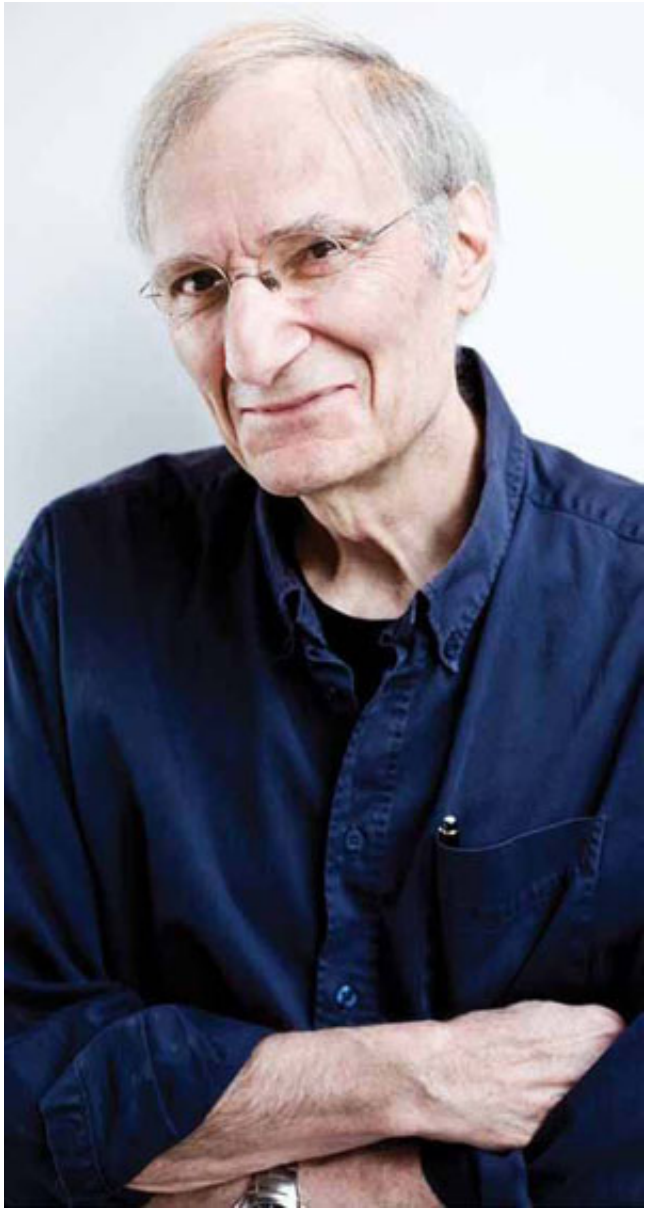
Martin Raff has used antibodies to examine membranes, immune cells, and shine a light on nervous system function. But he doesn't believe in waiting for the full story before publishing.



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It was the Vietnam War that led Martin Raff to a life in science. He was knee-deep in a neurology residency at the Massachusetts General Hospital in Boston when rumors suggested that America's draft law would soon change, making immigrant physicians like Raff eligible until age 35. "I would have been sent to Vietnam for sure," he says. Instead, Raff hotfooted it to Canada (he was born in Montreal), traded in his green card, and returned as an exchange visitor. The revised status excused Raff from military service—but it meant he had to leave the United States when his neurology training was complete.

That's when a friend sent him a one-page *Science* article about immunology research at the National Institute for Medical Research, Mill Hill, in London. Raff was intrigued, but colleagues told him that Mill Hill—home of luminaries like Peter Medawar—would be tough to get into. "So I went back to the article," says Raff, "and I couldn't understand most of it. But the person I could understand least was this guy Av Mitchison. I had no idea what he was doing. So I thought, well, maybe he'd be a good target." Raff figured few would want to work with a guy whose work was incomprehensible. "So I wrote to Mitchison and he said yes," says Raff. "And that was the best luck of my life."

A serendipitous scientist, Raff is full of counterintuitive advice for young scientists starting their careers. Here he shares some random thoughts about his life as a biologist, the dangers of peer review, and his love of Leonard Cohen.

LAB RAFF

Although he never received a Ph.D. —and had not done any real science—Raff was treated as a postdoc when he arrived at Mill Hill to work with Avrion Mitchison. That trust paid off. Within 2 years of his arrival, Raff had worked out ways for using antibodies to distinguish T and B cells. The approach allowed him to identify, separate, and study the origins and activities of each type of lymphocyte—and it precipitated publication of 13 papers, four of them in *Nature*. "Those years at Mill Hill were by far the most productive of my scientific life. It was really downhill from there," he says. "I had a sole-author *Nature* paper in my first year in science," says Raff. Mitchison had begun raising the first antiserum before Raff even arrived. "But when it came time to write up the results, he refused to put his name on the paper," says Raff. "That scuttled me right to the top. People began talking to me as if I were an expert in immunology—even though I knew bugger-all when I started."

In 1971, Raff and Mitchison moved to University College London. There, they submitted a program grant to the Medical Research Council (MRC), proposing to use the antibody-based approach to distinguish and manipulate cells in the nervous system. "Neither of us knew any neurobiology, really. So what we wrote was pretty naïve," says Raff. "But amazingly they funded it." Raff then renewed the grant every 5 years, eventually focusing his attention on the development of oligodendrocytes, the glial cells that myelinate axons in the central nervous system. That same grant provided his salary and research costs for the duration of his scientific career. "Needless to say, I am in the debt of the MRC."

RAFF'S RIFFS

"What's wrong with science today? Many things. And it's all scientists' fault," says Raff, who offered *The Scientist* some thoughts on learning to share, writing little papers, and taking the profit out of winning prizes.

"You really benefit from sharing everything: ideas, reagents, mice, everything. It pays back in spades. So my advice has always been to share everything."

The perils of peer review. "Publishing has become a nightmare. Particularly for young scientists, who can spend a year or two doing the experiments that referees demand. I think this is a terrible thing, because referees' experiments in my view can be dangerous. One, because you've put the student or postdoc into a position where they know that, if they get the results the referee wants, their paper will get into the journal and their career is on its way. If they don't, they won't get it into a high impact journal and they're in real trouble. That is just putting enormous pressure for selecting your data and cutting corners. So it's very dangerous. And secondly, I think referees are often asking for experiments that will increase the probability of the conclusions being right by 3 or 4 percent. It's putting a real brake on the progress of science. In the best of all possible worlds, what you would like is for all papers to be published, just making sure that the conclusions are reasonable given the observations. And then retrospectively assess the impact and importance of the paper."

Risky business. "We encourage young scientists just setting out to do conservative science. They leave a productive postdoc and get an independent position. Then, to get a grant, they more or less have to write a project on what they were doing as a postdoc. Which immediately sets them down a conservative pathway, often competing with their former mentor. It's not what you would like. We need a way to encourage young scientists to do bold and pioneering science rather than conservative science. That means you can't assess them after 2 or 3 years by their publications. You've got to give them more time and assess them by the importance and novelty of what they're doing."

What's in a grant? "It makes little sense to judge a grant mainly on the basis of the project. Because most of the time, the project isn't going to get done the way it's outlined in the grant. If you knew exactly what you'd be doing three to five years from now, you probably shouldn't be doing it. Because the results of what you do today may change what you should do tomorrow. What you really want to assess is track record. Somebody with a track record of continual productivity is likely to be productive in the next several years, so give them the bloody grant."

Name an intriguing problem yet to be solved. "Why are some cells small and other

cells big, even in the same animal? Why do we grow to be so much bigger than a mouse? You might say, 'Well, that's just genes.' Of course it's genes, but what genes? And how do they work? I'm not aware of more than a handful of labs working on cell size control, yet the problem of cell growth, how a cell enlarges, is as fundamental to life as cell division, how cells divide. Yet, there's probably a hundred times the number of labs studying cell division and cell cycle control than studying cell growth, which makes little sense."

"It's generally felt to be an admirable trait in a scientist to only publish big complete stories. My own view is that this is selfish and can be dangerous."

Are big prizes good for science? "I'm on the Lasker Jury. So I think about prizes from time to time and ask myself that very question. There are two main rationales for giving these prizes. One is that it creates role models for young scientists. Well we know that doesn't work, because big prizes have been given to scientists known to behave abominably. The other rationale is that it's a way of letting the public know that its support for science pays off. Because people generally are much more attuned to people than they are to abstract concepts and advances, this rationale makes sense. What does not make sense is the large amount of money that goes with these prizes, because none of the winners need the money—not for their science and not for their personal lives. And science has nothing to do with money in that personal sense. I think many scientists prize the fact that they're not evaluated by the salaries they earn. They're valued for their discoveries and that's the way it should be. It's kind of ennobling for the whole profession. I would reduce the money so that it becomes irrelevant."

What's mine is yours. "Your instinct when you're starting out is to be defensive and protect what you have. You've made a reagent, you've made a mouse, you've had an idea that somebody else could jump on and run with very quickly if they knew about it. So your tendency is to keep things to yourself rather than sharing. But it turns out that's the wrong choice almost every time. You really benefit from sharing everything: ideas, reagents, mice, everything. It pays back in spades. So my advice has always been to share everything. Until you get burned. And if you get burned, reconsider. I think it benefits the field and makes your life as a scientist so much more pleasurable. Sharing is not instinctive; it needs to be taught. But it's important, I think." *(See also Critic at Large, "One of the Good Guys" by H. Steven Wiley, in this same issue)*

Write little papers. "So you've made an interesting observation that you think has legs and you're pretty confident you're on the right track. At that point I think it's very useful to stop and draft a paper, with a title, results—even if you have to make

up some results because you haven't done the experiment yet—and a discussion or abstract to draw the conclusions. What you learn when you do that is (1) what it is that you think you have discovered, and (2) do your experiments really nail the conclusions? If not, what do you have to do to be able to nail them? And perhaps more important than all the other benefits, it tells you what you don't have to do, so you can avoid doing experiments that are not needed to nail the most important conclusions."

The approach lends itself to publishing experimental results in small installments—a recommendation that Raff says is generally frowned upon. "People are horrified whenever I suggest it," he says. "It's generally felt to be an admirable trait in a scientist to only publish big complete stories. My own view is that this is selfish and can be dangerous. Publishing small steps ensures that each step is secure before you move on. It also makes the findings publicly available early, and it benefits your students and postdocs. If you can find other scientists who buy into that, I'd like to know who they are. I'll send them flowers."

RAFF AFTER HOURS

Don't put off 'til tomorrow. "I am absolutely neurotic in being unable to procrastinate. If I've got something hanging over me for an hour, I find it unbearable. It means I have to do everything right away. This is a dangerous trait to have. Because of course it means that people will pile more and more stuff on you. If you're an editor, you're going to send more papers to this lunatic who sends reviews back within a day or two. It's a disability, but it's made me the free and easygoing guy that I like to think I am."

On the bedside table. "I tend to read nonfiction. It's part of a puritanical feeling that I should be bettering myself. The book I'm reading now has shaken me up to such an extent that I have trouble focusing on anything else. The name is "Family of Secrets" by Russ Baker. It's a book about the Bush dynasty, and it is frightening. It has shaken me to the roots and I may never be the same again."

In the current playlist. "I'm such a Leonard Cohen fan. Many people find this the most endearing part of my personality. We grew up in the same neighborhood, went to the same schools, same summer camp, same fraternity, same university. So I knew him quite well. But that has nothing to do with the fact that I think he's absolutely brilliant. You've got to listen to the words when you listen to a Leonard Cohen song. He's a poet."

Molecular Biology of the Cell. James Watson convinced Raff to join the author

team. "'You'll be doing a service for science,' Watson said. 'Besides, it doesn't matter what you do in science. If you don't do it, somebody else will do it within a month or a year or maybe a few years. But this book will be the most important thing you do in science.' I thought he was right when he said it. And I think he was absolutely right in retrospect. So it was the right thing to have done. No question."

RAFF'S GREATEST HITS

Used antibodies to separate and study mouse T and B cells.

Determined that B cells develop in bone marrow from pre-B cells. "This was an important contribution to our understanding of B cell development," says Raff. "And it just fell out of having markers for B cells."

Produced some of the first evidence that biological membranes are fluid, that membrane proteins can diffuse in the plane of the lipid bilayer, and that antibody binding can trigger the endocytosis and degradation of the cell-surface proteins it binds to.

Used antibodies to identify and manipulate oligodendrocytes and their precursors, the myelin-forming cells of the central nervous system (CNS).

Determined that oligodendrocytes and other glial cells arise in a set order and with predictable timing during CNS development, whether they're in the brain or in a culture dish. "That was a great surprise," says Raff. Because developmental biologists thought that developing cells needed spatial cues to tell them what to do —and when.

Identified and characterized an intracellular timer in oligodendrocyte precursor cells

that helps determine when the cells stop dividing and start to differentiate.

Discovered that animal cells need survival signals from their neighbors to avoid apoptosis. “We cultured cells from many kinds of organs and tissues, and we could not find an exception,” says Raff. “That may have been the only important idea I’ve had that turned out to be possibly right.”