What’s Wrong With Summer Stiers?

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Her breasts are beautiful. This is a surprise. Seeing them looking so healthy and normal reminds you how young this patient is and what her life might be like if her body hadn’t started to disintegrate in her childhood. If all you could see were her breasts, you would think she were perfectly fine. But that would be like the blind men trying to describe the elephant when each one focuses on a single part. Look at the rest of this patient’s torso, and you start to get a sense of the fuller story. A little bit higher, near the left clavicle, you notice a bump beneath the skin marking the implantation site of her vagus-nerve stimulator, which delivers an electrical impulse to her brain every three minutes to stave off the seizures that would otherwise plague her. A little lower, on the right-hand side of her abdomen, you see a hole and a permanently implanted tube through which she has hooked herself up to peritoneal-dialysis equipment every night for the past five years, to flush out the toxins that her ruined kidneys cannot.

The metaphor of the blind men and the elephant applies not only to the landscape of this woman’s body but also to the approach of just about every specialist who has seen her in the 20-plus years that she has suffered from her mystery disease. The limitation of this method is what took this patient — a petite, feisty, 31-year-old woman from Oregon named Summer Stiers — to this consultation room at the National Institutes of Health on a Thursday in early December, stripped down to her panties. Stiers was being examined by a dermatologist, Maria Turner, who is among the dozen or so specialists who would see her before the week was out. And even though Turner and the others are part of the innovative new Undiagnosed Diseases Program at the N.I.H., and even though they collectively represent the very best that American medicine has to offer, they still began by approaching the big picture of Summer Stiers the way most specialists do: like the blind men, one piece at a time.

The Undiagnosed Diseases Program was designed to move past that halting first step — the inevitable result of the organ-by-organ orientation of most medical specialties —
organ-by-organ orientation of most medical specialties — to achieve a more coherent view. Under the direction of William Gahl, a longtime N.I.H. investigator who is also the clinical director of the National Human Genome Research Institute, the program brings together scientists from most of the N.I.H.'s 27 research institutes and centers on a collegelike campus in Bethesda, Md. Organizational, it creates a kind of superdiagnostician, whose orientation would be to look at just one piece at a time but at the whole darn elephant.

The program's methodology is still evolving, but for the first dozen or so patients it worked this way: A primary-care physician sent in a letter describing the case, followed by reams of records documenting the diagnostic dead ends the patient had already confronted. Gahl personally reviewed all the cases and discarded about three-quarters of them, usually because the problem was insufficiently documented, seemed to be psychosomatic or, for some other reason, left Gahl with the impression that the N.I.H. had little new to offer. Then he took the most promising cases to his medical-review board, made up of several dozen clinical investigators from all over the N.I.H. The board reviewed 10 or so cases at each monthly meeting, out of which it accepted just a handful, the ones that seemed most likely to lead to a new insight into a known disease, or, even better, to a diagnosis of a disease never before seen. Then Gahl's staff arranged to bring in each patient for a week of assessment in Bethesda. There, the patient would meet an array of specialists who did physical exams, took histories and conducted whatever additional tests they needed: ultrasound scans, M.R.I. scans, X-rays, electroencephalograms, maybe a spinal tap or a biopsy of skin or other tissue.

This part of the process is familiar to most of these patients, who have usually been through something similar, in one medical center or many, during the years they spent being ill with no one knowing why. What's different about the new N.I.H. program is its collective approach. After the cavalcade of specialists, each with a favorite organ, parades past the patient's bedside, they gather in impromptu meetings to try to connect what they see to what others are seeing that they themselves might have missed.

This is especially important in someone like Stiers, whose doctor back home described what happened to her as a "cascading collapse of systems." Over the past 20 years, her health declined bit by bit, unpredictably, from her head to her toes: one eye removed, retinal bleeding in the other one, cavernous hemangiomas in her brain, kidney failure, intestinal bleeding, osteoporosis, bone-tissue death in both legs. She has been on disability since her 20s and spends her days sleeping, doing some sort of physical therapy or going to doctors.
Since last summer she has also received hyperbaric oxygen therapy, in which she lies in a high-pressure chamber. This relieves some of her symptoms, possibly by delivering more oxygen to her eye, intestines and muscles. On the bathroom door of her room at the N.I.H. hospital, she posted photos of some of those most important to her: her three cats and her doctor in Oregon, Robert Pinnick. In one photo she and Pinnick are dressed up for Halloween: he is in a big blue costume involving an inflatable swimming tube, and she is a five-foot-tall banana.

Stiers spent the week of Dec. 8 at the N.I.H., seeing doctors all day long. But it was only after she left that the real work began on figuring out what was wrong with her. Even now, two months after she was discharged, scientists are just beginning to use the DNA extracted from blood samples they took while she was there. They will be working on that DNA for months to come — looking for deletions or repetitions of bits of her genome, sequencing specific genes implicated in similar conditions — and culturing her skin cells to look for proteins whose presence or absence might be relevant, which will also take months. But even after all this effort, it is quite possible that Stiers's condition will never be diagnosed.

The time frame for the program's success must be measured in decades, Gahl says. And even then, for every diagnosis the group makes, he estimates that there will be nine cases that remain mostly unresolved. Among the two dozen patients who have been through the program so far, there have been just two diagnoses, when patients admitted for neurological symptoms were found to have rare forms of multiple sclerosis.

Gahl's projected success rate is so low because his aim is so high. His holy grail is a molecular diagnosis: finding not just a description of a new disease but also an understanding of how it works at the level of the gene. With this goal, the Undiagnosed Diseases Program aspires to be a model for how genomic medicine will be done in the 21st century.

“This is what we're really all about at N.I.H.,” says Gahl, a compact 58-year-old who tends to make dry jokes in his slightly gruff baritone about almost everything — except science. “We're in this business because we want to define and understand new diseases.” The expectation is that this work will offer important insights into the mechanisms of more common, more familiar diseases too. But knowledge can be double-edged: useful for the community at large, yes, and in some cases even helpful for the patient, but often incomplete, confusing or unbearably grim. Gahl worries constantly about taking away from his patients their last refuge: hope. When you're suffering from a nameless malady, it's easy to think that the only thing standing between you and a cure is the name itself.

**The limitation of knowledge** is something that troubles Gahl — or would trouble him if he allowed himself to dwell on it. Gahl has been at the N.I.H. for his entire career. He was born in a small town in Wisconsin, studied biochemistry as an undergraduate at M.I.T. and received his medical degree from the University of Wisconsin-Madison, where he also did his pediatrics residency and went on to earn a Ph.D. in oncology research. When he first arrived at the N.I.H. in 1981, it was as a fellow in the new field of medical genetics, back when scientists felt they were on the threshold of the era of gene therapy, when all you would need to do to cure a disease would be to find its gene, figure out what the gene did and imitate it. The ensuing years have shown how difficult it is to bridge the gap between the gene and the cure, which has been accomplished far less often than people once predicted. Despite the accumulating disappointments and false starts in genomic medicine, however, Gahl has never given up searching for the genetic bull's-eye.
As he described Summer Stiers to me for the first time in October, Gahl sounded like a mixture of teacher, scientist, enthusiast and old-fashioned healer. “It looks like she has leaky membranes; what causes that?” he began, as though he were a senior attending physician and I were a medical student on rounds. “She had a diagnosis as a child of Coats disease, where fluid leaks out of her eye, and then there’s a reaction; her eye was removed. Her kidneys are ruined; her gut is problematic, she had bleeding; her lungs are reasonably O.K.; she’s got calcification in her skin; her vessels leak.” Gahl was certain he would accept her into the program. “This is an absolutely great case,” he said. It had everything he was looking for when he first helped design the program: documentation of her long, perplexing history and the likelihood that she was suffering from something entirely new. He was also impressed with the patient’s good disposition and coping mechanisms, which at the time he knew about only because of how Robert Pinnick, her primary-care physician, described her in his introductory letter. “We appreciate your interest in helping us make a diagnosis in this wonderful 31-year-old woman,” Pinnick wrote, “whose indomitable will to survive and always positive and pleasant attitude make her case not only tragic, but intriguing and a joy to pursue.”

There was fierce competition among patients for a spot in the Undiagnosed Diseases Program, which began as a $280,000 pilot initiative last May. (It was later approved for full financing — $1.9 million for fiscal year 2009.) By the time Gahl showed me Stiers’s case files in his cramped, chilly office that October afternoon, he had received more than 1,000 inquiries. He was in the process of reviewing about 300 charts and had accepted 35 patients. Another 100 or so charts were circulating through the N.I.H. for review by relevant specialists, and Gahl expected that another 20 patients would be admitted to the program before the end of the year. Summer Stiers, as Gahl anticipated, turned out to be one of them.

**When I first spoke** with Stiers by telephone in mid-November, I could tell what it was about her that captivated Gahl. She was soft-spoken, with a lilting, little-girl voice, and even when she was telling me about the devastating series of physical breakdowns that have afflicted her, there was nothing complaining or self-pitying about it. Only once did she give a hint of her frustration, when she mentioned being told earlier that day that her phosphorus numbers were high, always a concern on dialysis. “They don’t know why it is, since I’m doing everything they tell me to do; I’m eating just what they tell me to,” she said. “That’s kind of what my whole life is. I follow directions — I’m a good little follower, I do what I’m told — and this happens anyway.”

Stiers was born in 1977 in Portland, Ore. She had a troubled childhood: her father left before she was born, and she remembers her mother as a distant, difficult parent. The first sign of Stiers’s health problems was that her teeth were weird. They were odd, small and sort of pointy, and she was told there were no buds for permanent teeth behind most of her baby teeth. When she was 10, problems started with her right eye: a black mass in her central vision resulting in several futile operations, which led to pain and inflammation and eventually total blindness in that eye. Her condition was diagnosed as Coats disease, a rare eye disorder, though her symptoms were not at all typical. “They told me there was a lot of pressure,” she said, “and they tried to take care of it surgically, like they did back then, cutting little slits to let the pressure out.” The operations only bruised and battered her; the eye hurt constantly, the vision was destroyed and finally, on her 14th birthday, Stiers had her right eye removed. A year later she received a prosthetic eye. She’s now on her third prosthetic, and the color matches her own blue-gray eye color so perfectly that it’s hard to tell which one is real.

When she was 15, Stiers dropped out of high school and ran away to Vancouver, Wash.,
just north of Portland. She doesn’t like to talk about why she left home, but she soon cut off almost all contact with her mother. When she was 18 she started having seizures — blank, absent periods in which she would find herself in a bathroom and not know how she ended up there. She was married at the time and working at a car wash, sometimes getting in the way of the cars during her seizures. She had to quit work, and she started looking for treatment.

Soon her husband left her, she told me, and Stiers called the only adult she could count on: Doug Ward, who had been married to Stiers’s mother for eight years and adopted Summer when she was a girl. They had not seen each other for years, but Ward and his current wife, Kim Plummer, drove a truck up to Vancouver and took Stiers home with them to Bend, Ore. At the time, Plummer was in her late 40s and childless. “Kim needed a daughter, and Summer needed a mother,” Ward says, explaining their unusual family arrangement. Since then, Plummer has been the only person Stiers calls “Mom.” Stiers has no interest in contacting her birth mother — though it might help the N.I.H. scientists in their analysis of her DNA to have samples from a biological relative for comparison.

Stiers’s medical problems escalated two years later, in early 2000. She was 22, and was five months pregnant by a new boyfriend. “I got up one morning and looked at my lower legs, and they were the size of my thighs,” she said. “I poked at them, and I had edema — of course I didn’t know what it was then — and I called the doctor, and they said, ‘Get in here right now.’ They airlifted me to the Bend airport and jetted me to Portland.” The doctors diagnosed toxemia, a serious and potentially fatal complication of pregnancy that includes high blood pressure and seizures. When they could not get her blood pressure down, Stiers said they told her, “We’re not losing both of you, we’re taking the baby.” Nine years later, the memory of that lost baby still seemed raw.

Stiers was told to go home and wait for her blood pressure to return to normal, but it never did. She was profoundly anemic, so she was hustled over to cancer specialists to be tested for leukemia or other bone-marrow cancers. She developed joint pain, so she was evaluated for autoimmune disorders like lupus and rheumatoid arthritis. She took Vioxx and Celebrex for the pain, but that led to uncontrollable vomiting. She stopped the painkillers and took steroids when the vomiting persisted.

It was two years before she was evaluated by a kidney specialist. He took a biopsy of Stiers’s kidneys and found that they looked odd, flecked with strange filamentous material whose origin no one could place. Within a year, Stiers’s kidney function declined, and she suffered from near-constant headaches, vomiting and diarrhea. Always slim, she lost 20 pounds. She was placed on kidney dialysis in October 2003. She immediately felt better and has been on dialysis ever since.

In the following years, new problems would emerge in the “cascading collapse.” Bleeding on the retina of her left eye, worsened by the blood thinner she took when she was on hemodialysis. Multiple bleeding sites in her brain, accompanied by areas of calcification, one or both of which probably caused her seizures. Pain and weakness in both legs, eventually diagnosed as avascular necrosis — bone death because not enough blood was reaching her extremities. Intestinal bleeding. Cessation of menstruation sometime in her late 20s. Insertion in 2007 of the vagus-nerve stimulator to stop the seizures. The emergence in her head of venous lakes, which are benign tumors caused by collapsing capillaries, accompanied by a palpable softening of her skull that Stiers calls “my sinkhole.” Development of dark, scaly patches on both legs, beginning in 2007, so rigid that it feels as if her legs are sheathed in stone, so painful she is forced to spend some days in a narcotic fog.
With each new diagnostic test her case grew more baffling. The first pathologist had never before seen the filamentous material he found on her kidney biopsy. Another pathologist saw something similar on a subsequent biopsy, taken from a nerve in her leg: again that filamentous material, which looked a lot like radiation damage. A gastroenterologist also mentioned radiation damage in describing her intestine's multiple fragile bleeding sites as seen on an endoscopy. But Stiers had never been exposed to radiation.

On the phone, despite the litany of physical decline, Stiers sounded as chipper as a character from “The Sound of Music” as she listed the things that make her happy: her three cats, which she calls “my children”; riding horses once a week for the hippotherapy to keep her legs strong; the “grandmas and grandpas” in her twice-weekly senior water-aerobics class, who watch out for her in case she has a seizure in the pool; Ward and Plummer; Dr. Pinnick. She also seemed to find it amusing that at the age of 31, her hair is almost entirely gray.

**Diagnosis is a complex mixture** of art and science. We may think we know how it works from watching “House” on TV: one brilliant mind throws all his attention at a problem, worries it like a rosary bead and finally has an “aha” moment in which he makes a connection that all the other doctors have missed. Often, on the show at least, it comes down to the insight of that individual, the person gifted, for whatever reason, with the ability to see colchicine poisoning when everyone else sees only a cough.

But in the real world of clinical diagnosis, there is no crabby genius spending days and nights at a whiteboard, enumerating and eliminating hypotheses, barking at his residents and taking a stab at a succession of hunches until he happens to hit on the one that explains everything. The best diagnosticians depend on induction rather than intuition. Physicians call it differential diagnosis, and it is taught in medical schools as a process of elimination that occurs in a particular order. You amass all the information — the patient’s medical history, the results of the physical examination, the findings of as many medical tests as you can think of — and you ask, What disease could explain all these findings? What else could explain them? What else?

On television, the mystery is always neatly wrapped up by the end of the episode. In reality, many medical mysteries are never solved. And by the time people with undiagnosed diseases make their way to the N.I.H., most of the logical diagnoses have already been considered and rejected, making a nice tidy ending even more unlikely.

Young physicians are often taught some variation of the catch phrase “When you hear hoofbeats in Central Park, don’t expect zebras.” In other words, focus on the most likely explanation for everything you observe. But for Undiagnosed Diseases Program patients for whom answers are so singularly elusive, those hoofbeats are likely to herald zebras after all. There are some 6,600 conditions currently identified, and most physicians are unlikely to encounter more than a fraction of them. That leaves thousands of others, any of which might come galloping into the N.I.H. at any time.

As in the other cases that will rotate through the Undiagnosed Diseases Program, Summer Stiers’s illness is not really undiagnosed; it is, if anything, overdiagnosed. She has had more than her share of working hypotheses over the past 20 years: leukemia, lupus, rheumatoid arthritis, ankylosing spondylitis, celiac disease, ulcerative colitis, Crohn’s disease. Each one was rejected in turn, either because it failed to explain everything or because objective testing ruled it out. With most of the common explanations eliminated, it was time to start thinking zebra.
Several days after I spoke to Stiers, I called Gahl at work to see what he was planning for her week at the N.I.H. in December. It was the day after Thanksgiving; Gahl rarely takes holidays. “The first thing doctors always think about is whether there’s a unifying hypothesis,” he told me. “When you get bizarre stuff like this, you automatically assume they are related. That was confirmed when they started to get biopsies of different tissues and they all looked similar.”

Based on the N.I.H. pathologist’s review of all the biopsy reports and slides submitted as part of Stiers’s case history, Gahl said he suspected the primary problem was in her basement membranes. The basement membrane is a thin sheet outside some tissues, on which a single layer of cells line up like tiles, all facing one direction to support the tissue’s architecture and to provide a barrier that keeps out damaging material. The membrane is composed of several types of protein, including collagens and glycoproteins, and it is found in just about every kind of tissue: skin, eye, muscle, the lining of the capillaries, the glomerulus of the kidney, the alveolus of the lung.

What pleased Gahl about the basement-membrane hypothesis is that it followed a rule of thumb in medicine known as diagnostic parsimony — also called Occam’s razor — which seeks a single diagnosis for all symptoms whenever possible. A problem with the basement membrane could, all by itself, explain almost all the organ breakdowns Stiers has experienced since the age of 10. “I would bet you practically anything that all these things are related,” Gahl said.

Before Stiers’s arrival the following week, Gahl planned to do some reading on basement-membrane disorders and to look for an expert somewhere at the N.I.H. “There are basic scientists here who study the basement membrane as their life’s work,” he said, referring to investigators who work only in the lab, examining cell cultures or animals rather than human patients. “We just have to find them.” In the sprawling bureaucracy of the N.I.H., a $28 billion federal agency that employs 6,000 researchers, it can be difficult sometimes to know who is who. A strength of the Undiagnosed Diseases Program is that it offers a systematic way to corral those investigators — about a quarter of them clinicians with medical degrees, the rest scientists with doctorates in a variety of biological subspecialties — and get a lot of them thinking about the same mystery.

Gahl tried to keep his expectations modest for Stiers’s week at the N.I.H. “Largely it’s to get a lot of consultations from all the smart people here and to synthesize their suggestions,” he said.

And a diagnosis for Stiers’s condition? Not by the end of the week, for sure, and possibly not even at the end of several months’ more lab investigations. “I was pretty explicit with her on the phone not to expect much of this program in terms of her own diagnosis,” he said, but rather to feel like part of a larger contribution to scientific knowledge in general, to the elucidation of a new disease. Gahl said he thought that she got it. He mentioned Robert Pinnick’s comment on Stiers’s “positive and pleasant attitude.” After his own phone conversation with her, Gahl said, “I think she sort of has an accurate understanding of the limits of what medicine can do for her.”

When Summer Stiers finally arrived at the N.I.H. Clinical Center on Monday, Dec. 8, her pleasant attitude was nowhere in sight. She and her traveling companions, Doug Ward and Kim Plummer, were still grumpy about the trip from Oregon. On better days they might have focused on the program’s largess — everything about this trip, from the airfare for Stiers and one parent to the hospital costs to lodging at the Edmond J. Safra Family Lodge — was free to them, all of it paid for by the N.I.H. But on the first morning, they spent a lot of time talking about their trouble driving from the airport to
Bethesda the previous night and going through security to get onto the N.I.H. campus and finding the cafeteria closed. Stiers settled down after she had a chance to order breakfast — an omelette with Cheddar cheese, tomatoes, onions, mushrooms and ham, and some apple juice to help her swallow the four pills she takes at the beginning of every meal or snack to help her regulate phosphorus — and her headache finally went away. As Plummer pointed out to me, Stiers is easily set off course; she needs all her emotional and physical resources to get through a day, and when anything goes awry, she tends to take it hard. But after this bad beginning, Stiers rallied and showed herself to be tougher than anyone expected.

The family looked like a band of aging hippies from the Great Northwest, with Stiers in a hooded red sweatshirt, jeans and big sheepskin boots. All of them have wild gray hair, making them look biologically related even though they’re not. Ward also has a big white beard, and all through this week in December, with Christmas decorations on every wall and a gingerbread-house contest in the hospital lobby, he was told more often than he could count how much he resembled Santa Claus.

After breakfast, there began the first of a dozen medical histories and physical exams that Stiers would go through over the next four days. The blind men approached the elephant, the specialists concentrating on the organs they knew best. Sometimes their listening skills were a bit deficient, sometimes they were as sharp as Sherlock Holmes’s. Almost everyone, for instance, heard Stiers say she began dialysis on Oct. 27, 2003. But only Lakshmi Gopal, the gastroenterology fellow, noticed the odd specificity. “Why do you remember that date in particular?” she asked.

“Because it’s when I started to feel better,” Stiers said. A small thing, but one more piece of the elephant, one more detail of how dreadful Stiers must have felt in the months her kidneys were shutting down.

Some of the specialists brought out the jokiness in Stiers, who has a racy sense of humor that emerges when she likes you; with others, she sat very still in exaggerated, strained politeness. She was stoic during every encounter. At home she sleeps 10 hours a night, naps for another 2 or 3, but here she soldiered through the long, repetitive days and never asked for a break. She said she was determined to use her time in Bethesda to help get some answers for others in the future. It was perhaps significant that, during her first formal interview with Gahl that day, her main question — which caught Gahl by surprise — was how she could donate her body to the N.I.H. after she died.

At the end of the long first day in Room 5-2624 in the northwest wing of the Clinical Center, Stiers started warming the bags of fluid she would need for her nightly dialysis treatment, and Gahl hurried back to her room to see how she was doing. James Balow, the nephrologist, who was last on the day’s lineup, stopped him in the hall. Balow wanted to offer his diagnostic suggestions, all of them kidney-related. Gahl listened politely, unconvinced; Balow’s hypotheses explained some of Stiers’s symptoms, but they didn’t explain everything. And Gahl was still looking for one elegant, simple explanation for the whole cascading collapse.

The potential limitation of Occam’s razor comes to the fore in someone like Stiers, whose disease is so protean and so complex. Sometimes simplicity is a good thing, but sometimes simplicity is just too simple. In the 1950s, a professor of medicine at Duke University, John Hickam, was said to have proposed an alternative to Occam’s razor that he called, tongue slightly in cheek, Hickam’s dictum: “Patients can have as many diseases as they damn well please.” Stiers might have something going on with her basement membranes, or some other problem that leads to lack of integrity in vessels.
throughout her body. But some of her symptoms might be secondary complications related only tangentially to the underlying flaw.

On Wednesday morning, Dec. 10, while Stiers worked her way down the long list of consultants — eye doctor, dentist, dermatologist, hematologist, acupuncturist — Gahl and Galina Nesterova, the genetics fellow working on Stiers's case, met in Gahl's office with Yoshihiko Yamada, a leading basement-membrane investigator at the N.I.H. Two geneticists from Gahl's lab also attended. Yamada described what can happen in laboratory animals when the basement membranes lack integrity, and there was a ripple of recognition around the table when he listed many of the symptoms Stiers has, too: gray hair, tooth abnormalities, muscle degeneration, vascular defects, cartilage and bone abnormalities and abnormal nails.

Would you recognize a nail abnormality related to basement-membrane dysfunction if you saw it? Gahl asked.


Yamada said there were at least 20 proteins, possibly many more, that express themselves in the basement membrane, meaning that if Stiers's basement membrane was involved, a defect in any of those proteins could be part of her molecular diagnosis. How to limit the search? A geneticist, Marjan Huizing, suggested figuring out first which tissue was damaged as a result of the primary disease, rather than as a secondary complication of kidney failure; this might determine which basement-membrane proteins to start with.

"O.K.,” Gahl said, turning to Yamada. Gahl summarized what they knew about Stiers so far based on her previous test results. "If we knew muscle wasn’t involved, and intrinsic neuronal tissue wasn’t involved, and bone is involved and vessels and renal tubules, then that may tell us what components to go after."

Yamada thought for a moment and suggested the protein fibulin, of which there are seven forms. “Great,” Gahl said, smiling for the first time that morning. He wrote it down as Yamada spelled it out, because Gahl was unfamiliar with the word and Yamada has a thick accent. F-i-b-u-l-i-n.

About 4 the next afternoon, Thursday, Dec. 11, Gahl asked all the consultants on Stiers's case to meet him at 4:30 in a small area outside her room. At least 16 specialists had traipsed past Stiers's bedside in the previous four days; almost all of them managed to carve out time for the spontaneous meeting. Not surprisingly, the dermatologist suggested a dermatologic diagnosis, Vogt-Koyanagi-Harada syndrome. The nephrologist, James Balow, still liked his kidney diagnoses. The rheumatologist didn’t want to rule out Sjogren syndrome just yet. “Any other specialists around here who want to explain your own favorite organ?” Gahl asked with a little chuckle.

The balkanization of medicine accounts for an increasingly constrained approach to diagnosis — an approach that, as Gahl's joke suggests, is defined by a specialist's focused knowledge rather than by some broader understanding of the patient. “This is partly because of how medicine is taught — how it has to be taught,” said Kathryn Montgomery, professor of medical humanities and bioethics and of medicine at the Northwestern University medical school in Chicago, when we spoke by telephone. "Doctors get educated to solve problems in their own terms. They've got only a certain set of information and experience at their disposal."

Few physicians are trained to look at the patient as a whole, Montgomery says, with the
exception of generalists like internists and pediatricians. In an era of increasing specialization, she sees the Undiagnosed Diseases Program as an institutional atavism, a way to reconstruct the old-school generalist “on a multiperson level.”

But the problem is not just overspecialization, Montgomery says; it’s the complex nature of diagnosis itself, and the difficulty of trying to teach the process in medical school. Because diagnosis involves so many intersecting and often incompatible parts, medical students have traditionally been taught to do opposite things at once when they meet a new patient: suspend judgment, but form an initial impression; look for a single diagnosis to explain all symptoms, but watch for co-morbidities; avoid the anecdotal, but pay attention to stories; expect the diagnosis to be a common disease, but don’t forget the rare ones. This dissonant approach was recently modified in some medical schools, according to Montgomery, with students now taught to begin with a “working diagnosis” that they refine as they accumulate data that either confirm or refute their first guess. But while the working-diagnosis method might clarify some things, Montgomery worries about what might be lost: a sense, as she wrote in her 2006 book, “How Doctors Think: Clinical Judgment and the Practice of Medicine,” of an alternative pathway. Because of the inherent contradictions traditionally taught in medical school, she wrote, new doctors have been able to achieve “a certain balance, a consciousness that, no matter which way they may work through a diagnosis, there is another way.”

Gahl’s way, at least in regard to Summer Stiers, had little room for contradictions. After hearing his colleagues’ thoughts at the Thursday-afternoon meeting, he mentioned his hypothesis that she had a defect in her basement membranes. He said his plan was to collect skin cells from Stiers, try to grow them in the lab and look for the seven forms of fibulin — the word that was dictated to him only the day before — as a first step in hunting down a possible genetic defect that might cause her basement membranes to leak.

“I don’t like it,” Balow said, ruffling the pages of Stiers’s chart with some irritation. “The basement membranes to me don’t look abnormal.” Gahl pointed out that the N.I.H. pathologist read the kidney biopsy as showing a “split basement membrane,” but Balow said what he saw on the biopsy looked more like a “split appearance; it’s not really split, it’s a double contour.” In any case, he continued, other diseases of the basement membrane of the kidney, like Alport syndrome, have a completely different appearance. Gahl parried, “But those are the known ones.”

Diseases of the basement membrane of the skin look different too, added the dermatology resident, listing a few. “Again, those are the known ones,” Gahl said, starting to sound a little testy. A variation of the zebra conundrum: If you have a completely unknown disease but a hypothesis based on some similarities to a few known diseases, how many dissimilarities are enough to toss out your hypothesis?

Everyone agreed that the stony, scaly plates on Stiers’s shins, the source of so much pain, were probably not a symptom of the underlying disease process, whatever it was. They also disputed her Oregon doctors’ conclusion that the plates were caused by calciphylaxis. The consensus was that the hardened skin on her legs was probably a result of a complication seen in dialysis patients who are given a particular chemical during an M.R.I. to make the brain structures show up better. The chemical, gadolinium, is now known to cause a stiffening syndrome in people whose kidneys are unable to clear it out of their systems. The trouble with her shins was taken off the table in the search for an underlying diagnosis.

On Friday morning, Dec. 12, Gahl presented a synthesis of everyone’s thinking during a
wrap-up session for Stiers and Ward (Plummer had already left for a weekend with her sister in Pennsylvania). He filled her in on the details of basement membranes and a related hypothesis, that there’s a defect in the region between cells known as the tight junction. He also told her that his colleagues thought that the problem on her lower legs was nephrogenic systemic fibrosis, not calciphylaxis. Stiers nodded sagely. Her lifetime of doctor visits had made her fluent in medicales, even though she has only a high-school equivalency diploma. She had just one question for Gahl: If this was an entirely new disease, was there any chance they might name it after her? She sort of liked the ring of “Summer’s syndrome.”

As a scientist, Gahl sees understanding disease at the molecular level as his ultimate ambition. But as a clinician, he sees its limits. “We have a two-pronged goal here at N.I.H.: medically helping the patient and advancing scientific knowledge,” he said. Molecular diagnosis, telling the story of the disease through the genes involved, is not necessary to accomplish the first goal of patient care; diseases are often diagnosed and satisfactorily treated even when the molecular basis is unknown, and discovering the genes involved does not always improve patients’ lives. But molecular diagnosis is an important part of accomplishing the second goal of scientific advance.

Many diseases are defined by their signs and symptoms alone, Gahl said, and that’s fine as far as it goes. But for a research institution, especially one that is seeing what might be the only patient with a particular disease, a description of signs and symptoms is not enough. What Gahl is looking for is the whole package: a defect in the patient’s DNA that points to a specific genetic mutation; evidence that explains how that mutation would cause the patient’s symptoms; and a clinical demonstration that the protein — or other chemicals — made by the gene is missing or defective, and that its derangement accounts for the symptoms.

A molecular diagnosis for Stiers, if one is to emerge, will probably originate in a laboratory at the N.I.H., perhaps in collaboration with one of the few state-of-the-art clinical laboratories scattered across the country that are part of the N.I.H. network. “We’re at the frontiers here; people don’t do this every day,” Gahl said. “We can’t say to a lab, ‘Give us a fibulin antibody test on this unstained kidney.’ We have to arrange to have them do that — or do it ourselves.”

The genetic work on Stiers’s blood and saliva samples began a few weeks after she went home to Oregon. In mid-January a colleague of Gahl’s, the geneticist Thomas Markello, received the results of a test known as a one-million-SNP array, and his computer analysis of those results is still under way. Each SNP (pronounced “snip”), which stands for single nucleotide polymorphism, represents a small change in the three billion nucleotides in the human genome. In isolation, any single SNP is likely to be of little consequence. But several SNPs in a row could represent a deletion — or, in some cases, a duplication — of several thousand nucleotides, which could interfere with the behavior of a known gene. Because of information gained from the Human Genome Project, which first sequenced the entire human genome in 2000, the location of SNPs can point scientists to which particular genes might be affected and what the functional consequences of a mutation might be.

Every person has about 50 SNP regions on a million-SNP array, most of them representing genetic variations that are either completely meaningless or that code for something harmless, like red hair rather than brown. Stiers had the expected number of SNP regions, about 47. The question now — which is still unanswered, five weeks after the test results came back — is which of those 47, if any, is related to her disease. Markello has spent the last month comparing Stiers’s SNPs to those of known disorders,
paying special attention to those found near genes involved in making basement-
membrane proteins like fibulin. An intriguing finding is a mutation on chromosome 9,
where both copies of a particular stretch of nucleotides are missing (chromosomes come
in pairs, and sometimes mutations occur in only one chromosome, sometimes in both).
Stiers is missing six SNPs in a row on that chromosome, representing a deletion of at
least 4,694 nucleotides, which intrigues Markello because the deletion is not far from a
gene whose absence causes a rare, always-fatal neurological disease. Stiers doesn’t have
that disease — the gene itself seems to be intact — but does her six-SNP deletion affect
how that crucial gene functions? “This change may be so far away from the start of the
gene that it has no effect,” Markello told me in an e-mail message. “But it is close
enough to begin the process of planning a cell-biology experiment with her cells to test
whether the gene [protein or other products] is being made at the same amount or not.”

While running computer analyses of Stiers’s results, which can be painstaking and
tedious, Markello has been buoyed by the million-SNP array results in an unrelated case
that came in about the same time from another Undiagnosed Diseases Program patient.
The patient, a 51-year-old woman, came to the N.I.H. in December complaining of vague
neurological symptoms — overall fatigue and burning and stinging in her feet and spine
— that seemed to become worse when she ate foods with spices, artificial additives and a
long list of other ingredients. The million-SNP array indicated a complete deletion of
about a third of both copies of a gene known to be involved in the digestion of certain
starches. It was never previously associated with any human disease. Now Gahl is
making plans to bring the patient back to Bethesda to look for a specific neurological
change that should occur in people unable to digest the starch normally. If the scientists
can confirm their genetic findings clinically, the program might have its first new
diagnosis.

In Stiers’s case, however, the search continues. While Markello conducts further
analysis of her million-SNP array, the geneticist Marjan Huizing and her colleagues are
cultivating samples of Stiers’s cells to look for fibulin directly, as well as for other
relevant proteins like those involved in the maintenance of tight junction cells. Other
investigators in Gahl’s lab are growing Stiers’s skin cells in culture — or, more accurately,
they are trying to. The fibroblasts, a type of skin cell, are barely growing in the dish. The
melanocytes, another type, are growing into a bizarre shape, with long, proliferative
extensions. Gahl said his team is trying to figure out what to make of these findings.
“Why cells grow in culture, why they don’t grow in culture, there could be 100 different
explanations,” he told me. “All we know is that it’s very unusual. It could be a measure of
the extent of the pathology in those cells.”

Like the scientists in the Undiagnosed Diseases Program, the patients also tend to have a
double mission. On one hand, they hope to advance scientific knowledge and leave
something useful behind; on the other hand, they’re hoping the information might
improve their day-to-day lives. In their unguarded moments, they even utter words like
“cure.” The double-edged nature of their motivation, the strange mix of altruism and
self-interest, is a source of tension for a man like Gahl. He is personally opposed to
pursuing diagnosis at any cost, having seen cases in which, as he puts it, “too heavy a
pursuit of these things can tear families apart.” Yet he is professionally dependent on just
that kind of determined, slightly desperate pursuit. If it weren’t for the courage and
single-mindedness of these patients, he knows that clinical research at the N.I.H. would
grind to a halt.

“It’s always a balance,” Gahl, the father of four grown children, said. “Everyone who’s
come here has already self-selected as being very, very interested in pursuing things; the
ones who aren’t interested we never see. What we really have to do is sort of modulate
these patients in the other direction.” Under the stress of an undiagnosed disease, he said, “people tend to react the same way they would react under other circumstances, just in a little more intense form.” How could it be otherwise? The prospect of physical decline in the face of an unknown future represents, after all, the essence of the human condition.

When the Undiagnosed Diseases Program’s first pediatric patient, 2 1/2-year-old Ragan Thursby of Florida, was admitted in October, Gahl said he thought he recognized the signs of parents who would go too far, to the point of pursuing every diagnostic option, spending money they didn’t have and shortchanging Ragan’s healthy older sister. Gahl later realized that he was wrong. After the first day, Ragan’s father sought out Gahl to demarcate his own bottom line: his unwillingness to put his daughter through needless pain for uncertain benefit. At that point Gahl decided it must be Ragan’s mother who was driven, without limit, to find a name for Ragan’s profound developmental delay, no matter what the emotional and financial toll. But the week at the N.I.H. seemed to shift priorities in Ragan’s mother as well. “I’m finished now,” she said at the end of the week. She was at last ready to turn over the search for Ragan’s mystery to the N.I.H scientists, she said, and was heading back home to Tallahassee to do what Gahl suggested: to continue to fight to provide Ragan with the best local services she could; and to take a breath and just love her little girl.

During each patient’s week at the N.I.H., Gahl’s staff usually builds in time for visits with consultants who focus on care rather than diagnostics: physical therapists, speech pathologists, pain experts and psychiatrists. This is the staff members’ way, it seems, of helping patients derive some personal benefit from the experience — a small thing sometimes, a party favor of sorts, but at least some tangible recognition of how central the patients are to the whole enterprise. Ragan Thursby left the N.I.H. with a lighter pair of orthotics that made it easier for her to learn to walk. And Summer Stiers went home with a CD to help her meditate her way through the pain in her legs and her back, as well as with a prescription for acupuncture.

Stiers, who has spent much time thinking about things like legacies, also went home with something else. When the wrap-up meeting with Gahl was over, she and Ward returned to her room to pack her things. They pronounced themselves satisfied with the way the week went. Before she came, Stiers told me as we hugged goodbye, she thought she couldn’t offer any real information about her disease until after she was dead and had donated her body to science. But, she said, “all these tests were something I could do and make a difference, so someone else wouldn’t have to go through this, having things go wrong and not knowing what is coming next.” She even dares to hope, she said, that the scientists might learn something that will point them to a way to ease her own psychic and physical pain.

Robin Marantz Henig, a contributing writer, is the author most recently of “Pandora’s Baby: How the First Test Tube Babies Sparked the Reproductive Revolution.”

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