in the competitive field of mapping disease genes, where large labs reign. Cox said he and Myers survive by "coming up with approaches that are tangential to what other people are doing, but are complementary in application." The approach has paid off, with a clever gene mapping technique called "radiation hybrid mapping," which Cox says makes possible a vast reduction of the effort required to find markers near a gene—and enables small labs to stay in the running.

But offering a couple of examples of small lab creativity doesn't prove that large labs are wastelands, according to UCLA immunologist Mitchell Kronenberg, who worked as a graduate student and a postdoc with Caltech's Hood. Hood counts 65 in his lab, not including several technical service groups that report to him; and for some people his name has become synonymous with large labs. That size helped Hood "develop a



Carnegie Institution of Washington

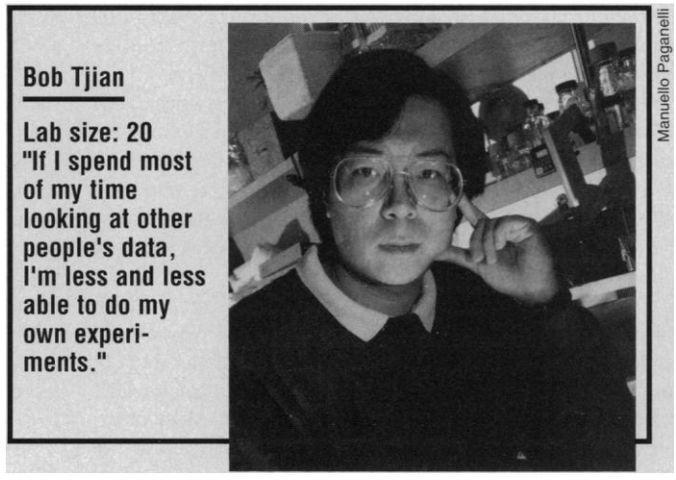
Steve McKnight

Lab size: 8
"I infuriate some of the people that work for me. I have to be careful not to crowd them. I can't help myself; perhaps it's my biggest flaw."

premier R&D workshop for biotechnology," Kronenberg says. "I don't know if he could have done that without assembling a lot of people and a lot of resources." The key to Hood's success, Kronenberg adds, is that his lab was doing cutting-edge science—and the needs of that science were driving technology development.

In the early 1980s, for example, many molecular biology projects were stymied by the lack of enough protein to get an amino acid sequence. Hood's lab conquered this bottleneck by developing automated microsequencing. Since then, his group has continued to take on technical challenges, improving techniques for DNA sequencing and synthesis of DNA primers—as well as pursuing key scientific questions.

Having a lab as large as Lee Hood's involves tradeoffs, some quite painful for researchers to make. One of the most difficult involves benchwork. The decision to leave the bench as one's career grows is another key element in a lab director's style that sparks debate. In a 1985 editorial in *Cell*, Jan Klein of the Max Planck Institute in Tübingen called it "perverted" to criticize a lab head for not working at the bench. "We are...paid for our intellectual capabilities," he wrote. "We should leave the routine to the technicians." Caltech's Hood agrees — he admits that he has lost touch with the hands-on skills but doesn't feel the loss compromises his ability to direct his lab. "Could I go [to the bench] tomorrow and do a perfect northern [RNA blot]? No," says Hood. "But can I look at a northern and know what it means? Of course."



But others with big labs worry that the loss of hands-on skill could have dangerous consequences for their scientific judgment. "If I spend most of my time looking at other people's data," says Robert Tjian, who studies transcriptional regulation at UC Berkeley, "I'm less and less able to do my own experiments, and eventually I'm not going to be critical enough, because I'm going to be out of touch." Tjian has managed to come up with a creative way to run a large lab of 20 people and still find time to work at the bench: Every Christmas, when there is a lull in other demands on his time, he goes back into the lab and does a project for 3 to 6 weeks. "I do it for therapy," he says, "and to learn a new technique."

But is having the boss routinely at the bench necessarily good for those in the lab? Not everyone thinks so. UC Berkeley's Rubin says working at the bench may in fact be a selfish thing to do, noting that back in the days when he ran a small lab and spent 40 to 50 hours a week on his own experiments, "I was telling everyone to 'go away, don't bother me, I'm busy with my experiment.' "

Other lab chiefs clearly manage to work at the bench without putting off those who need their guidance. Mark Schlissel, who is about to begin a job at Johns Hopkins University Medical School, says his graduate experience in Donald Brown's lab at Carnegie was shaped by the fact that he shared a research room with Brown and one technician. "I had access to him for half of every day for years," he recalls. When he began his postdoc in David Baltimore's lab at the Whitehead Institute, Schlissel recalls, one of the hardest adjustments was realizing that Baltimore wasn't there at the next bench, ready to "schmooze" about science.

Touching about as sensitive a nerve in the molecular biology community as the subject of benchwork is the quandary of focus: How narrowly or broadly should a lab head define the questions the lab will pursue? A broadly focused lab may provide postdocs with more opportunity to create projects they can take with them to new jobs. But it also requires a director who can keep track of many lines of research at once. And while a narrowly focused lab can make great progress in a particular direction, it can cause strife among lab members unless projects are carefully defined.

Like many heads of small labs, Carnegie's Brown keeps the focus on a single question—the regulation of gene transcription during development—and has no interest in following tangents that may lead elsewhere. "I don't feel the need to do all the science that can be done, that I can think of," he insists. For other scientists, however, the freedom to follow their curiosity wherever it may lead is what makes science worthwhile. Molecular neurobiologist Paul Greengard of Rockefeller University says his lab has grown to its present size of more than 30 people because he is continually asking himself whether the headaches of an expanding lab are worth the chance to pursue a new and "intellectually exciting" project. The excitement of new directions, he says, usually wins out.

Like Greengard, geneticist Gerald Fink, at the Whitehead Institute, also has an eclectic lab. "I don't have one project with 20 people doing parts of it," he says. "That's not my style." In fact Fink doesn't even focus on one system—his lab of about 20 people is divided between yeast and plants. Projects, he says, "range from secretion to gene regulation." Their genesis may be an idea brought in by a postdoc, or a tangent spun off from an ongoing project.

Fink says his postdocs and students are "captains of their own ships," and postdocs frequently take their projects with them when they go. One of Fink's former postdocs, Jef Boeke, cites that as an advantage. In Fink's lab he studied transposable elements in yeast, a project on which he has built his own lab at Johns Hopkins, without competition from Fink, who no longer works on the elements.

Even among the large labs, however, there are those that stay focused on particular questions. Berkeley's Tjian, for example, like McKnight, keeps his lab zeroed in on how proteins regulate gene transcription. When he first moved to Berkeley, Tjian says, he was dabbling in the areas of DNA replication and RNA processing as well. Spread so thin, he worried he wouldn't be able to make a significant contribution in any area. "Each one of those problems was huge if you wanted to dig to any depth," he says. "So I had to make a choice."

But within the tight structure of the Tjian lab, says postdoc Naoko Tanese, people have their individual identities and projects—a statement borne out by the fact that fully half of the 50 papers Tjian's lab has produced in the past 4 years have only two or three authors. And the lab's size and focus provide an advantage, Tanese adds, in that "there are plenty of people who work on something related." That means no one struggles with a technique for long, because there are others in the lab to help them.

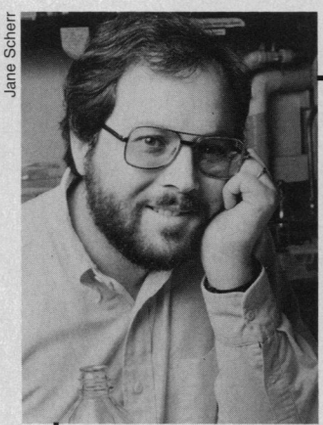
Regardless of the breadth of focus they prefer, lab heads must find a way to keep track of the science in their labs. Here too, there are great variations in style: in just how tightly or loosely they choose to hold the reins. Some feel it's enough to set the general intellectual direction with occasional discussions and let postdocs pick their own way. Others are inclined to decide which samples

should be run on tomorrow's gel. Some ex-members of Steve McKnight's lab complain that his vigilance gave them little room to be independent, a problem McKnight readily acknowledges. "I infuriate some of the people that work for me," he says. "I have to be careful not to crowd them. I can't help myself; perhaps it's my biggest flaw."

But as the lab grows beyond 10 or so, the potential for burdensome micromanagement is replaced by the challenge of keeping up. "I like to know details," says Charles Zuker, of UC San Diego. "I want to know exactly how the experiment was done." But with 18 people, following experiments to that degree is not trivial. Zuker has devised a clever—if heroic—scheme to overcome the problems of communication in a large lab: intensive nighttime meetings, after the regular workday, when people can be pried away from their benches.

Zuker studies phototransduction in the drosophila eye, and his group is divided into three subgroups, each working on the proteins involved in a different part of the process. Three evenings a week, beginning at 9 p.m., Zuker chairs a meeting with one of the subgroups, going over each member's data for the week in detail. During the day he has weekly meetings with the few lab members not in a subgroup. On Fridays the whole group meets to hear about one member's work.

Many heads of large labs use some variation of a plan like Zuker's to keep involved with the data on a weekly basis. But they also say the most important way to stay in touch is by wandering through the lab, dropping by people's benches, and talking with them one-on-one. "I wander around my lab and talk to people, 6 to 8 hours a day," says Berkeley's Rubin. Zuker, who worked as a postdoc with Rubin, agrees that this daily exchange was the most important link he had with his mentor, and one he emulates in his lab management as well.

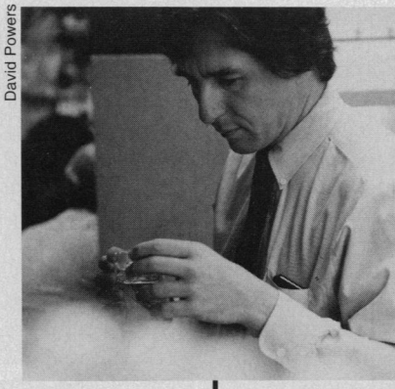


Jane Scherr

Gerald Rubin

Lab size: 20
"There are some parents who do a good job with 10 kids, and there are parents who do a lousy job with one."

Keeping in touch isn't just a way of organizing projects; it also helps ensure that no students or postdocs flounder because of lack of attention. Again, questions of lab style—and lab size—arise. Carnegie's Brown believes the best mentoring is done in small labs. He compares guidance of postdocs and students to raising children: "They're all different, and there is no generalization for the amount of time they need.…Some postdocs don't like to be bothered, and I stay away from them. But [in my lab] they will never fall between the cracks."



David Powers

David Cox

Lab size: 10
"Approaches that are tangential to what other people are doing, but are complementary" enable small labs to stay in the running.

Berkeley's Tjian acknowledges that "it's more of a temptation to ignore [floundering projects] in a big group, because you've got other good things going on." He says he relies on subgroup meetings like Zuker's to pick up on projects that seem to be in trouble. Postdoc Tanese says that system worked for her when she was spinning her wheels. Although her slow-moving project wasn't attracting Tjian's daily attention, he sensed the problem after a sub-group meeting and convinced her to switch to another project that had a better chance of quick success before she lost any more time.

But as labs approach the size of small corporations, it becomes almost impossible for one person even to touch base regularly with all lab members, something Caltech's Hood is quick to acknowledge. Most of his postdocs, he says, interact primarily with the senior person in their subgroup. "Some really want to relate to me," he adds, but "they have to be energetic enough to capture me." Indeed, says one ex-Hood student, with the combination of Hood's travel schedule and the lab size, some postdocs worked for months without interacting with their leader.

An often-raised question is whether this lab style—interacting with the lab through lieutenants who run big projects—leaves a lab director open to fraud. Hood, who recently had to retract two papers because of alleged fraud, refutes the notion that he is out of touch with his lab's publications. "I don't put my name on the paper unless I have made an intellectual contribution to it," he says, adding that this means going over data and drafts of the paper, although the writing is left to the first author. Ex-postdoc Kronenberg agrees that that is the case. Hood may not have been involved in the detailed planning of the experiments, he says, but "at the point of putting the paper together, he would look at it quite critically."

Indeed, while critics of large labs often claim that the directors stamp their names on papers they haven't even read, most cases of apparently gratuitous authorship involve not a single large lab, but a collaboration between labs, in which a lab head may become author on a paper he has had little to do with, simply because his lab provided reagents or services.

Apart from the issue of collaboration, directors of large molecular biology labs dismiss as totally unfounded the notion that they don't know what is in their labs' own papers. "I don't know why that myth got started," remarks Rockefeller's Greengard, who says he is intimately involved in writing every paper that has his name on it, from the planning of what data will go into the paper, to the rewriting and editing of the text.

In the end, biologists of all stylistic persuasions seem to agree, many different styles will work well in running a lab. What counts is not the specific style, but the quality behind it. "What I care about is the specific activity of the lab, the productivity per person," says Berkeley's Tjian. "If the number of good papers goes up roughly proportional to size, then you're OK." By that standard, Tjian and McKnight, for example, are on even par: Both Tjian's lab size and his total number of papers for the last 4 years are roughly 2.5 times that of McKnight, who works in the same field and publishes in the same high-quality journals

Another measure of merit may be the quality of scientists produced by a lab, and it is evident if one does a survey of bright young investigators that they come from labs with many quite different management styles. Just as their own personalities drew them to mentors with particular styles, they are carrying on their own science with that same degree of variety, prompting the conclusion voiced by Steve McKnight: "There isn't any one right way to do it, there are all different kinds of right ways." ■ MARCIA BARINAGA