Margaret MacMillan, M.D., thought she’d be in Minnesota for only a few months when she arrived in 1997. Having completed a fellowship in hematology-oncology/bone marrow transplantation at the Hospital for Sick Children in Toronto, she simply wanted to do another six-month fellowship at the University of Minnesota. “I had no intention of staying,” she says. “I knew no one. I just drove my car, loaded with my big old-fashioned computer and my bike,” she says, “and one thing led to another and 17 years have passed.”

One of those things was taking care of patients who had Fanconi anemia. John Wagner, M.D., now division director of the University of Minnesota’s Pediatric Bone Marrow Transplant Program, was performing transplants in children who had the inherited disorder; but in those days, three out of four patients didn’t leave the hospital alive following the procedure.

MacMillan saw both a tremendous need and a challenge. To her, the children were dying because physicians like herself weren’t doing a good enough job. “The need was there for somebody else to be interested,” she says. “I couldn’t turn my back on them; they so desperately needed help.”

MacMillan is one of the rare physicians who specialize in rare diseases, defined in the United States as conditions that affect fewer than 200,000 people. According to the National Institutes of Health’s Office of Rare Diseases Research, 6,800 rare diseases affect nearly 30 million people in this country. Physicians who develop expertise in one often join a small group who share their interest, and they’re sought out by patients coming from near and far. MacMillan’s come from all parts of the world.

Meeting a need
Fanconi anemia affects one in 150,000 people. Those who have the disorder are unable to repair DNA well. Thus, it manifests in a host of ways including congenital abnormalities such as missing limbs and defects in organs, heart and gastrointestinal problems, diabetes and even deafness. People who have the disorder also have a high risk of head and neck, gynecological and skin cancers. Eventually, they develop bone marrow failure, which leads them to MacMillan and her colleagues. The average age at which their patients undergo transplantation is 9 years, but MacMillan says they’ve done transplants in babies and adults as well.

Although bone marrow transplantation cures the hematological manifestations of Fanconi anemia, the procedure is risky for several reasons. Among them, people with the disease can tolerate only small doses (about a fifth of what others can) of the chemotherapy and radiation given prior to transplant. And their siblings may also have the disorder, making it more difficult for them to find a suitable donor.

About 15 years ago, MacMillan and other researchers at the university concluded that if they were going to improve upon the way they and others were doing bone marrow transplantation for Fanconi anemia patients, they needed to be ex-
tremely systematic and learn from every patient. Each year, the university performs transplants in 10 to 12 patients with Fanconi anemia, which is more than are done in all other U.S. hospitals combined. About 200 patients are followed in the U’s Fanconi Anemia Comprehensive Care Clinic.

Over the years, MacMillan and Wagner have inched forward in their understanding of how to do bone marrow transplants in patients with Fanconi anemia. “The first step was, we wanted the transplant to take and grow,” MacMillan says. “We just added one drug.” When it was shown Fanconi patients could tolerate fludarabine and that it allowed the grafts to grow, they worked on a way to prevent graft vs. host disease, a potential lethal transplant complication, by manipulating the donor cells before giving them to the patients. Because of their work, survival rates five years after transplant are up from 25 percent to greater than 90 percent.

For MacMillan, staying focused on Fanconi anemia hasn’t been difficult. “Scientifically, it’s a very fascinating disease,” she says, adding that that’s a good thing because it’s of interest to other scientists. Most recently, it attracted the attention of researchers working on breast cancer. About a dozen years ago, it was discovered that some patients with Fanconi anemia have two copies of the BRCA2 gene. “Now all of a sudden the breast cancer community is fascinated with Fanconi anemia,” she says.

MacMillan notes that discoveries made while studying a rare disease often have applications for other branches of medicine, and that’s been true of Fanconi anemia research. The first successful cord blood transplant was performed in a Fanconi patient, and fludarabine is now routinely given to anyone needing reduced-intensity preparation for bone marrow transplantation.

Part of what keeps her interested in Fanconi anemia research is that new questions continue to arise. For example, because of increased survival, they’re now asking, What are the long-term side effects of a transplant? and How can they make bone marrow transplantation less difficult for patients? “Truly, until 100 percent of the kids are cured, almost without effort, my job isn’t done,” she says.

A mentor’s gift
Like MacMillan, Mayo Clinic nephrologist Dawn Milliner, M.D., stumbled onto rather than sought out her interest in a rare disease. When Milliner started at Mayo nearly 30 years ago, her office was next to that of Lynwood Smith, M.D., whom she describes as “legendary” among kidney stone physicians and who had an interest in hyperoxalurias. As she tells it, he kept coming over and telling her about interesting patients. “He’d say, ‘What do you think we should do about this? What’s causing this problem?’ So I started seeing the patients with him,” she says. “After his retirement, he transferred all those patients to me, and the program just grew.”

Today, Milliner directs Mayo Clinic’s Hyperoxaluria Center and the Rare Kidney Stone Consortium. Although she sees patients with all kinds of kidney disorders, she’s especially known for her work in primary hyperoxaluria. “There’s hardly a week that goes by that I don’t see a few patients with this disease, and it’s a rare disease,” she says, adding that they receive inquiries daily from patients, family members and physicians from all over the world.

Hyperoxaluria is a condition in which there’s a high concentration of oxalate in the urine. It can be caused by multiple factors. Primary hyperoxalurias (there are three types) are caused by mutations...
in the genes that encode for specific liver enzymes. When the activity of one of these enzymes is deficient, the liver overproduces oxalate, and urinary concentrations can be as much as eight times higher than normal. Kidney stones are often the first clue that a patient has the disease. Untreated, hyperoxaluria can lead to kidney failure and deposition of oxalate in other organs. The incidence of type 1 primary hyperoxaluria is estimated at 1 to 3 per million people. Types 2 and 3 are even less common.

Milliner says part of her fascination with primary hyperoxaluria is that its effects are seen in people of all ages and are variable. The disease can become very severe in infancy, or it may not cause serious problems until a person is well into adulthood. And it’s challenging to treat. By the time people get to the point of needing dialysis, they have multi-system disease. “It’s the heart, the eyes, the bones. Many organs can be involved,” she says, adding that managing the life cycle of the disease calls on every skill she has as a physician.

“When it presents in its severe form, it’s devastating to the individual involved,” Milliner says, “or at least it has been historically.”

She has had a hand in altering that history. “What we’ve learned over the years is that we can do much better,” she says. Patients do better if they are diagnosed and treated early. If they still have good kidney function, they can be put on a treatment program to prevent formation of kidney stones and help preserve that function. If a patient is in kidney failure, he or she can be put on an intensive dialysis program and receive a transplant before serious complications develop.

Although Milliner plans to continue to do research on and see patients with primary hyperoxaluria, she sees her role shifting. She says at this stage in her career, she considers it her responsibility to engage younger physicians and scientists in the work. To them, she’d say there’s really one reason to devote a career to a rare disease: “By learning about it, you can do so much more to help patients. That’s really what’s driven my interest in a focused area. It’s that ability to make a difference for someone whose disease is poorly understood.”

**Intentional choice**

Unlike Milliner and MacMillan, pediatric neurologist Timothy Feyma, M.D., was intentional about developing expertise in a

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**Rare funding challenges**

In a world where funding for medical research is tight, dollars for research into diseases that affect only a few people are even harder to come by. Thus, researchers interested in rare diseases often find themselves working with patients’ families and advocacy organizations to secure support.

“I can’t say enough about the importance of patient advocacy organizations,” says Dawn Milliner, M.D., a Mayo Clinic nephrologist who’s specialized in a set of rare kidney diseases that include primary hyperoxaluria. In her case, the New York-based Oxalosis and Hyperoxaluria Foundation enabled her to establish the Mayo Clinic Hyperoxaluria Center and start a patient registry. With those in place, she and her colleagues have been able to secure National Institutes of Health (NIH) funding to establish a Rare Kidney Stone Consortium for the study of primary hyperoxaluria and three other rare kidney diseases.

Milliner says for many years, research funding, including most NIH grants, was directed toward common health concerns such as heart disease and cancer. About a decade ago, that began to change, and the NIH formed the Rare Disease Clinical Research Network, which funded 17 consortia, including the Rare Kidney Stone Consortium, which Milliner directs. The University of Minnesota’s Margaret MacMillan, M.D., says it’s still very difficult to get funding for research into rare diseases. “The NIH asks, How many people will this impact?” she says. “Even when you try to show that what we’ve learned has an effect on hundreds of thousands of people, they often look at, What’s your disease population?” And she points out that even though the NIH does some funding of research into rare diseases, there’s a lot of competition for those dollars.

For those reasons, she’s especially grateful for the support of the Kidz1stFund. Three years ago, during a four-hour initial consult about their son who has Fanconi anemia, Florida State University football coach Jimbo Fisher and his wife, Candi, proposed starting the fund. They’ve since raised and given more than $2 million to the University of Minnesota. “They realized time is not on their side because their son will need a transplant in the next few years and research is going to give him a better opportunity than he has now.” – C.P.
rare disease. While he was a neurology fellow at Seattle Children’s Hospital about five years ago, he realized the idea of having a discreet population of patients and an area of expertise appealed to him.

So when he learned that a position that involved working in the Rett Syndrome Clinic at Gillette Children’s Specialty Healthcare in St. Paul was open, he was intrigued, although he had encountered only two Rett patients at that point in his career. “I actually sought out the opportunity because it seemed like such a rare opportunity,” he says.

Rett syndrome is a neurodevelopmental disorder that affects one in 10,000 people, almost exclusively girls, who develop normally until about 15 months of age, when they can begin to have difficulties. Eventually, those difficulties may include problems with walking and talking, seizures, sleep problems and learning disabilities. It is believed to be caused by a spontaneous, rather than inherited, genetic mutation.

Because of Rett patients’ many needs, Gillette offers access to a team of specialists in a monthly clinic, headed by Feyma and pediatrician Art Beisang, M.D. Together, they follow more than 100 patients who come from Minnesota and other Midwestern states. Each month, they see about four or five, each of whom may present with a long list of problems.

In addition to seeing patients, Feyma has collaborated with University of Minnesota researchers to investigate a gaze-controlled communication device and with University of Alabama and Baylor researchers on a trial of a drug to promote neurogenesis. “We hooked our dingy onto their main boat,” he says, noting that Alabama has been involved in Rett research for 40 years. “I thought, you need study subjects, we’ve got 30 to 40 girls to work with up here.”

Feyma’s own research interests are more clinical and fundamental. “We don’t have baseline data on what Rett girls’ sleep is like, what are normal Rett girls’ abilities, are these girls in pain,” he says. “We’re trying to document some very basic data.”

Feyma says the families of his patients motivate him to continue his work. Yet he knows others scratch their heads when they learn he’s focusing on this disease. “A lot of people say, ‘How can you do that? It’s so depressing.’ ... I think it would be more tragic if I let these girls flounder.”

Carmen Peota is an editor of Minnesota Medicine.