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Healing and Discovering:

**Michigan's Ambitious MSTP Grads
Bridge the Clinic and the Laboratory**



THE

Translators:

They're Michigan's Elite Medical Scientists in Training

by Jeffrey Mortimer

Their ability to bring the language of the physician to the bench and the language of basic science to medicine is more important than ever

They are the shining stars in a constellation that many believe is shrinking just when it should be growing. They are the ones whose charge, in a sense, is to turn scientific headlines into medical ones. They aspire to careers in that region where the

Michigan, they are students — “fellows,” technically — in the Medical Scientist Training Program, one of 38 such programs nationally that are heavily funded by the National Institutes of Health. Launched in 1979 with an original class of three, Michigan’s MSTP now has 78 alumni and admits about 10 new fellows each year, or about five percent of incoming Medical School students.

They’re really smart, even by medical school standards. They’re so committed to their goals that they’ll spend up to twice as much time in training as they would for an M.D. or Ph.D. alone (an average of seven or eight years in the MSTP, plus internship, residency and post-doctoral fellowship). They’re also willing to accept the possibility that the financial rewards, and other forms of gratification, that they’ll reap from research will be less than those offered by clinical practice alone. Of the 16,000 who earn medical degrees annually in the United States, only 500, or a little over three percent, also earn Ph.D.s.

“The most important thing is that they are able to connect the worlds of medicine and basic science in a way that other people can’t,” says Ronald Koenig, director of Michigan’s MSTP since 1995 and an M.D./Ph.D. himself. “Part of the trouble with medicine in general is that everything is becoming very, very, very subspecialized, and that’s required because we’re getting so much more knowledge. But to really be able to diagnose and treat complex diseases, you have to get into the basic biology of the cell and how it works. And to have the best training to do that really requires you to



Photo: DC Goings, BMC Media

MSTP Director Ronald Koenig and Assistant Director Penny Morris

knowledge produced by basic science is applied to the maintenance and restoration of human health.

Toward that end, they earn both M.D.s and Ph.D.s, and most of them devote their lives, in one proportion or another, to both clinical practice and scientific investigation. Many of them also teach. At the University of

have a Ph.D., because that's where you learn how to ask basic science questions and how to answer those questions using modern tools."

"The MSTP is one of the highlights of our Medical School," says Dean Allen Lichter. "This is a very select group of individuals, highly motivated, and rare. As research has become more and more the province of Ph.D. scientists, we can't lose sight of the fact that individuals who are trained both on the Ph.D. side of the aisle and who also have rigorous medical training look at things in a unique way. They ask questions differently. They bring a really quite irreplaceable perspective to biomedical research and its advancement."

Ironically, at a time when almost daily exposure to scientific "breakthroughs" has made the public impatient to see them translated into medical treatments, the ranks of such versatile thinkers appear to be dwindling. According to a study by the Federation of American Societies for Experimental Biology, a professional group that represents biomedical scientists, the number of physicians who view research as their primary activity dropped six percent between 1980 and 1997. That may be in part because those who choose the dual path face a dilemma: industrial research offers little opportunity to practice, and clinical practice leaves little time for research.

M.D./Ph.D.s can be successful in getting grant funding, however. "Of the Ph.D.s who apply for grants, an M.D./Ph.D. is far better able to compete for money," says George DeMuth, the MSTP's first director. "And," Koenig adds, "we have Michigan MSTP graduates succeeding nationally in faculty appointments at academic medical centers all across the country, such as Harvard, the University of Pennsylvania, Washington University-St. Louis, the University of California-Irvine, and the University of Virginia."

The training itself is well funded, too. The NIH's National Institute of General Medical Studies supports Michigan's MSTP to the tune of about \$1.2 million a year, and the Medical School adds another \$600,000. Michigan's commitment to MSTP from the beginning has made it one of the biggest in the country.

MSTPs nationally "vary a lot in size," says Koenig. Michigan's currently has 70 participants. "In terms of NIH-funded positions, we are one of the biggest," he says.

"The size of the program is an important issue," he adds. "If it's very small, then it's easy for the people to interact but it may not be so easy to find people you want to interact with. You may not find people like you, with similar interests. Also, the programs have less diversity, and I think diversity in social and academic interests is important in terms of the cross-fertilization of ideas and educational and personal growth. But if the program is too big, then it's really hard to interact as a group. You never get to know half the people in the program and it's just too impersonal. There's some size in the middle that represents a good compromise and I think we're in that ideal range now."

But how to balance what's ideal educationally with pressure to enlarge the pipeline? The question of optimal size is "a difficult one to answer," says Dean Lichter. "There are those who say we should grow this program as big as we can because of its obvious importance. On the other hand, our school is of a finite size and there are many competing and worthy demands on our resources. I think the MSTP as it stands now is reasonably sized, but if proposals come forward to allow it to expand somewhat, they will be looked at with interest."

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Ronald Koenig

“Ph.D. training is so basic science-oriented that it can be difficult for a Ph.D. to have a medical perspective, to know how these basic science things really relate to a human being, to understand what the problems are that patients actually get,” says Koenig. “It’s important to connect those two.”

The strongest demand for M.D./Ph.D.s is “probably in academia right now,” says Koenig. “There’s been a tremendous growth in the number of basic scientists working in clinical departments; I’m an example of that. The advent of molecular biology has allowed really clinical problems to be addressed in a very basic molecular way. An M.D./Ph.D. is a natural person to fill that niche because they can see patients as well as do basic research.”

Although he has no hard data, Koenig estimates that MSTP graduates typically devote about 75 percent of their time to research, which would make academia a most attractive venue for them, given that few others allow, much less support, such breadth. But a few do choose to focus on being practicing physicians, and the “M.D.” part of the mix is significant for all, from an affective as well as an intellectual perspective.

“Part of the interview process [which typically takes at least two days] is for the Medical School to evaluate whether the candidates are indeed capable of succeeding in the M.D. part,” says Morris. “There’s a need to see evidence that these students have some sense of service and community and working with people. There’s a stereotypical Ph.D. candidate who would rather be in the lab and not need to communicate, but the medical schools are insistent that they choose applicants who not only have good academic credentials but also have provided evidence that they can serve the community, that they have some hospital or service experience.”

“Ph.D. training is so basic science-oriented that it can be difficult for a Ph.D. to have a medical perspective, to know how these basic science things really relate to a human being, to understand what the problems are that patients actually get,” says Koenig. “It’s important to connect those two. After all, the ultimate goal of

biomedical research is to make patients better, either to prevent diseases or treat them. Understanding the patient is a very important part of that.”

Pharmacology professor Benedict Lucchesi is an M.D./Ph.D. He earned both degrees at Michigan in the early 1960s, long before there was an MSTP, much less NIH funding or structured programs, when students and interested faculty were obliged to cobble together their own arrangements. Although his first love was and is research, he has always valued the extra dimension of his medical training.

“I think the double degree is extremely important,” he says. “I wish everybody had the opportunity to go that route, particularly those that remain in an academic setting. It taught me the language of the physician, and it gave me a deep appreciation for the problems that the physician is confronted with every day, the fact that the answers aren’t always there. There’s a lot of trial and error, a lot of prayer that you’re doing it right.”

Moreover, says Dean Lichter, “There is a continuing need to make sure that those two facets of medicine do not become completely compartmentalized and stop speaking to one another. This is a cadre of individuals who serve as important translators between these two groups.”

The admissions process for the MSTP is, like medicine itself, part art and part science. “We get about 140 applicants a year,” says Assistant Director Morris. “We interview maybe 45 of them, and then we choose a class of approximately 10 new fellows. People who want to get both degrees are unusual, a very special breed. Our task is to find out who among those who apply really and truly know what they’re getting into. For example, all of our applicants have to already have a substantial amount of research experience. They

Photo: DC Goings, BMC Media



Benedict Lucchesi

can't just say, "This sounds like a good idea."

Morris points out that almost all the directors and assistant directors of the NIH-funded MSTPs know each other, and not only compete for the brightest stars but

also cooperate with each other. "It's not unusual to have people apply to multiple programs and get multiple acceptances," she says. "Then our task is to make a good match for the student."

Research interests usually constitute the major component of such a match. "The top 10 medical schools tend to be not terribly different from one another," says Kirk Frey, an original MSTP fellow and one of two members of its first graduating class. "So most students are making their decisions of where to attend on the specifics of graduate school offerings and the scientific interests of the faculty." Frey is now a U-M professor of radiology and neurology, as well as a senior research scientist at the Mental Health Research Institute.

"We're lucky in that this is such a big medical center that almost any research interest would be well represented here on the faculty," says Koenig, "but occasionally there is an applicant who has a very, very narrow research interest. For him or her, this may not be the best place. If there's only one person here who's an expert in that area, suppose that faculty member leaves or the student comes and decides that they don't have a good personal chemistry with that mentor? I think it's important that whatever the person perceives their research interest to be, it's likely there are going to be several outstanding mentors here for them.

Most applicants are not that focused in their interest, so it's not an issue."

Another element might be called simply "chemistry," when it seems as if the person and the institution just belong together. "Some applicants, when I talk to them about their own research or about the University of Michigan, just have a certain sparkle in their voice and eyes that makes me think this person would be great here," says Koenig. "I must say that response isn't unique to me. When I see that sparkle in an applicant, most of the other interviewers feel the same way. It's a little bit hard to know exactly what it is."

Recreational activities and even the size of Ann Arbor can also tip the scales one way or the other. "The School of Music here is very strong and there are a lot of musicians in our program," he says. "Someone who is musically oriented might want to come here because they know they could find people to play music with or take lessons from. I usually tell them, 'Yeah, if you can find the time.' Sometimes there are things that make me feel a person would not be a good match here. I've met a lot of people that wouldn't feel right if they lived in a city that had less than five million people in it, so Ann Arbor probably wouldn't be the best place for them. It isn't the best place for everybody. There's nowhere that's the best place for everybody."

From its inception, one of the Michigan MSTP's defining qualities has been its efforts to support its participants' collegiality, including social events during the school year and a scientific retreat in northern Michigan each summer that features homemade entertainment in addition to the presentation of papers.

"There have been programs elsewhere that were cut back because students didn't feel there was a sense of community," says

Morris. "You did your med school, you did your Ph.D., you came out educated, but you did it by yourself."

There are "both educational and social reasons" for this approach, says Koenig. "These students span a gigantically broad array of research interests. It's not like graduate students in the Department of Biochemistry; they're all interested in biochemistry, so it's natural for them to be together. For us, it's not so natural, so we work hard to get people together and feeling cohesive. The advantage to that is they may find there are commonalities between them. After all, the tools of science are fairly common among broad areas. If they get together and talk, they can start developing cross-fertilization and an exchange of ideas that would never happen otherwise.

"And I think it's important to have a social aspect to this interaction because it's a long program. People are typically in the program eight years, seven if they're lucky. Nobody's life goes smoothly for eight years nonstop, and I think it's really helpful to be able to talk to peers who have been through similar things, who have faced similar issues. Besides, when most people hear you're an M.D./Ph.D. or you're doing this combined training, they think you have to be some sort of mutant, and it's good for people to interact socially and realize that these are real people."

Both Healers and Scientists:

For MSTP Grads, the Lure of both Clinic and Lab Will Shape their Careers

Catherine Keegan **Applying Developmental Biology to the World of Babies**

It makes perfect sense that Catherine 'Katy' Keegan, a 1996 graduate of Michigan's MSTP, is now working on adrenal gland development, even as she finishes her clinical fellowship in pediatric genetics. She can do research, see patients, and help kids.

"When you're in the lab, you're always relating your experience back to the clinical realm, to a patient that you've seen or some sort of clinical problem," she says. "When you translate over into the clinical world, especially for me now doing genetics, I think about a lot of patients that I see in terms of how studying that disease or that problem could be approached from a basic science standpoint."



Photo: Cheryl McIntire, BMC Media

Her Ph.D. is in cellular and molecular biology, and her role in the lab illustrates how research has become a "team sport," so to speak. "I'm working on understanding how different genes function together to result in normal adrenal development. If this process is disrupted, it can result in life-threatening adrenal insufficiency," she says. "I feel like I'm following along the career path that I had intended to follow, based on this training that I've received."

Relating it to children completed the picture. "My Ph.D. research mentor, Sally Camper, did developmental mouse genetics, so I sort of had an interest in development from working in her lab," she says. "And I found that children were the patients I enjoyed working with most. The more I thought about it, the more I felt pediatrics would be a good basis for what I wanted to do. When development goes wrong, that often results in a baby with a birth defect. Understanding that whole process from the scientific level all the way through a clinical level is very interesting to me."

John Germiller **"Michigan was an easy choice."**

"It's extremely hard to have a career where you're a good scientist and also a good surgeon," says this fourth-year surgical resident in otolaryngology and 1997 MSTP grad. "Being a good surgeon requires that you operate a fair amount to keep your skills up and get enough experience with your hands. Being a good researcher requires devoting a lot of time to being in the laboratory. To be honest, there are only a few people that do both really well, and I don't fool myself that I'll become the first person who is a great surgeon and a great scientist and has time for everything."

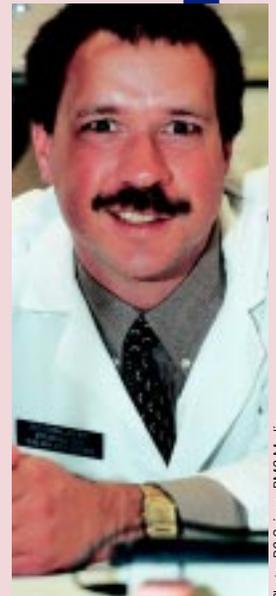


Photo: DC Goings, BMC Media

"The surgical disciplines in general seem to be aching for M.D./Ph.D. surgeon-scientists, so I knew there would be opportunities, no matter what specialty I went into." Michigan's was his first choice among the MSTPs that he applied to. "There are a lot of great MSTPs and great medical schools, but there were very few that had strength in both medicine and in the type of biomedical engineering that I was interested in," says Germiller. "There were few that even had Ph.D. programs in bioengineering, and fewer still that had real strength in biomechanics. Michigan was an easy choice."

"And my experience with the MSTP at Michigan was outstanding. It really allowed me to be exposed to a variety of disciplines and researchers, and they were very supportive of my desire to make my Ph.D. research project interdisciplinary — my goal was to understand how mechanical forces influence the development of bones in the fetus and the embryo — and they helped me out with the logistics of getting that done."



Kirk Frey **Seeing Clinical Problems in a Different Way**

The multiplicity of hats worn by Kirk Frey (M.D., Ph.D. 1984), a member of the original MSTP class, reflects the range of his interests and training: he's a professor of radiology and neurology, as well as a senior research scientist at the Mental Health Research Institute and co-director of the Movement Disorders Clinic. "About 20-30 percent of my time is oriented towards clinical care or the use of clinical examples in

resident and medical school education," he says. "About half of my time is spent in basic neurochemical research, and the remainder is in clinical research, where I utilize my clinical contacts, particularly in the Movement Clinic, to recruit patients for clinical research protocols that are under way in my laboratory."

Patients are the focus for academic physicians, too, not only to be cared for, but also to be learned from. "There are situations where the clinical problems presented by patients serve as a focus for a research direction," he says, "or you'll be presented with a clinical situation that offers a unique insight into a disease mechanism or human biology, and if you weren't tuned to look for it or ask the right questions, it might go untapped."

About his MSTP experience Frey says: "There were a number of very successful role models, not only in the immediate area that I had chosen for my studies but in clinical medical science in general. It was very enlightening, and the MSTP was key in exposing us to them."

Charles Neal **Asking Questions about the Development of the Newborn's Brain**

Charles Neal (M.D., Ph.D. 1991) sought an MSTP because "it became really clear to me that answering the questions I was really interested in, how the brain works and knowing the brain, could be helped much more by understanding the human condition. Medicine seemed like the way to go, but I didn't want to do straight medical school."

He became enamored of neuroanatomy en route to his doctorate in anatomy and cell biology, and he became enamored of pediatrics during his rotation through it. "I fell in love with the kids," he says, and did his residency, including a year as chief resident, at the University of California at San Francisco.

Neal was the only one of the M.D./Ph.D.s he knew during his residency who went back to the lab. While that decision necessarily came at the expense of clinical work, it did not come at the expense of compassion. His particular interest is in the long-term effects on the brain of drugs administered to premature newborns.

"Newborn premature babies are undergoing a tremendous number of stresses that they wouldn't normally undergo, because their brains finish developing outside mom," he says. "Not only light and sound and cold and pain and being separated from their mother, but we also give them a lot of drugs to help keep them alive, including opiates and glucocorticoids, a steroid hormone. We give premature babies a fair amount of that, so my research is going towards learning how it affects the development of the stress system in the brain and whether it has an impact that may be permanent."



Heather Burrows

Immediate Gratification in Pediatrics



Photo: DC Goings, BMC Media

Even though she says “We didn’t come to any grand conclusions,” Heather Burrows’ (M.D., Ph.D. 2000) study of cell development in the anterior pituitary was named one of the Rackham Graduate School’s four most distinguished dissertations in 1999. She followed that in 2000 with the George R. DeMuth Medical Scientist Award for Excellence, given to a graduating senior in the MSTP “who has demonstrated outstanding accomplishments in research and who exhibits the personal and professional qualities desired in the complete physician.”

Despite such honors, she’s one of the few MSTP graduates to choose clinical practice over research, at least for now. “Research is more about delayed gratification and medicine is more about immediate gratification,” says the pediatrics intern at University of Michigan Hospitals, “and it’s easier to get hooked on instant gratification. I’m definitely going to do clinical work. I’m still interested in research, but I’m not sure how to incorporate it right now.”

Burrows describes the Michigan MSTP as “a great program. I’ve always been very happy that I picked U-M for my M.D./Ph.D.,” she says. “The two women whose labs I worked in — Sally Camper and Audrey Seasholtz — were wonderful mentors; they took that job seriously. One of U-M’s strengths is a youngish faculty that’s very involved in the lab and with graduate students. It’s important to get that kind of exposure. And the MSTP office is very supportive and nurturing; they look out for us. During the interview trail, I didn’t always get the feeling that some of the other programs would do that.”





George DeMuth

THE MAN WHO MADE MSTP A REALITY AT MICHIGAN

More than 21 years ago, the University of Michigan Medical School became the first state-supported medical school in the country to become part of the national Medical Scientist Training Program network supported by the National Institutes of Health.

The program's inception at Michigan can be attributed to the efforts of George DeMuth, professor emeritus of pediatrics and communicable diseases, who, in 1979, wrote the proposal to the NIH, building the case for Michigan's participation based on its strengths not only in medicine but in public health, pharmacy and biology as well. He was also careful to demonstrate the excellence of those medical students then working toward their doctorates at Michigan. "There weren't too many," he recalls, "but they were very strong and they made a very good impression. We asked them to talk basic science, not medicine, because the site visitors from NIH were all scientists. Our message was, 'If we can do this without NIH support, think what we could do with it.'"

DeMuth, whose medical stops prior to joining the faculty at Michigan in 1959 had included the Cincinnati Medical School (his M.D. and residency), the University of Michigan (his internship), as well as post-doctoral fellowships at both Cincinnati and the University of California, San Francisco, set his sights on attracting some of the best applicants from the pool of perhaps 100 candidates available nationwide at that time, all of whom had at least a dozen schools to choose from. He also began recruiting some of the most outstanding minority scientists, largely thanks to prodding from Charles Neal, M.D., Ph.D., who

applied to the program late in 1983, too late to receive funding, but who sold himself anyway on the basis of his academic strengths and his own Minority Access to Research Careers fellowship.

"George is wonderful; I really love the man," says Neal, now a researcher in U-M's Mental Health Research Institute and a lecturer in pediatrics. "I was a very outspoken person, and George was very patient with that. I'm sure a lot of it came from insecurity and culture shock, and me not knowing if I fit in here. At 24 I probably just seemed angry. But I made sure I did well in classes. I didn't want to let anyone down, particularly myself, and I didn't want George to second-guess his decision to help me out here, and I don't think he ever did."

The quality of DeMuth's personal relationships with MSTP fellows was a key ingredient in the program's success at Michigan, many of them say today. "George raised us and then he booted us out of the house and told us we could make it," Neal says. "He was supportive, and he'd give advice if you asked for it, but in general the message was, 'You've got what it takes, now go out and do it!'"

"I always felt as though he was looking out for my best interests," says Catherine Keegan, M.D., Ph.D., a 1996 MSTP alumna and now a house officer in pediatrics. "We got tremendous support from both the Medical School and from the Rackham School of Graduate Studies, and that, I think, was a result of George's early work to promote the program."

For Catherine Keegan and for many others, MSTP at Michigan means George DeMuth. "Without George," she says, "the MSTP at Michigan would not be what it is today." 