Lab Extraordinaire

Giving high-powered scientists a free hand, even under crowded conditions, results in impressive achievements at the Laboratory of Molecular Biology of Britain's Medical Research Council

By JULIE ANN MILLER and
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MRC, Cambridge Evening News

John Kendrew shows the Queen a three-dimensional model of the myoglobin protein.

As a chemist working on a biological problem in a physics department in the 1940s, British scientist Max Perutz was insecure — about his position and his future funding. But taking a long shot, he convinced the British Medical Research Council to employ him and a colleague as a new, two-person research unit for "the Study of the Molecular Structure of Biological Systems"; the title was nine years later shortened to "Molecular Biology."

Since this rather humble beginning, the unit's staff has expanded to include an array of high-powered scientists whose work has been central in putting biology on its modern footing. Under Perutz, and more recently Sidney Brenner, the MRC Laboratory of Molecular Biology has forged an impressive record of scientific achievement, reflected by the Nobel Prizes awarded to the MRC with almost predictable regularity.

This year's Nobel Prize in Chemistry to Aaron Klug for detailed elucidation of biological structures (SN: 10/23/82, p. 261) is just one more jewel in the crown. Two years earlier Fred Sanger was awarded his second Nobel Prize — the first was for methods for studying proteins, the second for methods for studying DNA. Earlier Perutz and his colleague John Kendrew received a Nobel Prize for work on the structure of hemoglobin. And Francis Crick won with James D. Watson for the work done there leading to recognition of the double helical structure of DNA.

What's so special about the MRC lab? Certainly the physical plant appears perfectly ordinary, even a bit dowdy. It occupies several floors in a squared modern building that's part of a hospital complex on the outskirts of Cambridge. But inside is evidence of the odd array of forces that make the laboratory exceptional.

Many university labs are cluttered, but at the MRC clutter is worn like a merit badge. Most striking in the decor are dusty, oversized models of a virus, a DNA molecule, a protein sitting on stair landings or dangling from ceilings. Halls are lined with equipment, both instruments in use and monuments to achievements past. Some old pieces of equipment are kept limping along because they are original prototypes of instruments now widely used. The older instruments are held in affection because they've worked so well for so long, even without the streamlined conveniences of later models. But the labs are jammed also with a great deal of new equipment, the best and most modern instruments.

Crowded in among the instruments, new and old, are scientists working elbow to elbow, often stepping, literally, on one another's toes. But such proximity does not seem to spill into many clashes of temperament. Some of the inhabitants even bemoan the fact that since the laboratory has expanded to include two stairwells, everyone does not encounter every other colleague daily on the stairs. The lab is determinedly congenial, and overcrowding is merely a fact without being a troublesome factor.

"The MRC is an excellent environment for doing everything; it always has been," says John Sulston, one of its members. "Young scientists invariably fall in love with this place. And if they're bright, they flower here."

"We usually do get very good young people here," says Sanger. "And they keep us alive with their new ideas."

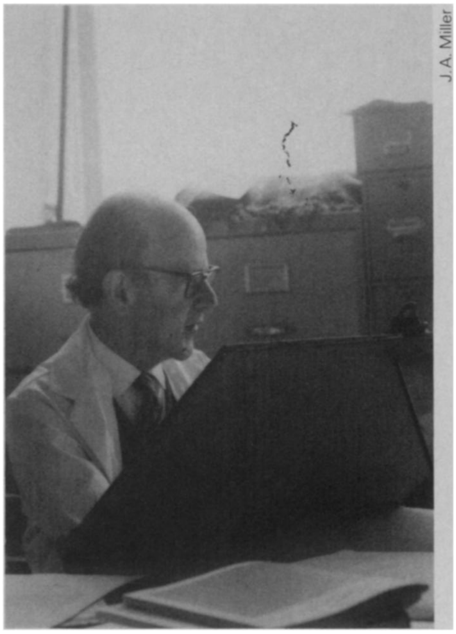
Among the young scientists are many Americans who gravitate to the laboratory for a few years of grooming as "post-docs" after getting their Ph.D.s. They seek the opportunity to do unfettered research in a scientifically unfettered atmosphere. "The place is very unAmerican, very refreshing," says one such post-doc, referring not to a subversive atmosphere but to the fundamental character of the place. "Very little of what lulls American professors into nonresearch activities happens here," he explains. At the MRC investigators have little administrative work and few funding worries or time-consuming committee and teaching duties. "American science

Jeffrey L. Fox, a senior editor at Chemical and Engineering News, *and Julie Ann Miller visited the Medical Research Council Laboratory of Molecular Biology in Cambridge.*

carries those obligations and the pressure to build an empire. That doesn't happen here, or doesn't have to. A surprising number of established people are still doing experiments themselves, instead of worrying about the bureaucracy," the post-doc says.

"The only deliberate policy has been to appoint people of outstanding talent and give them a free hand. This is the only policy that leads to good scientific work," says Perutz, who still influences important matters at the lab. Perutz is a cheerful, deceptively mild-mannered man who seems more like a scholarly don, well-steeped in classical languages, than a Nobel Prize-winning X-ray crystallographer.

The deft hand of Perutz is credited with working many quiet wonders over thirty years. "We endeavored to create a congenial atmosphere," he says. "There's no recipe for this; it needs warmth and human feeling, and having a genuine affection for your colleagues and respect for their scientific work." Thus, there is little or no hierarchy or bureaucracy at the MRC for most of the scientific staff. They're just members whose work is judged on its scientific merits.



J. A. Miller

Max Perutz

J. A. Miller

Aaron Klug

"A man who works alone has just as good a chance for promotion as one who directs a lot of people," Perutz explains. "A's career is not blocked by B's. And criticisms often come from below. Any student can tell you you're a damn fool. We avoid the dreadful hierarchy of the German system where the rule is that you don't contradict the head of the lab. The opposite applies here: You do contradict the boss because, more often than not, he's wrong."

Perutz and his colleagues also point with pride to the sociable touches at the lab, particularly the canteen on the top floor where staff members congregate for morning tea and afternoon meals. The food itself is consumed with almost Spartan indifference, by and large being something less than gourmet. It's really just a prelude, and meal trays are quickly pushed aside for the real nourishment — talk, talk and more talk. The canteen is high enough to provide a grand view of the surrounding lush countryside from windows open on three sides of the building. But nobody takes much note once a scientific discussion begins to brew.

The canteen atmosphere helps nourish what's considered another important element of the lab's overall success — free-flowing collaborations. Young scientists arrive at the MRC with their projects ostensibly outlined and their mentors selected. But in practice, intellectual alliances at the MRC are remarkably fluid, and everything is done to encourage that flexibility. "The expertise available here is marvelous," Perutz says. "If anything, we want to force collaboration between different parts of the lab."

"People here on the staff are more reflective, and the Americans more frenetic," says British staffer Peter Lawrence. "The Americans probably keep us from going to sleep." In turn, the Americans undoubtedly benefit from building up the intellectual independence that's thrust upon them at the MRC. "Those who come here end up in better shape than their colleagues who stay behind in the U.S. and work as pawns for someone else," he claims.

There is a growing gulf between the American style of doing science and that practiced at the MRC. And most MRC staffers staunchly defend their ways. "Here people do their own work," Lawrence continues. The sure sign of success in the United States is growth in grant support, inevitably accompanied by the need to be a lab manager instead of being directly involved in research. "It doesn't seem efficient to take people, chosen for their competence in a laboratory doing research, and have them stop doing their own work so soon," Lawrence insists. Twice recipient of the Nobel Prize, Fred Sanger says, "The MRC has allowed me to just do research. I have been keen not to get involved in teaching and administration because I am not particularly good at it."

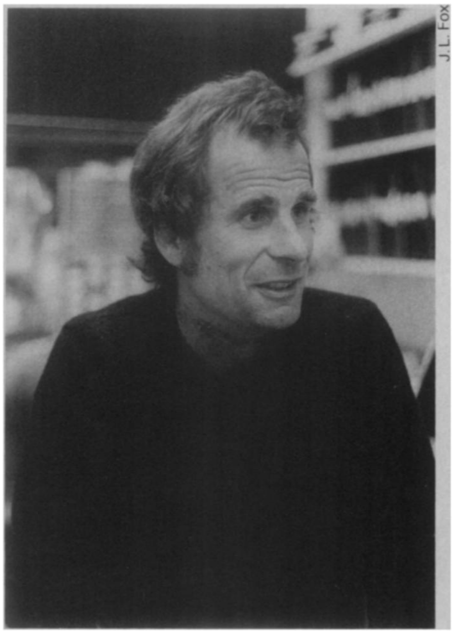
If the MRC wisely insulates its staff from the necessity of doing managerial work, it also tends to cut it off from involvement in decision making that affects the lab, some members complain. A ruling oligarchy holds sway at the MRC and tends to exert paternalistic control that rankles some on the permanent staff. "The people running this place have gotten older," says one such scientist. "If an oligarchy becomes aged, they may not always make good decisions. When they were younger they had directive power. But now the younger people have no such power."

The rumblings of discontent sound, for instance, when the lab adds on new staff people without allowing current members to voice objections. "Some of us have complained bitterly for not being consulted," says another of the middle-rank scientists, adding ironically: "We never have had the opportunity to exercise the 'wisdom' of being young. Besides, some of us 'Turks' are getting old; we might be 'young Turks' until we retire."

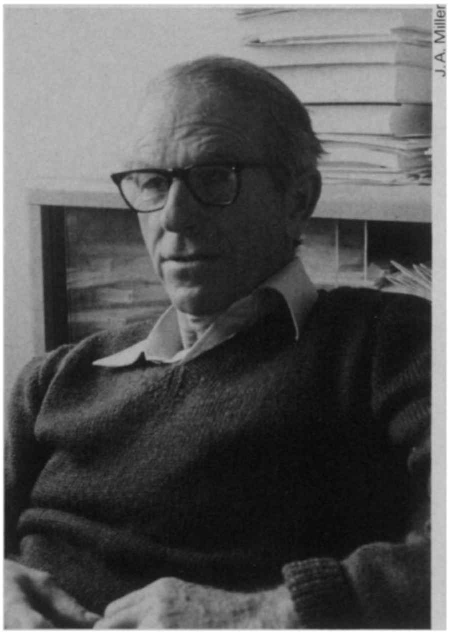
But if there are occasional, even bitter, disagreements about management policies, the younger scientists admit an advantage of the MRC far more important in their eyes. The older scientists, although they may dictate in administrative matters, never interfere with their younger colleagues' scientific activities.

Under the free set-up of the MRC, there is no shortage of ambitious men and women to tackle difficult questions. Lab director Sidney Brenner, for example, is credited with instigating a whole new chapter of biological research. He prompted a school of scientists, now numbering more than a hundred around the world, to study the lowly worm, a nematode with the scientific name *Caenorhabditis elegans*. "Brenner invented the worm as a modern system for studying development," one of his colleagues explains. Brenner expects it to make puzzles of development accessible to the powerful tools of molecular biology and genetics.

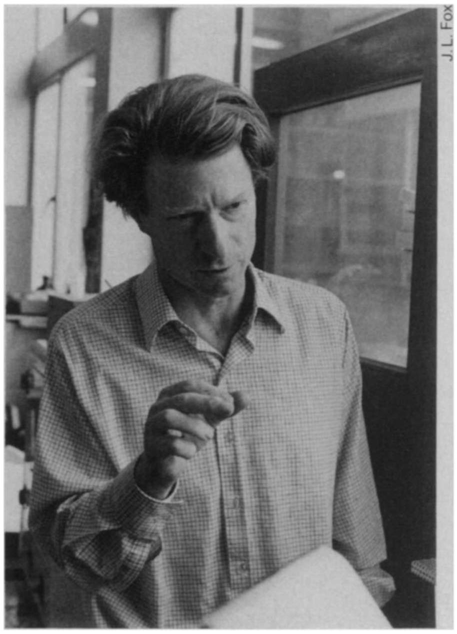
An amazing feat, recently concluded at the MRC, is the complete description, cell-by-cell, of how a nematode develops. It is an example of a project too big to be tackled by most sensible scientists working under the typical confines of university jobs. However, John Sulston at the MRC has painstakingly watched under a micro-



Peter Lawrence



Fred Sanger



John Gurdon

scope all the steps of how nematodes grow from a single fertilized egg to an adult of about 550 cells. In pages of diagrams resembling bunches of red, green and blue sketched balloons, he has recorded the history and fate of every cell as it grows, migrates, dies or divides. "In the worm we really know where all the cells come from," he says. Many basic questions about how this animal develops can be answered from this extensive description, and scientists are predicting that some of the answers will be applicable to larger animals as well.

Frogs are about the largest animals now being used as research subjects at the MRC. Before moving to the MRC, John B. Gurdon established an international reputation by cloning a frog from genetic material taken from a pre-tadpole embryo.

Now, in the interest of understanding how genes are turned on or off during development, Gurdon's work has shifted largely from whole frogs to amphibian eggs. He and co-workers inject genes from a variety of sources into eggs to identify the gene-controlling factors. "We have to go at things gently; so far we can only ask for the minimum result," he explains. "But the most interesting problem is the one of gene control."

The world of the MRC does not turn solely on the worm and the frog. Other scientists are studying problems that range from molecules to muscles. One of the greatest strengths of the MRC has been the group of scientists who analyze the structure of biological molecules. For decades Perutz, for example, has studied such proteins as the oxygen-binding component in blood. Even now he persists, intent on perfecting an analysis that his peers have acclaimed for years.

"People are very keen on their work here," Perutz says of his colleagues. But the same must be said for him, as he shuttles between office and lab to take intermittent readings in an ongoing experiment. "I'm still working on hemoglobin," he apologizes. "We crystallographers are fanatical about fine precision of structure." He is in the midst of a project that subjects hemoglobin to synchrotron radiation to get new data, and he plans to spend at least a year figuring out what those data mean.

Others at MRC also have compiled impressive successes in describing molecular structures. Aaron Klug, for instance, has put much of his effort into understanding small organisms, such as viruses. The tobacco mosaic virus, one of his pet projects, is some ten times larger than a hemoglobin molecule. "To solve its structure, we had to develop new analytical techniques. The problem was difficult and unorthodox," Klug says.

His contributions include a means to construct three-dimensional images from two-dimensional pictures obtained from high-powered electron microscopy. "Anybody working on organized structures, whether they be cell walls, ribosomes, chromatin, or protein fibers in muscles, can use this technology," he proudly adds. "This place is a bit like a physics lab, with a good workshop to make equipment. That's one of the secrets of our lab." He says, "Most of us who started as physicists have had to acquire our biology over the years."

It was interest in long-range, esoteric questions about the immune system that unexpectedly led Cesar Milstein and his associates to monoclonal antibodies several years ago (SN: 12/30/78, p. 444). They developed a technique for generating large amounts of a single (monoclonal) antibody from descendents of hybrid cells composed of a tumor cell and an antibody-producing cell of the immune system. Worldwide, interest has since turned to monoclonal antibodies, first from the research community, but also from people with a more practical and sometimes entrepreneurial bent. For instance, companies that make the materials for clinical diagnostic tests are including monoclonal antibodies in their kits. The antibodies are also being developed as tools to purify valuable molecules, as tags to identify cells, and as part of a system to deliver drugs to specific targets in the body.

"The fact that this technique is now used so widely comes as a surprise even to me," Milstein says. "I didn't think it possible, when you do one experiment, that something could be so widely applied." But research, turned into useful technology, can take on a life of its own.

To some extent the success of the lab is simply a self-perpetuating phenomenon: the MRC's good record attracts good people to come and do more good work. And at the MRC they are gracious enough toward one another to permit individual styles to flourish, from the brash to the modest. For example, according to laboratory lore, it was only after drinking a few glasses of champagne to celebrate his second Nobel Prize that Sanger announced to his colleagues, "I *am* good."

For everyone at the MRC, there is the thrill of gambling on unguaranteed pursuits. And that is often when science is the most rewarding. Sanger puts it succinctly: "I tend not to plan too far ahead. Usually I give the wrong answer about what I will do next." □