JOBS IN BIO-MED I

Doctor-Doctor: Growing Demand For M.D.-Ph.D.s

Despite arduous years of education, more and more ambitious students seek dual degrees.

Back in the mid-1980s, immunologist Carl Nathan, then of Rockefeller University, gave a talk at Genentech Inc. in San Francisco, and heard something he couldn't quite believe. Scientists at the biotech company had recently isolated the DNA that codes for interferon-gamma, a powerful intercellular signaling molecule. An M.D. researcher, Nathan had injected interferon-gamma into the lesions of six patients with leprosy; the point of his seminar was to describe some promising results, including a burst of immune activity in those lesions. But the first question from the audience was more fundamental. "What's leprosy?" asked a young Ph.D.

Nathan was nonplussed. "Here was someone associated with this amazing achievement, a very early cloning of an immunological molecule, and he didn't have enough of a general biological background to understand the implications of what had been done." The gulf between basic science and medicine, Nathan realized, was far wider than he had imagined.

BUTCH USERY/DUKE UNIVERSITY MEDICAL CENTER

Patient care. Duke's Sal Pizzo (pictured with students Charleen Chu and Tim Oury) uses TLC to guide budding M.D.-Ph.D.s.

Today Nathan, now at Cornell University Medical College, runs an M.D.-Ph.D. program in which 77 students at three institutions are schooled in the ways of the ward as well as the lab. Such programs have blossomed in the past decade, ever since James Wyngaarden, a former director of the National Institutes of Health (NIH), warned in the *New England Journal of Medicine* in 1979 that physician-scientists were becoming an endangered species. Wyngaarden's oft-cited paper and a 1981 follow-up tick off the reasons M.D.s were—and still are—opting out of research: Clinical medicine pays better, research dollars are dwindling, and it's tough to keep current in science while practicing medicine.

Wyngaarden and others saw danger in this trend, since physician-scientists are the major conduit for the application of basic science to human disease. With fewer investigators, the fear was that the medical profession would not be able to take full advantage of the biological research explosion. So more and more funders, led by NIH itself, supported programs designed to produce dual-degree students. In the 1960s, NIH sponsored several dozen students at a handful of programs; today, nearly every medical school in the country offers a dual-degree program. NIH's Medical Scientist Training Program (MSTP) funds about 800 students, and other programs support perhaps an additional 1600, according to NIH estimates.

Being a twofer. But are these students committing to double trouble? Although medical educators praise the combination degree, some participants say they are dissatisfied with their long and sometimes winding career paths. A Ph.D. takes perhaps from 4 to 7 years, but a dual-degree demands at least a decade of training. And two degrees aren't the only recipe for creating a physician-scientist, since M.D.s can get research training, and Ph.D.s can study human diseases.

Nonetheless, squeezing two types of knowledge inside one mind is proving increasingly popular. One reason is that M.D.-Ph.D.s are actively recruited in hot fields such as gene therapy and immunology. Also, the lengthy training seems to work: M.D.-Ph.D.s tend to accumulate weighty stacks of publications and grants, and the demand for dual-degree holders is rising at research-oriented medical schools. There's also a financial edge: Research pays less than clinical practice, but M.D. researchers pull higher salaries than Ph.D.s. "If I were starting all over again, I'd do an M.D.-Ph.D.," says Purnell W. Choppin, M.D., president of the Howard Hughes Medical Institute. "It is these people, trained in both medicine and research, who will know where both problems and opportunities exist in biomedical science."

When Choppin was a young physician in the 1960s, the norm was for M.D.s interested in research to get their scientific training after residency, without getting another degree. That's the route taken by such research luminaries as new NIH Director Harold Varmus. But in the next century, physician-scientists—especially those in leadership positions—are likely to have two degrees, not one.

Long climb to the top. Designed for the chronic overachiever, M.D.-Ph.D. programs are not for the fainthearted. Students typically start with 2 years in medical school to learn the basics of medical science, followed by 3 to 5 years (or more) of graduate school to get a Ph.D., then a final year or two of clinical work. After receiving their M.D.s in their late twenties or early thirties, they face yet another round of training. Most do a medical residency of 2 to 7 years and/or a postdoctoral research appointment of 1 to 3 years. Only then do these 30-somethings look for jobs that exploit their unique skills.

Take the career of gene therapist James M. Wilson of the University of Pennsylvania. Now 38, Wilson followed the fast track for M.D.-Ph.D.s, getting both degrees at the University of Michigan by age 29. Then he did a residency in internal medicine at Massachusetts General Hospital. By then he was 31, but he wasn't done yet. Next came a postdoc with gene therapy pio-

neer Richard Mulligan at MIT's Whitehead Institute. Finally, in 1988, at age 33, Wilson became an assistant professor at the University of Michigan; this year, he moved to the Unversity of Pennsylvania Medical Center to found a new gene therapy institute, and he expects to begin a clinical trial of gene therapy for cystic fibrosis later this year.

Was it worth it? Wilson thinks so. "During any working day, I have to draw on all of my experiences," he says. "I go to the lab, and we might have a meeting to talk about new vectors [to put genes into cells], new approaches to gene transfer, or the cell biology of the lung. Then I go to the clinic, and maybe we're admitting a patient for a trial, or meeting to talk strategy for our next clinical trial, or I have to talk to the FDA."

Medical Scientists Trained by NIH

1982	690
1983	678
1984	692
1985	713
1986	701
1987	768
1988	770
1989 (est)	767
1990 (est)	802
1991 (est)	815

Source: NIH

Steady rise. All NIH pre- and postdoctoral research training programs increased by 3.7% from 1982-91 while the Medical Scientist Training Program grew by 18%.

Some might say he's a bit of a masochist, but Wilson is a firm believer in dual-degree programs and—job hunters take note—he is actively recruiting M.D.-Ph.D.s for six positions at Penn's new Institute for Human Gene Therapy. "Making progress in this field requires collating information that spans basic science and medicine. The people who will move the field forward are those who early on can make key decisions and pull together disparate things," he says.

Although genetics is perhaps the most obvious field for M.D.-Ph.D.s, it isn't the only route to success. Pathologist Salvatore Pizzo of Duke University now directs Duke's M.D.-Ph.D. program, and was one of its first graduates. For his Ph.D. thesis, Pizzo studied the biochemistry of how blood clots dissolve, a process called fibrinolysis. Then, after getting his M.D., he worked on a clinical study of blood clots in women taking birth control pills. The study concluded that deficiencies in blood clot dissolution were responsible for at least some of the heart problems in these women. Pizzo went on to show that exercise improved clot dissolution.

Could he have done such work without both degrees? "Definitely not," says Pizzo. "For me, the worth of both sides of the training was absolutely clear. I came here a hard-core chemistry major, knowing nothing about coagulation, and I got interested in it on the wards. Then I went to grad school, where no lab was studying this question per se but they had the capacity to do it, and I did it. And then, since I had a clinical understanding of thrombosis, I got hooked into that clinical study."

Good track record. Like Wilson and Pizzo, most M.D.-Ph.Ds seem to be doing exactly what their program directors had hoped. The course of study is intense, but the dropout rate—from the MSTP programs, at least—is surprisingly low—less than 10% overall, according to NIH. The rate was less than 2% at the top programs. Of the graduates of eight top programs, 90% are in academic or institutional research, according to an analysis published in *Academic Medicine* in 1991 by Joseph Martin, dean of the school of medicine at the University of California, San Francisco. About 6% of the M.D.-Ph.D.s were in private practice, and 4% were at NIH or in private industry, according to Martin, himself an M.D.-Ph.D. Early on, critics of dual-degree programs feared that students would eventually spurn research training and use the program as a free ride to medical school and clinical practice. But by now it's clear that the vast majority of graduates are truly interested in research.

"These programs are one of the best mechanisms we have in this country of producing biomedical researchers. They have a stellar track record," says Bill Kelley, M.D., chief executive officer of the University of Pennsylvania Medical Center, who hopes to expand Penn's M.D.-Ph.D. training program. Indeed, dual-degree holders are making their presence felt in elite institutions. At the Johns Hopkins University School of Medicine, for example, in the early 1960s only about 3% of assistant professors held both degrees; now 11% do.

Ambivalence. Despite all these marks of success, some dual-degree students are nonetheless ambivalent about whether their years of extra training were worth it. A common complaint: Their Ph.D. work often has little bearing on their clinical experiences or even on subsequent research. After finishing their residencies, students usually make a fresh start in research, because their interests have led them to fields widely divergent from their Ph.D. work, which was completed at least 4 and often 6 or 7 years previously. "In many cases, in the field of anesthesia at least, the Ph.D. they got is just wasted" because it has no bearing on current research in anesthesia, says M.D. anesthesiologist Bryan E. Marshall of the University of Pennsylvania.

Indeed, exposure to the nitty gritty of medicine does seem to alter students' research interests. At Duke, for example, medical as well as M.D.-Ph.D. students compress the usual 2 years of coursework into a single year, then spend a year working in the hospital. After being exposed to patients, about half the members of the class switch research fields, says Pizzo. Even students whose interests don't change are likely to be rusty at research by the time they emerge from several years of clinical training. "It's one of the big, unsolved problems," says David Blake, Ph.D., executive vice dean of medicine at Johns Hopkins University.

In defense of the current system, directors like Nathan argue that the purpose of the Ph.D. is not to serve as a direct prelude to later research but to learn rigorous analytical skills. "They've learned a way of learning, not a technique," says Nathan of dual-degree students. "Sure, it's hard to go back and forth, from reading *Science* to reading the *New England Journal of Medicine*. You lose momentum and you're always behind in both. But that's life. And it gets easier every time."

A different sort of criticism of the M.D.-Ph.D. comes from hard-core research types who wonder whether the M.D. may be superfluous. "If you're doing basic science, an M.D. is helpful but not worth the time it takes to get there. If you're not seeing patients, you can get what you need by reading. You don't need the hands-on stuff," says David Wages, an M.D.-Ph.D. pathology resident at the University of California, San Francisco (UCSF), who describes himself as "at best ambivalent" about his dual-degree experience. Joe

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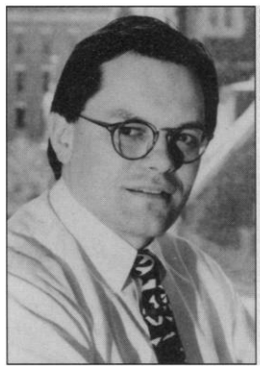
Cruz, M.D.-Ph.D. radiology resident, also at UCSF, similarly advises students to spend some time in a hospital before they sign up for the whole package. If he'd taken his own advice, Cruz says, he probably would have chosen to get only a Ph.D.

Of course, because he has an M.D., Cruz will be better paid than his Ph.D. colleagues. In 1992-93, M.D. assistant professors in basic science departments at medical schools averaged about $57,000 in salary—compared to $47,000 for Ph.D.s, according to the Association of American Medical Colleges. In clinical departments, the salary gap is even wider: The average salary for M.D. assistant professors is $109,000, more than twice that of Ph.D.s.

Alternative paths. If a Ph.D. researcher wants only to learn some human biology, there are more efficient routes than med school. Blake reports that Johns Hopkins, which plans to increase its M.D.-Ph.D. program, also has a new program to teach graduate students human pathophysiology and genetics, to broaden their knowledge base without requiring work with patients. Alternatively, institutions such as Howard Hughes support programs to give physicians research training later, after their residencies—and without the thesis requirements of the Ph.D. That's the time-honored fashion of creating a physician-scientist, and proponents argue that there are good reasons for it. After getting their M.D.s and doing residencies, physicians' research interests are likely to be quite focused, and they are mindful of the urgency of their research, points out oncologist Bill Kaelin, an M.D. researcher at the Dana-Farber Cancer Institute. "You realize that people are dying because of the time it takes us to unravel these questions, and your tolerance for delay goes way down. Anybody who's spent a month in an oncology clinic realizes that there's more to life than the number of *Science* or *Nature* papers on your CV."

But such later research experience is usually not as rigorous or as fundamental as full-blown Ph.D. training. Getting both degrees is a more efficient way to guarantee excellence in both fields, says Hopkins' Blake. "Too many physicians have been led to believe that you can be a productive scientist just by spending a year in someone's lab. No matter how good you are, that's unlikely."



PETER LESTER

Worth the grind. "During any working day I draw on all my experiences," says gene therapist Jim Wilson.

There's another, even simpler alternative to dual-degrees: Work in teams made up of both M.D. and Ph.D. individuals. That's already standard practice in many biomedical labs. But dual-degree fans insist that having both perspectives in one mind offers unique advantages. And sometimes it takes someone who is part of both worlds to seed a collaboration. Linda Baum, M.D.-Ph.D. assistant professor of pathology at the University of California, Los Angeles, once questioned the value of her hard-won degrees. But now she spends 25% of her time doing clinical work, 75% doing research on human tissues, and says her training was worth it. Each week, she works with clinical pathologists and Ph.D. researchers, people who might never meet if she was not involved. "My adviser is right. I can cross the line because I know medicine," she says.

Life in the fast lane. Still, the long hours and delayed gratification mean that M.D.-Ph.D.s are not for everyone. Indeed, one reason for the apparent success of these programs is their raw material: A highly select group of young scholars who have already proven their dedication to coursework and research. "These students are like gold. Everyone wants one in their lab," says Nathan of Cornell. Most students have had extensive research experience as undergraduates or even in high school, and they're eager for more. They lap up special seminars and programs like the "Clinical Investigators Breakfast Club" at the tri-institutional program (Cornell, Rockefeller, and Sloan-Kettering Institute) in New York City.

But even these students find that their path to the top is not always smooth. For example, after being trained in critical thinking, newly minted Ph.D.s must plunge into the rigidly hierarchical world of the hospital—and often it's a shock. "You've been a senior graduate student, essentially independent, and you go to a situation where suddenly you're everybody's boy," remembers Cruz of UCSF. What's more, M.D.-Ph.D. students sometimes feel unusually lonely, since by the time they return to med school, their classmates have moved on without them.

Such problems seem most acute at the newer programs, NIH officials say, with older programs having evolved structures to ease the transition points and offer support to students. For example, at Duke, one of the older programs, students seem to be thriving on a steady diet of faculty attention. "You have to give them some TLC," says Pizzo, who meets the first-year students once a week for lunch, organizes picnics, and sees to it that everyone remains part of the medical school social scene. And because Duke's regular medical school program has an unusual schedule, the M.D.-Ph.D. students retain the camaraderie of their class for 3 years instead of just 2.

For some grads, at least, that satisfaction continues once they take their place in the research world. At 34, neuroscientist and Duke grad Randy Gollub is just beginning her first real job at Harvard University and Massachusetts General Hospital. But the late start doesn't bother her. "My training was awesome," she says. "I don't regret any of it. The two degrees is such a smart thing to do, because you have at your fingertips twice the database. You can ask the right questions." Gollub uses the drugs given to schizophrenic patients as tools to explore how the brain works. She relies on a body of clinical literature, as well as her own experience with patients, to guide her research. "The clinical research told me where to go in the brain to do my basic science, what structures to look at, and why."

Examples like Gollub's explain why M.D.-Ph.D.s are becoming a fixture of the biomedical research landscape. One degree is still enough for many careers, of course. But in the competitive world of medical research, tomorrow's leaders are increasingly likely to have two.

–Elizabeth Culotta

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—Duke graduate Randy Gollub