As a disease detective at the NIH, William A. Gahl unravels the cause of illnesses that have stumped other doctors.

Interview by Brendan Borrell

The patient had endured 20 years of pain: her calves had turned into two bricks, and she now had trouble walking. A slew of doctors had failed to treat, let alone diagnose, her unusual condition. So when her x-rays finally landed on William A. Gahl's desk at the National Institutes of Health, he knew immediately that he had to take her case.

Gahl is the scientist and physician who leads the Undiagnosed Diseases Program, which tries to unravel the underlying causes of, and find therapies for, mysterious maladies and known but rare conditions. Louise Benge's x-rays had revealed that blood vessels in her legs and feet bore a thick coat of calcium that restricted blood flow. Benge's sister, Paula Allen, along with several other members of the family, also shared the disorder. Over the course of several months Gahl identified the genetic root of the disorder—a mutation in a gene that regulates calcium—and he went on to propose a treatment with drugs already on the market. He continues to assess the treatment's value.

Gahl, 61, gravitated to disease detective work because of an early passion for the kind of puzzles found in a distinctly different discipline. He dreamed of becoming a mathematician until he took a biochemistry course as a college sophomore at the Massachusetts Institute of Technology. At the time that his interest shifted, scientists were beginning to recognize that a wide range of rare genetic diseases responsible for heartbreaking physical deformations and retardation can arise from a single, defective enzyme.

The potential to solve such challenging medical puzzles and help patients appealed to Gahl, who went on to make key discoveries in the treatment of cystinosis, Hermansky-Pudlak syndrome (albinism), and other little-known disorders before launching the NIH's Undiagnosed Diseases Program.

IN BRIEF
WHO
WILLIAM A. GAHL
WHAT HE DOES
Tries to deduce the causes of diseases that elude diagnosis by other physicians
WHERE
National Institutes of Health’s Undiagnosed Diseases Program
RESEARCH FOCUS
Connects genetics with pathology to understand mysterious illnesses
BIG PICTURE
Uses the most advanced medical technologies but is philosophical about the limits of what the healing arts can accomplish.
Undiagnosed Diseases Program in 2008.

Although Gahl embraces cutting-edge medical technology and has butted heads with the U.S. Food and Drug Administration to improve the availability of treatments for patients with rare diseases, he remains philosophical about constraints on medicine imposed by a world in which health costs seem to go in only one direction. In a recent interview, Gahl discussed the problems he faces as a medical detective and as an advocate for his patients and others like them. Edited excerpts follow.

SCIENTIFIC AMERICAN: How do you decide which cases to accept?
GAHL: We want to make diagnoses, but we also want to advance medicine and science. We consider whether a patient might have a new disease and whether we have a chance to find the genetic and biochemical basis of it. There really is a huge amount of judgment involved, and we rely on our consultants, many of whom are experts in the particular symptomatology, to give me an opinion, and then I make a final decision on which cases to accept.

I would say, 90 percent of the time, it’s straightforward whether we accept a case or not. A few cases are really tough judgment calls. Of the 1,700 files we have received, we have accepted about 400.

How do people find you in the first place?
They generally hear about us from the press and from advocacy groups. Some of our colleagues have heard about the program, and of course those are the best cases. Anyone is free to apply as long as they provide their medical records and a letter from their doctor.

What was the first step after you accepted Louise Benge and her sister as patients?
At this point, we had already seen their x-rays and other medical records, and they needed to come to Bethesda for about a week so we could conduct our own tests and obtain biological samples. Because both parents were healthy, we knew that the disease was caused by a recessive mutation. Each parent must have had only one copy of the genetic mutation, whereas the affected children would have two copies. We first identified the general region where the mutation was located in the genome and then used targeted sequencing to find an error in a specific gene, called NT5E, involved in producing the nucleoside adenosine (involved in a wide range of biochemical processes). We also found two separate families with a similar condition and identified their mutations.

Once you’ve identified the mutation, are you done?
No, the next step is to connect the genetics with the pathology. Cynthia St. Hilaire in the lab of Manfred Boehm, an expert in cellular and molecular biology of the cardiovascular system, cultured the patients’ skin cells for a series of in vitro experiments. By inserting a normal copy of the NT5E gene into the cells, they showed that the cells could function normally. Then they did a second experiment, adding adenosine to the cells, and found that calcification was also reduced. These experiments gave us a better understanding of the role that adenosine plays in regulating calcium. For various reasons, we can’t just give patients adenosine, but we think we can treat this condition with a class of osteoporosis drugs known as bisphosphonates. We’re still waiting to see whether these drugs work.

You have two professions, as both doctor and scientist. What is the difference between seeing a patient and doing science?
One has to be dispassionate in both worlds and also passionate in both worlds. Seeing a patient is more complicated than doing science because the human being has so many aspects. There’s the family, the relationship with you, the trust or lack of trust, and the hope, and a huge amount of follow-up and responsibility are needed. We can drop experiments, but we can’t drop patients.

You can become emotionally attached to patients, but you shouldn’t become too attached, because many of those patients are going to die. It really is a bal-

Rare diseases as individual diseases are really uncommon, but as a group, they are not. Everyone in the country knows a family member or friend who has one.
I believe a society is measured and judged by how it treats its least fortunate. Patients with rare diseases are abandoned people. They’re abandoned by the medical profession, and they’re often isolated by their relatives and friends because they can’t put a name to their disease. Many of them will go into their doctors’ offices and even their doctors will not want to see them, because without a diagnosis the physician feels very uncomfortable and inadequate.

There are cases where we will confirm a patient’s worst fears of a poor prognosis, and they will thank us for it and hug us because now they have some idea of what’s going on in the future. The uncertainty is gone. They can put a label on it, and this means an awful lot to people. More than I would ever guess.

It’s also important to recognize that there are examples where the findings in a rare disease have applicability to common diseases. By studying Louise Benge’s condition, for instance, we have identified a new pathway that alters calcification in blood vessels and bones. This discovery may have implications for heart disease, where calcium builds up on the coronary arteries, restricting blood flow.

Have you ever tried to estimate what the cost is of a single diagnosis through the program?

In the first two years, my service saw 160 patients and provided about 50 diagnoses, including about 15 that were of really rare known diseases. The cost was about $5 million, so that is about $100,000 apiece. Keep in mind, some of these patients have already had million-dollar workups. They’re gone to the Mayo Clinic, Cleveland Clinic, Johns Hopkins, Harvard, Stanford, before coming to us.

On the other hand, our work provides ancillary benefits. We’ve discovered one new disease, and the program has provided the groundwork for finding many new diseases. We expanded our knowledge of several disorders, such as congenital disorder of glycosylation type 2B and identified a mutation involved in a neurological disease that involves spinocerebellar ataxia and spastic paraplegia.

For those we didn’t diagnose, we provided hope and symptomatic therapy, so I think the money was well spent.

But there must be a financial limit that your group sets?

We don’t have a lot of restrictions on how we spend our money, but we have only a total amount in the kitty. So we have to make triage decisions the same way that people make life and death decisions on a battlefield. Those triage decisions will have to do with monetary resources and physician time resources.

When we gauge the value of a diagnosis, we have to do it against the value of the next patient’s diagnosis or that of 10 other people. Basically all patients want us to pursue their diagnosis to the ends of the earth. Important determinations must be made. We will not be performing whole-genome sequencing, but we will sequence just the coding portions of the genome, known as the exome. On the other hand, we can also gain a great deal scientifically if we spend more to sequence an entire family. We make judgments that incorporate both the probability of success and the financial cost.

If doctors wanted to start ordering exome sequences for diagnosis in their practices, would that raise legal issues?

Currently whole-exome sequencing is not approved for clinical laboratory testing. We use it to find the gene that is causing the disease, at a cost of about $4,000; that price is going down rapidly. Once we’re pretty darn sure of the gene, we order the certified test and pay for it. Then we can tell the patient the diagnosis. Right now if doctors in the field have a patient with a degenerative disease such as spinocerebellar ataxia, which can have many different known genetic causes, they have to order tests through commercial molecular diagnostic firms that have patented each of those gene tests separately. That can cost tens of thousands of dollars.

What’s going to happen, I think, is that sequencing companies will routinely begin to interpret their tests for physicians, in which case legal issues may start to come into play.

Do you worry about other issues that may arise when whole-genome sequencing becomes more widespread?

What if there’s a risk factor for disability and that risk factor becomes part of the patient’s record and somehow the insurance companies get access to it? Those are the things that might come out from whole-genome sequencing, and I think our society has to deal with how we’re going to protect patients from discrimination that might emanate from that. When people submit themselves to whole-genome or whole-exome sequencing, they should be given the opportunity to decide how those data are handled.

You have often been compared to Dr. Gregory House, the fictional television medical sleuth and Vicodin addict. Have you been contacted by the show in any way?

I don’t think they want to contact me. I was interviewed for CNN, and they asked how I would compare myself to Dr. House. I said, “Well, I wouldn’t, because I’m not a sociopath, for one thing, and I’m not on drugs.” But the big difference is that our patients have chronic diseases that won’t be solved in 60 minutes. They’re true human-interest stories. They aren’t made up. These patients are enough to make you cry.

Brendan Borrell is based in New York City and frequently writes about science and the environment for Scientific American and Nature.

More to Explore


Medical Mysteries and Rare Diseases. William A. Gahl gives a talk at TEDxCMU. http://bit.ly/6U5D4

Scientific American Online

See a video of Louise Benge and Paula Allen at ScientificAmerican.com/wov2011/diagnostics.