Undiagnosed Diseases Program

Press Coverage

– a collection of press clippings collected
since the Program launch in May 2008 –

Undiagnosed Diseases Program Launch

Public Advocacy Briefing and Media Briefing

May 19, 2008

NIH Director Elias Zerhouni joined Clinical Center Director John Gallin, NHGRI Clinical Director and UDP director William Gahl, and NIH Office of Rare Diseases director Stephen Groft in announcing the new program on May 19, 2008. The telebriefings were moderated by Larry Thompson, chief, NHGRI Communications and Public Liaison Branch. Also on hand was an NIH patient Amanda Young of Conyers, GA.

From left, Dr. Groft, Larry Thompson, and Dr. Gahl anticipate the start of the telebriefings.

Gathered around the conference table in the Clinical Center Medical Board Room are, from left, Dr. Groft, Larry Thompson, Dr. Gahl, Dr. Gallin, Amanda Young and her mother, Lisa Young

From left, joined by Dr. Zerhouni, Ms. Young delivers her statement about receiving a diagnosis after living many years with an unknown disease.

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May 19, 2008

U.S. Department of Health and Human Services
NIH News
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NIH Launches Undiagnosed Diseases Program

Clinical Researchers to Tackle the Most Puzzling Medical Cases

Amanda Young's extremely rare disorder was diagnosed by Dr. John Gallin at the NIH Clinical Center.

Bethesda, Md., Mon., May 19, 2008 — The National Institutes of Health (NIH) today announced a new clinical research program that will aim to provide answers to patients with mysterious conditions that have long eluded diagnosis. Called the Undiagnosed Diseases Program, the trans-NIH initiative will focus on the most puzzling medical cases referred to the NIH Clinical Center in Bethesda, Md., by physicians across the nation.

"A small number of patients suffer from symptoms that do not correspond to known conditions, making their care and treatment extraordinarily difficult. However, the history of biomedical research has taught us that careful study of baffling cases can provide new insights into the mechanisms of disease — both rare and common," said NIH Director Elias A. Zerhouni, M.D., who has made a point during his six-year tenure at NIH of encouraging trans-NIH initiatives. "The goal of NIH's Undiagnosed Diseases Program is two-pronged: to improve disease management for individual patients and to advance medical knowledge in general."

The new program, which got under way over the past month, is the culmination of efforts by William A. Gahl, M.D., Ph.D., clinical director at the National Human Genome Research Institute (NHGRI), part of the NIH; John I. Gallin, M.D., director of the NIH Clinical Center; and Stephen Groft, Pharm.D., director of the NIH Office of Rare Diseases (ORD). With the program infrastructure now in place, the program is ready to accept patients, the first of which is expected to be seen in July 2008.

"The NIH Clinical Center, the nation's clinical research hospital, provides an extraordinary environment for excellence in both patient care and collaborative clinical investigation," said Dr. Gallin. "This new program will capitalize on a rich set of skills already at the Clinical Center to help patients with unusual medical conditions. These patients often partner with us in clinical research to identify new diseases or new treatment."

To evaluate each patient enrolled in the new program, NIH will enlist the expertise of more than 25 of its senior attending physicians, whose specialties include endocrinology, immunology, oncology, dermatology, dentistry, cardiology and genetics. Dr. Gahl, who is an expert on rare genetic diseases, will serve as director of the new program.

"We have developed a stringent referral process to ensure this program deals with those cases that have truly confounded medical experts," Dr. Gahl said. "We will be very selective when it comes to patient eligibility. Our focus is strictly on conditions that have not been diagnosed."

To be considered for this NIH pilot program, a patient must be referred by a physician and provide all medical records and diagnostic test results requested by NIH. Patients who meet the program's criteria — as many as 100 each year — will then be asked to undergo additional evaluation during a visit to the NIH Clinical Center that may take up to a week.

Two nurse practitioners will manage patient recruitment and logistics for the new program, which will utilize existing facilities and staff already at the NIH Clinical Center, NHGRI and ORD. Funding for the program includes $280,000 per year from the ORD.

In organizing the Undiagnosed Diseases Program, NIH has reached out to patient advocacy groups that often serve as a source of information and support for people struggling with mysterious ailments. "We hope to build upon our strong working relationships with

many patient advocacy groups. These organizations provide a crucial link in our nation's efforts to improve human health through biomedical research," said Dr. Groft. "We hope that this new partnership of NIH researchers, advocacy groups and patients will give hope for many Americans who now face troubling medical symptoms with no clear diagnosis."

For more information about the Undiagnosed Diseases Program, go to: http://rarediseases.info.nih.gov/Undiagnosed. Physicians and patients with specific inquiries may call the NIH Clinical Center clinical information research line, at 1-866-444-8806.

The NIH Clinical Center (CC) is the clinical research hospital for the National Institutes of Health. Through clinical research, physician-investigators translate laboratory discoveries into better treatments, therapies and interventions to improve the nation's health. For more information, visit http://clinicalcenter.nih.gov.

The NIH Office of Rare Diseases stimulates and coordinates research on rare diseases and supports research to respond to the needs of patients, healthcare providers and the research communities involved in the care, treatment, and evaluation of products for the prevention, diagnosis, or treatment of these conditions. For more information about ORD and its programs, visit http://rarediseases.info.nih.gov.

The Office of the Director, the central office at NIH, is responsible for setting policy for NIH, which includes 27 Institutes and Centers. This involves planning, managing, and coordinating the programs and activities of all NIH components. The Office of the Director also includes program offices which are responsible for stimulating specific areas of research throughout NIH. Additional information is available at http://www.nih.gov/icd/od/index.htm.

NHGRI is one of the 27 institutes and centers at the NIH, an agency of the Department of Health and Human Services. The NHGRI Division of Intramural Research develops and implements technology to understand, diagnose and treat genomic and genetic diseases. Additional information about NHGRI can be found at its Web site, www.genome.gov.

The National Institutes of Health — "The Nation's Medical Research Agency" — includes 27 institutes and centers, and is a component of the U.S. Department of Health and Human Services. It is the primary federal agency for conducting and supporting basic, clinical and translational medical research, and it investigates the causes, treatments and cures for both common and rare diseases. For more, visit www.nih.gov.

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Associated Press

May 19, 2008

Those with rare diseases offered a chance for free treatment

By LAURAN NEERGAARD – 15 hours ago

WASHINGTON (AP) — They're the cold cases of medicine, patients with diseases so rare and mysterious that they've eluded diagnosis for years.

The National Institutes of Health is seeking those patients — and ones who qualify could get some free care at the government's top research hospital as scientists study why they're sick.

"These patients are to a certain extent abandoned by the medical profession because a brick wall has been hit," said Dr. William Gahl, who helped develop the NIH's new Undiagnosed Diseases Program. "We're trying to remove some of that."

The pilot program, announced Monday, can only recruit about 100 patients a year. But federal health officials hope that unraveling some of these super-rare diseases in turn will provide clues to more common illnesses.

"We believe this is not only a service to be rendered, but also knowledge to be gained," said NIH Director Dr. Elias Zerhouni.

About 10,000 new patients a year sign up for roughly 1,500 different research studies, many of them for rare diseases, at the NIH's Bethesda, Md., hospital, the innocuously named Clinical Center.

The new mystery-disease program is aimed at people with the rarest of the rare diseases — even those with truly brand-new ailments — who otherwise would be turned away because there are no studies, yet, for their conditions or a researcher specifically tracking their symptoms. It doesn't promise a diagnosis, but the chance to be reevaluated by a team of renowned specialists.

Amanda Young of Conyers, Ga., illustrates patient frustration. By age 3 1/2, she had suffered repeated lifethreatening infections that left doctor after doctor baffled. At 8, a scratch turned gangrenous, requiring her leg to be amputated. Yet under the microscope, her immune system seemed normal except for an unexplained low white blood cell count.

In 1990, not long after that amputation, her desperate parents brought her to NIH, where the hospital director "made us a promise," Young recalled. "He told us he would never give up on me."

It took until 2003, but Young got a phone call: "My disease finally had a name."

Gene research had uncovered a previously unknown immune-system pathway — showing NIH's Dr. John Gallin that Young harbors an extremely rare mutation, named IRAK4 deficiency, that means she lacks a protein key for that pathway to work.

There's no treatment yet. But Young, now 26, continues to volunteer for research in hopes of one.

To be considered for the new program, a doctor must refer a mystery patient to the NIH and send all medical files for evaluation. Accepted patients will undergo up to a week's additional testing at the Clinical Center, for free.

For more information, see http://rarediseases.info.nih.gov/undiagnosed or call 1-866-444-8806.

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News
May 19, 2008

Health agency puts spotlight on mystery diseases

NIH launches programme to help patients with undiagnosed conditions.

Meredith Wadman

The NIH's Clinical Center in Bethesda will soon be investigating patients' problem diagnoses.*Duane Lempke, Sisson Studios, Inc.*

Each time she goes to see a new doctor, Marianne Genetti takes with her a thick folder bulging with notes. The folder contains her medical records, but despite the number of doctors she has seen, nowhere in the sheaf of papers is a diagnosis.

Genetti, the founder and executive director of Florida-based patient activist group In Need of Diagnosis, has lived for decades with a mysterious malady in which mucus glues her lungs to her diaphragm, leaving her breathless. The problem once caused one of her lungs to collapse, requiring emergency surgery.

Genetti says there is no clinic she can attend to get a diagnosis. "I have a wonderful medical team," she says, "but they have no place to send me."

Today, that may change for Genetti and others like her, with the launch of a programme for undiagnosed diseases by the US National Institutes of Health (NIH).

Based at the agency's Clinical Center, its huge hospital in Bethesda, Maryland, the programme will enlist the expertise of more than 25 senior NIH doctors with a wide range of specialities, from endocrinology to genetics.

Although tricky medical cases have long been referred to the NIH, those patients have been directed to individual clinics with specific areas of expertise. This was unfortunate for patients who didn't neatly fit into one of those categories. The new programme will allow consultants in diverse fields to share their expertise when dealing with puzzling individual patients.

Looking at the patients in this multidisciplinary way could finally provide a long-awaited diagnosis, the programme's backers hope.

Expert opinions

Although some expected culprits, from autoimmune disorders to rare mitochondrial diseases, will probably be found, other patients may shed light on completely unknown medical problems. The goal, says NIH director, Elias Zerhouni, "is two-pronged: to improve disease management for individual patients and to advance medical knowledge in general".

"It gives me great hope that it's going to be a place where we can confidently send people who in the past we might have had to turn away empty-handed."

Mary Dunkle
National Organization for Rare Disorders

The programme will be staffed by two nurse practitioners, funded by an annual grant of $280,000 from the NIH's Office of Rare Diseases (ORD). But its impact could go beyond the 50–100 patients it will treat each year, says the programme's director, William Gahl, a rare-disease expert at the National Human Genome Research Institute.

Gahl hopes that the clinic will yield information for the rest of the medical profession. "The intellectual synergy of this is really significant," he says. "It's not something you can put a dollar figure on."

Into the unknown

The problem of undiagnosed patients emerged when the ORD surveyed several years' worth of questions fielded by the information centre it runs in partnership with the genome institute. "Around 6.6% of the questions we were getting related to undiagnosed diseases," says ORD director, Stephen Groft. "That becomes a major problem when you extrapolate to the entire population."

Patient advocates agree. "The single most consistent issue that people who call us are dealing with is the difficulty of getting a diagnosis," says Mary Dunkle, a spokeswoman for the National Organization for Rare Disorders in Danbury, Connecticut. "People are very hopeful and actually excited about this. It's something that patients feel hasn't received a lot of attention."

There will be plenty of candidates for the new programme: the NIH has already received unsolicited copies of some patients' details, as word has spread among patient groups.

Patients will nevertheless need to be referred by a doctor, Gahl says. "We have developed a stringent referral process to ensure this programme deals with those cases that have truly confounded medical experts," he says. " We will be very selective when it comes to patient eligibility."

That doesn't deter Genetti, who is pretty sure that she will qualify, once her wait for the programme's details is over. "As soon as I know on Monday, I'm going to call my neurologist and ask if he would like to refer me there."

Dunkle is optimistic that the programme will help many others in the same boat: "It gives me great hope that it's going to be a place where we can confidently send people who in the past we might have had to turn away empty-handed."

Newsweek

HEALTH

June 9, 2008

The Genetic Detectives

A new government program will study, diagnose and ultimately treat people with mysterious diseases.

By MARY CARMICHAEL

FOR THE FIRST FOUR YEARS of his life, Zachary Townsley was a medical mystery. His mother, Janine, noticed something strange about him at six months: he had "a little hump in his back." The family pediatrician said not to worry, but by one year, Zachary had a new symptom: at an age when most babies were starting to walk, he wasn't crawling. The Townsleys went to a neurologist, but he couldn't find a diagnosis that would explain Zachary's troubles. The results of a chromosomal test came back clean. Occupational therapists, physical therapists, speech therapists, an audiologist: none of them could tell the Townsleys what their son had. By the time he was almost 4, Zachary was walking, but with bent knees. He had developed a speech impediment, and his once angelic facial features had begun to grow in odd proportions. Other kids stared at him on the playground. Clearly, something was wrong. But what on earth was it?

SPECIAL CASE: *Zachary, 8, has a rare metabolic disorder*

Zachary's story is sadly familiar to millions of Americans who suffer from—well, it's hard to say what they suffer from, and that's the problem. Twenty-five million people are currently afflicted with rare diseases, and for many of them, a proper diagnosis can take years or decades, if it comes at all. Some of these conditions are so new that they don't have names yet. Those that do have names—Blackfan Diamond anemia, periodic paralysis, Hermansky-Pudlak syndrome—may strike just a few hundred or a few thousand people. They can mimic much more common ailments, masquerading as high blood pressure or fatigue. Patients who have them may be misunderstood and misjudged, and they have no choice but to go untreated: doctors throw up their hands in confusion, friends wonder if the symptoms are all in the head. Often, when patients do finally get a correct diagnosis, irreversible damage has already been done. "If they go for 20 years without a diagnosis they can accrue all sorts of complications," says Dr. William Gahl, the clinical director of the National Human Genome Research Institute. "By the time they know what it is they have, they're medical disasters."

Last month it seemed these unfortunate patients might be getting a major new source of help. On May 19, the National Institutes of Health revealed its new Undiagnosed Diseases Program, an interdisciplinary center for studying, diagnosing and ultimately treating patients with unidentified illnesses. In a teleconference, NIH director Elias Zerhouni hailed the initiative's potential, noting that its use of genetics and genomics could be "transforming." Amanda Young, a 26-year-old woman, offered hope, too: she told how she'd waited 20 agonizing years until the NIH's Clinical Center diagnosed her with IRAK-4 deficiency, an extremely rare genetic mutation. Gahl, who heads the new program, also spoke. But his message was more subdued. "This is a research program," he said. "We won't be able to help everyone who seeks our care." Later, in an interview, he worried that his part of the message might have been lost: "A lot of people are going to hear this as 'oh, they have a diagnosis for me.'"

The Undiagnosed Diseases Program may be innovative, but it's also very small. It is equipped to see no more than 100 carefully chosen patients a year, and it consists of just three full-time staffers: two nurse-practitioners and a scheduler, who is suddenly very busy. In the first two weeks of its existence, the program received more than 200 phone calls from desperate patients in and outside the United States. All of them wanted to come to the NIH for full, extensive evaluations. "We're being inundated," Gahl says. The new institute can lean on doctors at other NIH centers for help, but all those docs have day jobs. So, for that matter, does Gahl: he has a lab with multiple ongoing experiments, and the new institute takes up only a third of his time. He hopes the NIH (which is already strapped for cash) will send more funding and employees his way. Until it does, the best the program will be able to do for most patients is guidance by phone call.

Ultimately, what rare-disease patients need is for the program to match or at least approach the success of the Orphan Drug Act, which leverages the enormous resources of Big Pharma for small markets. The legislation is celebrating its 25th anniversary this year, and talk about transformative: it has increased the number of drugs developed for rare-disease markets by about thirteenfold. These drugs are often costly, but they can be the happy endpoint of a rare-disease patient's journey; once a diagnosis is finally given, they allow for something to be done about it. Zachary Townsley, now 8, is one of their beneficiaries. A month shy of his 4th birthday, he was diagnosed with Hunter syndrome, a metabolic disorder that affects only 500 Americans. In October 2006 he began taking Elaprase, a newly approved orphan drug that was—and still is—the only treatment on the market. It is not a cure, but some of his symptoms have improved, and it is far better than the recommendation doctors originally gave Janine Townsley: "Love him, take good care of him, pray and go home." ■

PHOTOGRAPH BY JEFFERY SALTER—REDUX FOR NEWSWEEK

NBC NIGHTLY NEWS WITH BRIAN WILLIAMS

June 24, 2008

The NBC Nightly News story about the Undiagnosed Disease Program depicted activity in the NHGRI lab. Shown at the bench is Ann Smith, Office of the Clinical Director, foreground, and Roxanne Fischer, Human Biochemical Geneics Section.

NBC NIGHTLY NEWS WITH BRIAN WILLIAMS

June 24, 2008

NIH to study rare disorders, medical mysteries

ANCHORS: BRIAN WILLIAMS

REPORTERS: MARTIN SAVIDGE

LENGTH: 453 words

BRIAN WILLIAMS, anchor:

We mentioned this before the break. Thousands of Americans each year become seriously ill and don't know why, suffering from conditions that are so rare and mysterious there is no diagnosis. Now a group of experts is taking on what could be thought of as medical cold cases. Our report on this tonight from NBC's Martin Savidge.

TEXT:

Medical Mysteries

MARTIN SAVIDGE reporting:

For 27 years, Amanda Young has lived with a mysterious illness that strikes with little or no warning. It's cost her her leg and several times nearly her life.

Ms. LISA YOUNG (Amanda's Mother): I carried Mandy into a doctor's office and I said, `Please help me. She's dying.'

SAVIDGE: Growing up, she was rushed to the hospital more than 100 times. Yet no doctor could tell her why.

Ms. AMANDA YOUNG: My question was always, `What is wrong with me? Why do I keep getting this?'

SAVIDGE: The National Institutes of Health estimates more than 10,000 people each year say they suffer similar medical mysteries.

Dr. WILLIAM A. GAHL (National Institutes of Health Undiagnosed Diseases Program Director): There's a whole cadre of them out there that really, medical profession does not know about yet. Those are the ones we're after.

SAVIDGE: Now the government's top research hospital will focus its vast resources and best scientists on solving these baffling health puzzles.

Dr. GAHL: Our mission is to do clinical research and describe these new disorders.

Hi, Brenda. Nice. How are you doing?

SAVIDGE: Initially the undiagnosed diseases program will accept only about 50 to 100 patients. There's no charge and no promise of a cure. But there is excitement.

Dr. JOHN GALLIN (National Institutes of Health Clinical Center Director): One, because we think we can help a lot of patients. But, two, we think the patients can help us answer some very important questions about fundamental biology.

SAVIDGE: That could help millions of people suffering more common illnesses and the program could spot new diseases before they spread. It was the NIH that finally diagnosed Amanda with a rare genetic mutation.

Ms. A. YOUNG: The name is Irak 4 Immune Deficiency.

SAVIDGE: There is no treatment yet; but for Amanda and her family, just understanding is a huge relief.

Ms. L. YOUNG: We had waited 20 years for somebody to put a name on what was wrong with her.

SAVIDGE: And as anyone with a mystery illness will tell you, with a name and a diagnosis comes hope.

Ms. A. YOUNG: God gave me what he gave me for a purpose, and my purpose isn't over yet.

SAVIDGE: Martin Savidge, NBC News, Atlanta.

WILLIAMS: When NIGHTLY NEWS continues here in just a moment, why some are deciding that making a run for the US border might not be worth the risk these days.

JAMA®
The Journal of the American Medical Association

July 2, 2008

MEDICAL NEWS & PERSPECTIVES

US Launches Undiagnosed Diseases Program

Bridget M. Kuehn

IT TOOK MORE THAN 20 YEARS FOR PHYsicians to finally identify the disorder that caused Amanda Young to experience frequent life-threatening infections. By that time, Young, now 26, had spinal meningitis 3 times and had undergone amputation of her leg with hip disarticulation after a minor scratch lead to gas gangrene.

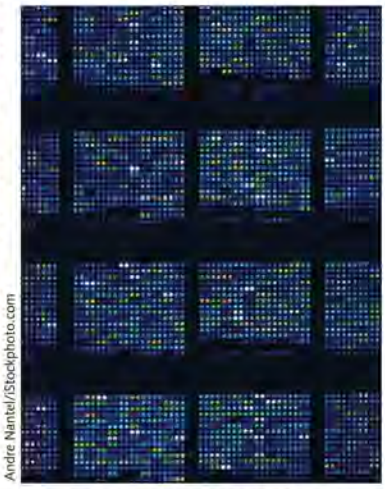
Unable to find an explanation, some physicians and hospitals simply turned Amanda and her parents away. But a referral to John I. Gallin, MD, at the National Institutes of Health's (NIH's) Clinical Center in Bethesda, Md, led to Young's condition being identified as a rare genetic disorder that leaves her unable to produce IRAK-4, a key protein of the innate immune system.

In an effort to speed the process of diagnosing rare diseases in patients like Young, the NIH launched the Undiagnosed Diseases Program in May, which researchers also hope will ultimately lead to a better understanding of many rare diseases or unusual manifestations of more common diseases (http://rarediseases.info.nih.gov/undiagnosed). The NIH's Clinical Center has the unique capacity to draw on an array of new tools, such as proteomic and genomic techniques, that are making the program possible, explained NIH Director Elias A. Zerhouni, MD.

DIAGNOSIS DIFFICULTIES

Physicians deal with about 6600 different conditions and 6000 of them are rare, Zerhouni said. It is difficult for clinicians to have the skill sets and experience necessary to quickly identify them all, as well as common diseases that present in an atypical fashion.

As result, many patients spend years seeking a diagnosis, going from specialist to specialist, looking for answers. The process can be financially and emotionally draining, said Mary Dunkle, vice president for communications at the National Organization for Rare Disorders (NORD). On average, it takes patients with rare diseases 5 to 7 years to get a diagnosis, said Dunkle, noting that calls from patients with undiagnosed diseases are among the most common to the organization.



Andre Nantel/iStockphoto.com

Scientists are using microarrays and other molecular tools to help patients who have rare disorders that have eluded diagnosis.

"People [with undiagnosed diseases] who contact us are overwhelmed and desperate and don't know where to go," she said.

But now clinicians can tap into the expertise at the NIH by referring such patients to the Undiagnosed Diseases Program. A panel of 25 NIH physicians from an array of specialties will review the cases and determine which patients should be assessed at the NIH Clinical Center. Those who are selected will undergo a week-long evaluation at the center, with their travel and treatment costs covered by the program, and any of dozens of specialists from the NIH may be called in to consult.

Some patients also will be invited to participate in studies at the NIH. After the consultation, patients will be referred back to their clinician for ongoing care.

The NIH Office of Rare Diseases is providing $280 000 per year in funding for the program. In addition to using existing staff and resources at the clinical center, the program will employ 2 nurse practitioners to oversee patient recruitment and other logistics.

RESEARCH OPPORTUNITIES

"Besides providing hope and information for the [patients with undiagnosed diseases], this program offers unique opportunities for discovery," said William A. Gahl, MD, PhD, clinical director at the National Human Genome Research Institute.

Gahl said that as the physicians in the program develop more experience with diagnosing these cases, they will try to develop a protocol to help other physicians' workup for patients with conditions that previously eluded diagnosis.

Not all patients who enter the program may ultimately be diagnosed, and even when a condition is identified, a useful treatment may not be available. For example, there is no treatment or cure for Young's condition. But she said she finds solace in knowing what is wrong, receiving support from the clinical center staff, and participating in research at the center that may one day help others.

"All we've ever wanted was for my disease to have a name, for someone to tell me what was wrong, and Dr Gallin did that for us," Young said. □

NEUROLOGY TODAY

July 8, 2008

NIH Launches Undiagnosed Diseases Program

BY ELIZABETH STUMP

A new clinical research program at the NIH aims to help neurologists and other physicians resolve longstanding, undiagnosed medical conditions.

The intramural Undiagnosed Diseases Program is a collaboration of efforts spearheaded by William A. Gahl, MD, PhD, clinical director at the NIH National Human Genome Research Institute (NHGRI); Stephen Groft, PharmD, director of the NIH Office of Rare Diseases (ORD); and John I. Gallin, MD, director of the NIH Clinical Center (the NIH hospital). Dr. Gahl will serve as the director of the Undiagnosed Diseases Program.

In a teleconference for reporters on May 19, NIH Director Elias A. Zerhouni, MD, noted that 6,000 of the approximately 6,600 conditions physicians deal with are rare. Generally, rare diseases have a prevalence of fewer than 200,000 affected people in the US. For these patients suffering from symptoms that do not correspond to known conditions, their care and treatment are extraordinarily difficult, so the new NIH program intends to alleviate the burden by offering its vast expertise, he said.

Only patients at least six months old with a longstanding, undiagnosed medical condition — despite ongoing care and follow-up by a physician — and who are capable of travel are eligible to be considered for the research study. They must be referred by their physician, nurse practitioner, or physician's assistant in their own community, who will be required to submit all medical records and test results to the NIH.

Participation in the program will be decided by a medical review board, chaired by Dr. Gahl, composed of approximately 25 NIH senior attending physician-scientists in a range of specialties like psychiatry, neurology, oncology, ophthalmology, endocrinology, oncology, pediatrics, dermatology, dentistry, and genetics.

One or two patients a week and up to 100 patients a year will be chosen for the program. Upon acceptance, patients will visit the NIH Clinical Center in Bethesda, MD, to enroll in a study and undergo a weeklong evaluation by a multidisciplinary clinical team, led by one of the senior attending medical board reviewers.

The findings and recommendations will be sent to the referring physician responsible for long-term follow-up care. And as for further research on a patient's rare condition, it will be "pursued if there is a good chance that new insights will be gained from the case," said Dr. Gahl.

The research study is now accepting applications, and the first patients are expected to be seen in July 2008.

For more information about the NIH Undiagnosed Diseases Program, visit: **http://rarediseases.info.nih.gov/Undiagnosed** or call the NIH Clinical Center at (866) 444-8806. ▪

Genome Technology
JULY/AUGUST 2008

July 2008

A Home for Medical Mysteries

Three divisions of NIH teamed up to form the new Undiagnosed Diseases Program. Its director talks about origins of the effort, patient demand, and how genomics will play a key role.

The National Institutes of Health recently launched the Undiagnosed Diseases Program, a clinical research initiative linking NHGRI, the Office of Rare Diseases, and the NIH Clinical Center. NHGRI's clinical director, William Gahl, will serve as director of the new unit. GT's Meredith Salisbury caught up with him to find out more about the program, which aims to serve annually as many as 100 patients with longstanding, undiagnosed illnesses. Demand will likely be much higher, though: Gahl reported that in the first two and a half days following the program announcement, NIH received 125 inquiries from patients looking to be included.

GENOME TECHNOLOGY: How did the idea for this program come about?

WILLIAM GAHL: The NIH has had individual investigators who study unknown diagnoses within their own area of interest for a long time. This differs because it's very generic — in other words, you don't have to have a specific area that's affected and then go to [a specialist.] In this case, you know you just have something that may have a lot of different symptoms. You don't know what doctor to go to, and we figure that out.

The Office of Rare Diseases receives all sorts of inquiries about this disease, that disease. The people who are inquiring are inquiring about where they can go to get a diagnosis. That prompted the Office of Rare Diseases to invest in this type of a program, and then we in the intramural portion of the NIH serve as the conduit for that venture.

GT: NHGRI's involvement in the program points to specific attention to genomic technologies being used in this. Why is that?

WG: We're able now to eliminate many, many diagnoses and sometimes to identify the causative agent because we're able to identify the genes. Technically we have a lot more ability, and especially over the last five, 10 years, many of the syndromes and disorders that have no known basis now have a molecular basis. When that happens you can look for mutations in the causative gene and then either rule it in or rule it out as the cause. So that's an enormous advance and gives us all sorts of weapons.

GT: Are there specific tools that will be used in trying to make these diagnoses?

WG: We'll use what's available in terms of mutation analysis and sequencing, and we might use some further advances that aren't broadly used in the genetics and medical community — sequencing of genes has become enormously faster and cheaper and we have access to that here. [The tools] will also be customized to a particular case.

WILLIAM GAHL

GT: With all the groups involved in the program, where exactly does it live within NIH?

WG: The support is from the Office of Rare Diseases, but it's being administratively conducted by NHGRI because we have access to the Clinical Center and the Office of Rare Diseases doesn't [divisions within the NIH's Office of the Director cannot use the clinic]. They need an arm with access to the Clinical Center, and NHGRI is that arm. The Clinical Center is making some contributions to this too — they're supplying office space for the nurse practitioners that we hired and clinic space.

The New York Sun

July 9, 2008

Search Is On for New Diseases — and Their Cures

By JAY AKASIE, Special to the Sun | June 9, 2008
http://www.nysun.com/health-fitness/search-is-on-for-new-diseases-and-their-cures/79563/

PATIENTS WHO HAVE HAD SCORES OF TESTS FOR UNEXPLAINED CONDITIONS THAT DOCTORS HAVE SO FAR BEEN unable to diagnose may yet have treatment options under a new National Institutes of Health initiative.

A director of the Undiagnosed Diseases Program, William Gahl, said he expects the NIH effort will be a way for physicians to discover new diseases — and then attempt to begin finding cures for them.

Recent advances in genetics — including biochemical genetics, or the study of "inborn errors of metabolism" — and the completion of the human genome map are allowing medical researchers to pinpoint many genetic defects and diseases that until recently were undetectable. This is why geneticists such Dr. Gahl will form the cornerstone of the NIH program announced last week.

Dr. Gahl has conducted research and treated patients at the Bethesda, Md., medical complex for 25 years. He has an office drawer filled with unexplained combinations of symptoms for which there are no known medical explanations. When asked to pull a random case file from the drawer, Dr. Gahl pointed to an instance of abnormally shaped blood platelets that doctors at the NIH had never before seen in a patient.

The idea behind the Undiagnosed Diseases Program is that, with blood platelets, for example, hematologists may have come across more than one instance of a similar condition. If the NIH program can detect examples of the condition in more than one member of a family, then patients can know, at the very least, that they have a genetic disease on their hands.

"But it's a new disease that you won't find anywhere in the genetic literature," Dr. Gahl said. "Sometimes a person will get, say, a muscular disease that he'll attribute to the environment, like living above a 'Love Canal' situation. In most cases, though, it's genetic."

The NIH plans to admit just 100 patients to the on-site program; children will account for about one-third of the enrollment. "We'll be very selective when it comes to patient eligibility. Our focus is strictly on conditions that haven't been diagnosed," he said.

The most significant reason for the stringent screening process is because the majority of people who think they are sick with an undiscovered disease simply haven't been diagnosed properly, according to Dr. Gahl. The NIH also expects that hypochondriacs — that is to say, physically healthy people who nonetheless worry excessively about being sick — will naturally apply to the program.

The New York Sun

"There will be a mixed bag of applicants," he said. "Some of them should have had more tests locally; it's only a matter of receiving the right test to discover the disease. And then others will actually have new diseases."

In addition to Dr. Gahl and his team of geneticists, there will be 25 specialists in the NIH program, including doctors specializing in endocrinology, immunology, oncology, dermatology, dentistry, and cardiology. They will all attend a regularly scheduled board meeting to consult with each other about the patients in the program. "We're taking advantage of intellectual synergies," Dr. Gahl said.

"This is an important project that will assist patients with undiagnosed disorders that run in families," the chairman of the Department of Genetic and Genomic Sciences at the Mount Sinai School of Medicine, Dr. Robert Desnick, said. "If the genetic defect is identified, then it may be possible to develop therapies using a variety of new techniques."

The NIH program could also be a boon for pharmaceutical companies developing new drugs, according to Brad Kloza, a director of ScienCentral, a Manhattan-based firm covering scientific research for local broadcast news affiliates.

"New diseases can't be a bad thing for pharmaceutical companies. But the specifics of what's discovered will determine whether or not it's a particularly good thing," he said.

Mr. Kloza said big pharmaceutical companies don't often invest a lot of money looking into cures for rare diseases because the payoff can be too low. "You would tend to assume that undiscovered diseases are rare ones," he said.

On the other hand, pharmaceutical companies are good at finding new markets for existing drugs, and those new markets often come from the discovery of new, rare diseases, Mr. Kloza said.

Oct 22, 2008

Fox 5 Helps Girl With Mystery Illness

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MyFoxNY.com -- The nation's top researchers took on the case of a little girl with a mysterious illness. Fox 5's Dr. Sapna Parikh reports.

The nation's top researchers took on the case of a little girl with a mysterious illness.

Abbreviated broadcast news transcript: [Anchor:] We are very happy to tell you about the -- a little girl getting help with an illness. [Correspondent:]The parents were desperate to figure out what was going on with their daughter. Exhausted after two days of intense medical testing and over two years of searching for an answer for their little girl. This was a happy baby until she was 10 months old, then she never learned to walk or talk and doctors around the country cannot explain why. It is a different kind of moving disorder. She is now part of a brand new program at the National Institutes of Health. The goal is to solve these serious cases. The patient comes here for about a week and is of value weighted by over 25 different specialists. This is the Undiagnosed Diseases Program. The treatment is free. Doctor William Gahl is the program director and he says they have to be highly selective and will accept no more than 100 patients a year. [Dr. Gahl:] What we think we can offer is a different perspective and also we have state of the art a genetic analysis. [Correspondent:] From morning until evening she goes from specialist to specialist all in an effort to solve her case. [Dr. Hallett:] She is moving her body around like that. [Mom and Dad:] It is a busy day. We are doing everything we can do to help her. The doctors want to help and also learned from every single patient. The information will go to advance health care for all of us. As much as we want to help, someone else can get help. [Correspondent:] For now, the testing continues but there is no promise of a diagnosis. [Dr. Gahl:] The issue with the little girl is whether or not she has an infectious problem that caused her to have a deficit within her brain or whether she has a genetic problem. [Correspondent to the parents:] How do you do it? [Mom:] We get that question sometimes. Do I have a choice? [Dad:] You have to do what you have to do to get your child through. I love her so much. I will not give up on her. [Anchor:] lot of work being done to help children like this.

Alex Witchel: Rupert Everett, Out and About Jon Mooallem: The Great Whooping-Crane Con

The New York Times Magazine

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The Medical Detectives

Some patients have spent their lives suffering from mysterious diseases that no one can conclusively diagnose. A team of N.I.H. researchers is working against time to find answers where other doctors are not equipped to go. BY ROBIN MARANTZ HENIG

Home Pharmacy The view from Summer Stiers's apartment in Bend, Ore. Photograph by Katherine Wolkoff for The New York Times.

QUOTED. NOTED.

"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. This is an absolutely great case."

Dr. William Gahl, in "What's Wrong With Summer Stiers?"
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COVER STORY 2.22.09

On the cover: Summer Stiers receiving a hyperbaric treatment at Bend Memorial Clinic in Oregon. Photograph by Katherine Wolkoff for The New York Times.

Over two decades,
she has suffered retinal bleeding,
seizures, bone death
and kidney failure.
But no one
knows what's really wrong.
Now a team of medical
experts at the National Institutes of
Health is trying a new
way to diagnose what ails her —
and others who are suffering
from mysterious diseases.

What's Wrong With Summer Stiers?

BY ROBIN MARANTZ HENIG

Photographs by Katherine Wolkoff

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 — 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. Organizationally, it creates a kind of superdiagnostician, whose orientation would be to look at not 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 com-

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Dr. William Gahl, director of the Undiagnosed Diseases Program at the N.I.H.

mon, 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

PHOTOGRAPH BY KATHERINE WOLKOFF FOR THE NEW YORK TIMES

A geneticist described what can happen in lab 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 and abnormal nails.

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.

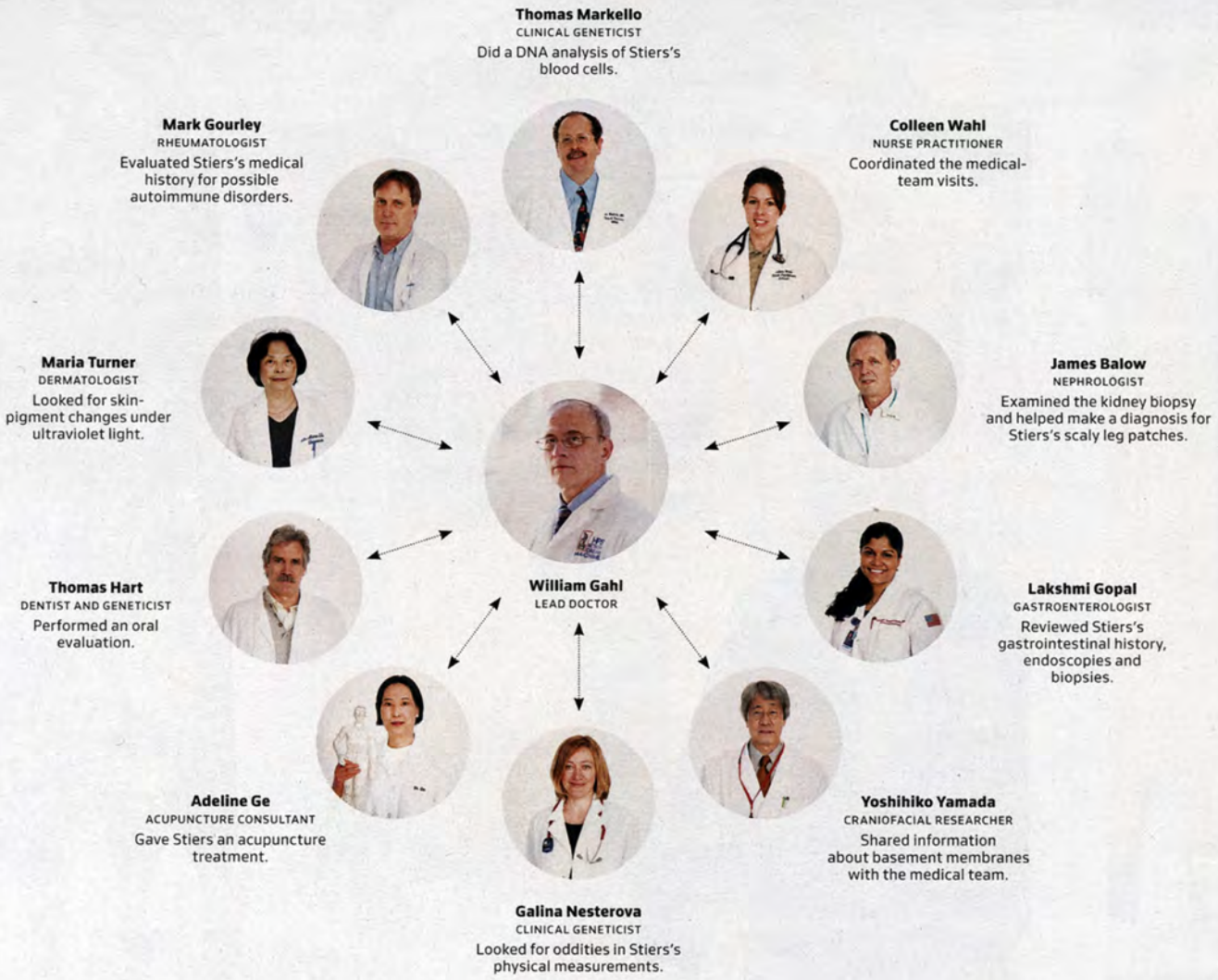
Young physicians are often taught some variation of the catch phrase "When you hear hoofbeats in Central Park, don't expect zebras." In other words, focus on the most likely explanation for everything you observe. But for Undiagnosed Diseases Program patients for whom answers are so singularly elusive, 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.



Team Summer

Some of the doctors and clinicians who worked on the case of Summer Stiers in the Undiagnosed Diseases Program of the National Institutes of Health in Bethesda, Md. In a time of specialization, the N.I.H. program attempts to reconstruct an old-school generalist on a multiperson level.

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

PHOTOGRAPHS BY KATHERINE WOLKOFF FOR THE NEW YORK TIMES

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,

Stiers, back in Bend, Ore. "I'm a good little follower," she says. "I do what I'm told." But her body is nonetheless in a "cascading collapse."

? Stiers 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.'

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.

"Not in the human," Yamada said with an apologetic smile. "Only in the mouse."

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 *Continued on Page 42*

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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.

Gahl 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.

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 medicalese, 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, 2½-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. ■

CNNhealth.com

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Vital Signs with Dr. Sanjay Gupta

Solving Medical Mysteries

May 28, 2009
http://www.cnn.com/video/#/video/international/2009/05/28/vital.signs.mysteries.bk.a.cnn?iref=videosearch

By definition, they are rare. Mystery diseases, often misdiagnosed or misunderstood. The chances of getting one is small. But add up all the conditions and the number of people affected, it's larger than you might think. By some estimates, hundreds of millions of people worldwide.

Virtually every family in the country will know someone who has one of these rare diseases. From a one of a kind program outside Washington, D.C., to doctors taking on a forgotten killer in the remote reaches of bolivia, solving medical mysteries in this edition of "vital signs."

Hello and welcome to "Vital Signs," a global look at health that knows no boundaries. I'm Dr. Sanjay Gupta, CNN's chief medical correspondent and a practicing neurosurgeon. The medical world is based on specialization. If you have a heart problem, visit a cardiologist. Skin problem, go see a dermatologist. Eyes, ophthalmologist. You get the picture. But what if you have a condition that doesn't fit neatly into any of these disciplines, one symptom seemingly unrelated to the next? The **Undiagnosed Diseases Program** at the **National Institutes of Health** doesn't promise any new tests or any piece of new technology, but it does promise a new approach.

They'd rather not talk about their illness. >> and this one was outside the lincoln memorial. >> They'd rather show you pictures from a day of sightseeing in Washington, D.C., and if you didn't know this was a hospital room, you might think they were like any other pair of vacationing sisters. But it was the illness that brought Paula and Louise here to the **National Institutes of Health**. >> That's where it started was in the calves of the legs. >> For decades, the sisters have dealt with extreme pain in their legs. Without knowing why. >> They won't do surgery. It's too dangerous. They can't do that. too far gone. >> So we're going to be down in radiology.

Doctors in Kentucky gave the two little hope When it came to diagnosing their mysterious condition, even less hope when it came to finding a cure. >> They just really don't know what's going to happen. >> Without options at home, Paula and Louise turned to the NIH and to Dr. William Gaul. >> Ladies, hello. >> Good morning. >> I understand you had a visit with some of our sights downtown. >> Yes. It's good. >> did you have trouble walking there? did your feet hurt you? >> oh, yes. >> a lot? >> a lot. >> okay. >> The sisters are exactly the sort of patients Gaul had had in mind when he started the Institute's **Undiagnosed Diseases Program** last year. > > >

August 27, 2009

LAST CHANCE CLINIC

Some diseases defy diagnosis. **Brendan Maher** meets two people who hope that the US National Institutes of Health can help.

Dunham Aurelius is eager to take his shirt off and show his scars. One, a centimetre wide and roughly 20 long runs up his lower back and is from the placement of a steel rod to straighten his spine at the age of 14. Two others, looking like bullet wounds, are above his left buttock. But it's not his scars, nor his barrel-chested physique that have earned him the nickname 'ultimate fighting champion'. His urologist bestowed that title because of the fact that since the age of 22, Aurelius has passed a dozen and a half kidney stones — many, he's proud to say, without assistance. Aurelius is 39, a sculptor and a former triathlete with curly blond locks and a surfer's drawl. His wife, Michelle Barry Aurelius, jokes that he's like a human oyster. But the stones he grows are no smoothened pearls. At the cinema in 2008, Aurelius stepped out to use the bathroom. When he returned, he handed her the four-millimetre wide 'barnacle' of calcium phosphate his body had just expelled. She had noticed he was quiet that evening.

On a February morning this year, Aurelius and Barry are waiting in a hospital room in the sprawling Clinical Center on the campus of the US National Institutes of Health (NIH) in Bethesda, Maryland. They have travelled here from their home in Santa Fe, New Mexico, so that a small team of clinicians and research scientists can try to diagnose the mysterious disease that has dealt Aurelius more urological pain than most should have to bear. When William Gahl, the team's lead investigator and clinical director at the NIH's National Human Genome Research Institute (NHGRI) enters Aurelius' room at 9:50 a.m., he has a gaggle of clinical-genetics fellows in tow. He rattles through an introduction to Aurelius, and then stops himself. "Why don't you tell us," Gahl says, picking his words carefully, "why are you different from the average person?"

"There's nothing so complicated for a patient as not being able to put a name to their disease."
— Carl May

Elsewhere in the Clinical Center, another far-from-average person is awaiting time with Gahl. Sally Massagee, a 54-year-old certified public accountant from Hendersonville, North Carolina, is watching a neuromuscular specialist remove three deep-red slivers of muscle from her bicep. Although she was nervous going into the biopsy, Massagee jokes that she can spare the tissue. A little more than a decade ago, she started putting on weight. By the spring of 2007 she had gained nearly five kilograms on a compact 1.68-metre frame — all of it muscle. People around her thought she was training for competitive bodybuilding, but pain stopped her doing any exercise but tennis. Eventually she outgrew her clothes.

Massagee and Aurelius have few, if any, symptoms in common. What they do both have is a spot in the NIH's Undiagnosed Diseases Program, an effort to identify and characterize previously unknown diseases by drawing on the institution's 6,000 clinical and biomedical experts and the medical technologies at their fingertips. Gahl, a medical geneticist specializing in metabolic disorders, started the programme in May 2008 with $280,000 in pilot funding from the NIH's Office of Rare Diseases. It received $1.9 million more in its first year, and has been approved as a fully fledged NIH programme at $3.5 million per year for the next five. Patients such as Aurelius and Massagee (pictured above) hope that this financial and academic wealth can finally provide the diagnosis that has eluded all the other specialists they have consulted over the years. "There's nothing so complicated for a patient as not being able to put a name to their disease," says Carl May, a professor of medical sociology at Newcastle University, UK, who has studied doctor–patient relationships in chronic disease. "If we can't put a name to it, it's hard for others to see or understand, and most importantly to believe, that something is legitimate or warranted."

M. BARRY AURELIUS; NIH; S. R. MASSAGEE

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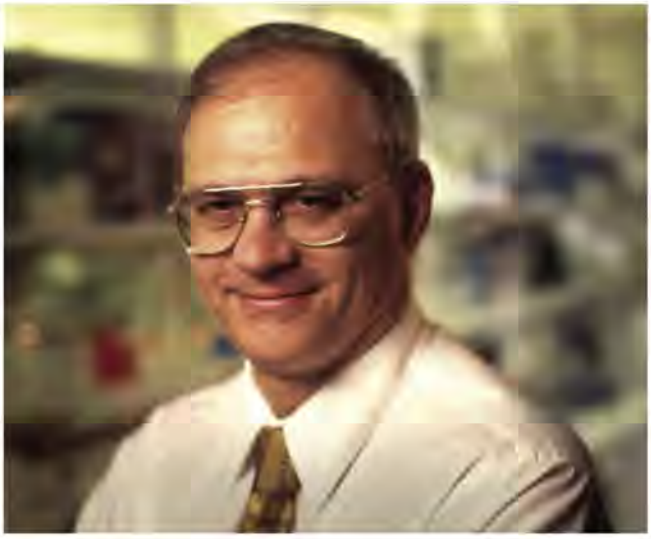

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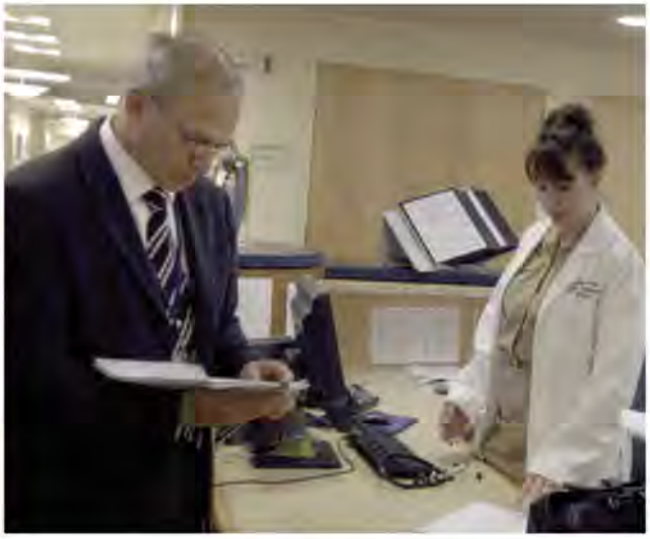


L. SPILLERS

Team leader William Gahl and nurse practitioner Colleen Wahl work on finding new diagnoses.

The researchers want a diagnosis, too — but their motives are somewhat different. For them, Aurelius, Massagee and the other individuals are also a research opportunity, the chance to discover a new disease and potentially one that can be characterized at a genetic level. This could provide a new foothold in understanding human biology and perhaps the origins of other, more common diseases. Such diagnoses can result in high-profile publications and spur the development of new fields. As Clemens Bergwitz at the Massachusetts General Hospital in Cambridge puts it, the programme allows scientists to "make use of the human mutation pool".

That approach is not new: throughout much of medical history clinicians with just the right background have stumbled on just the right patients to come up with a new diagnosis. Gahl says that one way of thinking about the Undiagnosed Diseases Program "is to reduce that need for serendipity" by setting out to find the unusual cases and throw at them everything research has to offer, including individualized sequencing of candidate genes and a genome-wide scan of genetic variations. "The sort of modern twist to this classic approach is the molecular-biology techniques available," says NIH endocrinologist Michael Collins, who has been working on Aurelius's case.

Aurelius and Massagee spotlight the relationship between subject and scientist at its most focused, modern and expensive. The question is: what, if anything, will each side gain?

Stony symptoms

Aurelius reclines in a hospital bed while Gahl runs through his medical history. The stones are generally calcium phosphate. The largest two-to-three-centimetre stone was removed by surgery, which resulted in a perforated colon and left Aurelius with the bullet-hole scars in his back. He has regular gastrointestinal discomfort, and Aurelius says that he has very high calcium and vitamin D levels in his blood. Gahl asks how calcium in food affects him. "I avoid it in most cases. It makes me feel distended. If I had a bowl of ice cream I'd be miserable."

"Ever take a vitamin D pill?" Gahl asks.

"No, but we could try it!" says Aurelius. Like others involved in the programme, Aurelius is happy to be a part of it even though he knows the chances of a diagnosis, let alone a treatment, are low. It means he hasn't been given up on. "Most doctors would throw their hands up," Aurelius says, describing his quest over the years. Gahl, no enemy to truth in levity, replies: "We may too, but we'll do it behind closed doors, after you're gone."

After Aurelius is sent off for a bone-density scan and an ultrasound on his kidneys, the closed-door discussion begins. Gahl meets with a group of experts working on the case: Collins, nurse practitioner Colleen Wahl, pathologist Panagiota Andreopoulou, and attending genetics fellow Galina Nesterova. The meeting moves quickly as they bandy about the names of genes that might be responsible for Aurelius's unusual blood test results.

At first the talk centres on a protein called fibroblast growth factor 23 (FGF23), which lowers phosphorus absorption and, through a series of regulatory loops, helps to cap the production of active vitamin D. Too much vitamin D can result in high calcium levels in the blood and urine — hypercalciuria — which leads to kidney stones. Nesterova, who worked as a nephrologist in Russia before coming to the United States, has another idea. She suggests looking at two genes, *CYP27B1* and *CYP24A1*, that activate and deactivate vitamin D, respectively. Her hunch is based in part on some ongoing work with two sisters with elevated vitamin D levels and highly calcified kidneys, who she also suspects of having mutations in these or related genes.

Collins is sceptical, not wanting to close the door on alternative explanations. Aurelius has low blood phosphorus levels, and Collins wonders whether the underlying problem could lie in the kidneys: if they are excreting too much phosphorus, this would feed back to the body, instructing it to manufacture more active vitamin D. He posits a mutation in one of the genes for a sodium/phosphate transporter, called *SLC34A3*, in the kidney tubule wall that may be causing Aurelius to dump out phosphorous.

"It's neat that in-house, we've got Mike," says Gahl later, referring to Collins. "He knows 100 times as much about this as me." Collins was first introduced to Aurelius's case through a monthly meeting for the Undiagnosed Diseases Program in which upwards of 50 basic- and clinical-research scientists sit and listen to presentations on potential patients to decide who should be invited into the programme. During the screening process they try to pull out diseases with simple genetic roots, ones probably caused by a single mutated gene, or a deletion or duplication of a large chunk of DNA. Maybe there is a mention of a family history in a chart, or signs that the symptoms are related to an organ system in a way that suggests a single unifying cause. Complex disorders

NIH

with roots in multiple genes have to take a back seat, says Gahl: "This is triage, and triage means you go after what you can do." Since its inception, the programme has received more than 2,100 inquiries from doctors around the world, reviewed more than 900 full applications and, so far, seen little more than half of the 160 patients that, like Massagee and Aurelius, have been invited to come for an intensive week of tests and consultations.

As Nesterova and Collins spar collegially, Gahl finds a possible way to settle the debate. "Let's get the FGF23 back and have a plan then," he says, referring to a test already requested that will measure the amount of the hormone in Aurelius's blood. A high concentration might change the types of genes that they would test, probably striking *SLC34A3* from the list.

Less than an hour after talking vitamin D metabolism, Gahl is discussing muscle physiology and genetic tests he hopes to run on Massagee's blood. Like Aurelius, Massagee has already been through three and a half days of testing and has just a few more appointments to go. One of these is a wrap-up interview with Gahl and a different team of specialists, including Justin Kwan, the doctor who did the muscle biopsy, and clinician Irini Manoli from the NHGRI.

Accompanied by her husband, Massagee is dressed in velour tracksuit pants and an oversized man's dress shirt. She looks fatigued, but alert, her brown eyes peeking out over her puffy, muscle-tightened cheeks. When in 2008 doctors at Duke University Medical Center in Durham, North Carolina, did a magnetic resonance imaging test to try to diagnose her condition, they were shocked to see that even the orbital muscles that control her eye movements seemed to have doubled in size. Massagee says that when she had been exercising, the muscles had tone, and she believes many of the specialists she saw suspected she was taking steroids. Now the muscles are rock-hard, painful and toneless, weighing her down and leaving her exhausted.

Massagee's case has also drawn in experts from across the NIH, including Alexandra McPherron of the National Institute of Diabetes and Digestive and Kidney Diseases. For her PhD thesis, McPherron characterized a protein that doubled the skeletal muscle of mice when it was mutated (A. C. McPherron, A. M. Lawler and S.-J. Lee *Nature* **387,** 83–90; 1997) and she's worked on it ever since. Later named myostatin, the protein was found to be the molecular culprit behind heavily muscled cattle, sheep, dogs and in one reported case of a human — a baby boy born in Germany with massive muscles in his thighs and upper arms (M. Schuelke *et al. N. Engl. J. Med.* **350,** 2682–2688; 2004). So, when a muscle-laden woman was accepted to the Undiagnosed Diseases Program, myostatin — and McPherron — were on Gahl's mind. He sent over photos of Massagee and eventually went to visit McPherron in her office. "I've never met a patient before," McPherron says. But she agreed to get involved with this one.

Experts gather for monthly meetings at the NIH Clinical Center (left) to discuss which patients to admit.

NIH

"The physician in me is interested in helping people. The scientific part of us goes after the new disease areas."
— William Gahl

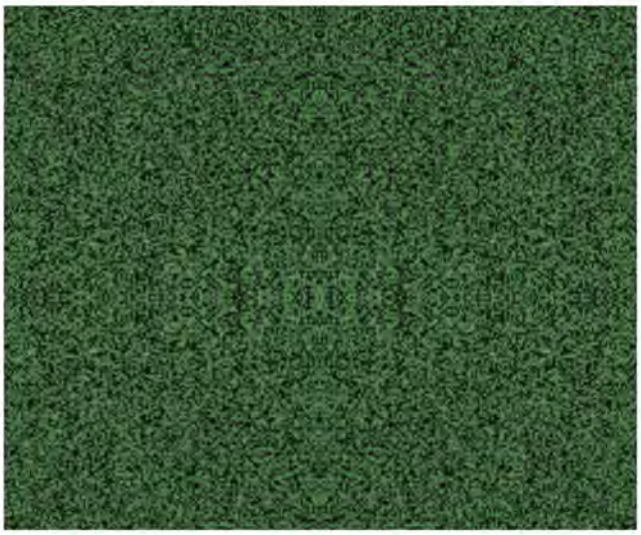
A question of need

Humans present experimental challenges that McPherron's mice do not. "The big question," she says, "was, do I want a muscle biopsy?" McPherron would need some tissue to do a thorough analysis of Massagee's myostatin expression levels. She knew the discomfort involved, but the only material already available was old and not prepared in a way that would allow protein extraction and RNA analysis. "I was hemming and hawing," she says, but when the rest of the team decided to go for it anyway, she decided she should be there to see Massagee and to carry the tissue back to the lab herself. The main results Gahl's team wanted would be coming from the biopsy tissue, both from McPherron's lab and from the laboratory at the Armed Forces Institute of Pathology (AFIP) in Washington DC that would be doing a full histopathological work-up.

There are other tests to run. Gahl explains to Massagee the purpose of a 'million SNP array', an assay that is used commonly in research genetics but rarely in clinical diagnostics. The array looks for single nucleotide polymorphisms (SNPs), spots in the genome that differ between individuals with relatively well known frequency. The SNPs serve as landmarks and if one that is expected to neighbour another is missing or doubled up, it can show where DNA has been deleted or duplicated, perhaps pointing to the genetic root of a disease. Gahl's team does an assay for everyone who enters the Undiagnosed Diseases Program, and often for their family members too.

Gahl appears to take a certain pleasure in explaining the method, but he seems to lose Massagee while trying to explain such concepts as 'loss of heterozygosity'. Still, he is patient with her, mirroring her wonder over how some tests work and assuring her that it is pointless for the time being to worry about what the results might mean for her children. "We're operating on best guesses and a lot of ignorance," he says.

M. BARRY AURELIUS



T.C. MARKELLO

The DNA of sculptor Dunham Aurelius was analysed with a 'million SNP' array.

But of course the patients do worry. Just days before Aurelius and his wife arrived in Bethesda, they found out that she was pregnant. Although extremely early in the pregnancy, they told the doctors in case there was anything they should know. The results of genetic tests take on greater significance when another generation could inherit the result. Aurelius explained the frustration of not knowing what to expect from his body or for his children. "Everything's good with me, but I have this alien disease. I keep wondering what's going to happen."

At the end of a week of tests, Massagee and Aurelius are discharged and return to their homes to await their results. "It's going to be nice to be able to walk out of here, if not with a diagnosis, with at least the next step," says Aurelius. Massagee effuses gratitude and says how wonderful everyone at the NIH has been.

"At its best it is a wonderful place," Gahl says, adding dryly, "at its worst it's a government organization."

Over the next few months, work starts on the data from Massagee and Aurelius. The test for the FGF23 levels in Aurelius's blood comes back normal. Nesterova had already begun to sequence *CYP27B1* and *CYP24A1*, and in May she finds that one copy of Aurelius's *CYP24A1* is missing three base pairs. This 'microdeletion' is not currently listed in any databases of known human variation, suggesting that it may be a novel change. It could be disabling or at least limiting Aurelius's ability to deactivate vitamin D, explaining his high levels of the vitamin. Then again, it could be harmless. "It's hard to put the weight of significance on these findings, for now," Nesterova says.

Collins still favours his hypothesis about the sodium/phosphate transporter, and at his urging Aurelius consents to send DNA samples to a programme, run by Bergwitz, that is sequencing genes that code for various versions of the transporter. Others with mutations in these genes have low phosphate levels and bone disorders such as rickets. "Our interest is to find more mutations," Bergwitz says, ones that create different symptoms. These could reveal what parts of the genes and their corresponding protein actually do, be it ion-pumping mechanics or insertion into cell membranes.

The million-SNP arrays come back with reams of data. Thomas Markello, who runs the studies for the programme, says that they spit out many hits but little in the way of answers. Raw data suggest that each person has between 3 and 10 positions in the genome in which both copies of a given genetic region are deleted, plus 50–200 instances each of single-copy gene deletions and duplications, any of which — or none of which — could be involved. "This is not what most physicians are used to seeing," Markello says. So far, the SNP arrays have helped with just one diagnosis. But this is a research programme, and part of the research is to determine how useful these techniques can be. Moreover, the data and samples, stored at the NHGRI, may still prove informative for future studies. Markello calls the programme "training wheels" for using whole-genome sequencing in the clinic, in which the number of genetic differences found in a given individual will go up many orders of magnitude but their clinical significance will be even harder to tease out. In the near future, he says, those in the programme will have their entire genome sequenced.

"It's going to be nice to be able to walk out of here, if not with a diagnosis, with at least the next step." — Dunham Aurelius

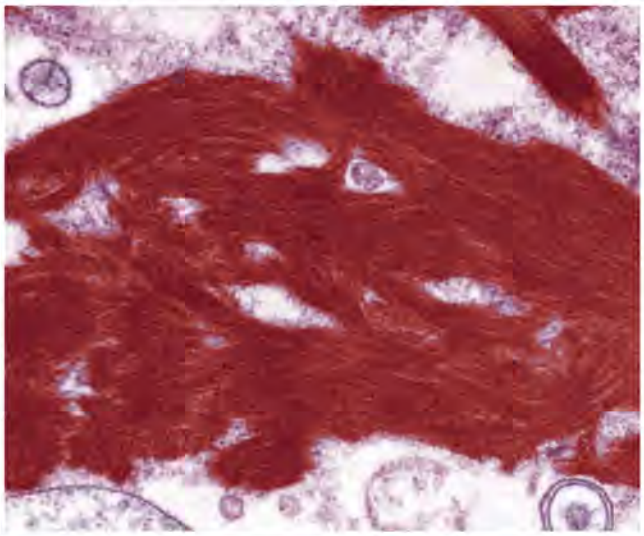
Hints of progress

On 8 April, Massagee e-mailed Manoli, her main contact point at the programme. Massagee was more fatigued than ever, having to stop what she was doing every 20 minutes and take a break. Work was becoming difficult, and she couldn't walk more than a block without losing her breath. Manoli called her back that day to ask if she could come back to Bethesda for more testing. Although the full report from the AFIP had not yet come back, the pathologists had found hints that proteins were building up in the walls of the blood vessels that feed Massagee's muscles.

On her second visit to the NIH, Massagee got her diagnosis. She had amyloid light-chain, or AL, amyloidosis, a rare disorder that is tied to the bone marrow's abnormal production of immune cells that make immunoglobulin proteins. Excess immunoglobulin accumulates into the proteinaceous build-ups that were lining some of her blood vessels.

Around 1,200 to 3,200 cases of AL amyloidosis are reported each year in the United States. Amyloid can build up in pretty much any tissue or organ, but Massagee's presentation in skeletal muscle is especially rare. The researchers do not know why the immunoglobulin caused her muscles to bulk up. But happily for Massagee, her heart muscles seemed to be unaffected and there was no serious damage to her kidneys, which can lead to death. Manoli contacted Morie Gertz, who studies the disease at the Mayo Clinic in Rochester, Minnesota, and pushed for a swift appointment. Gertz's team saw Massagee the following week to determine whether she would be a good candidate for a clinical trial

S. R. MASSAGEE



S. GSCHMEISSNER/SPL

Sally Massagee and her husband found out she had a type of amyloidosis, which causes protein build-up in tissues.

to treat the disease with chemotherapy and autologous bone-marrow transplantation.

She was. On 19 June, Massagee underwent the bone-marrow transplantation procedure. Afterwards she developed a condition called peri-engraftment syndrome, a poorly understood complication of autologous transplants that made her very sick. But now she says she's feeling stronger every day. Her doctors are uncertain whether treatment of the haematological condition will reverse the build up of muscle. But Massagee says that her muscles feel softer to the touch already, and that she considers the NIH programme to have saved her life.

Gahl's team was also pleased to get a diagnosis, even if it was one that is not new to medicine. None of their hunches about the involvement of myostatin came true. But McPherron is keeping Massagee's muscle sample in the freezer. She hopes to use it to investigate how the accumulation of immunoglobulin led to such an overgrowth of muscle. One idea is that the build up, or an inflammatory response to it, activated the satellite stem cells that normally divide to create new muscle tissue. But anything McPherron could do with it would be extremely preliminary.

"Our time will come with respect to new diseases," says Gahl. "We're very pleased to find different presentations of known disease, and I wouldn't discount the learning process." The team has made other such diagnoses. Gahl says that they have recognized a handful of cases of multiple sclerosis for patients enrolled in the programme and they were able to diagnose an atypical case of lymphoma simply from a chart review. But these are the happy endings. There are still upwards of 50 open cases in Gahl's files. May, the sociologist at Newcastle University, says that the doctors involved in the Undiagnosed Diseases Program are unusual in this sense because they know that the vast majority of their cases will never be solved. "There is a conflict there between having someone who is an interesting case and somebody who is going to be evidence of one's failure."

Gahl brings up one other statistic, and it's clear that it weighs heavily on him. Twelve of the patients who applied to the programme have died so far. One of these, a young woman called Summer Stiers, had serious symptoms affecting many of her organ systems and was the subject of several news stories earlier this year. The tests that Gahl's team ran when she was at the NIH generated few concrete leads. Stiers decided, with her local doctors' acquiescence, to discontinue the regular dialysis and other treatments that had been keeping her alive. She died within three days. Stiers had called Gahl a few days before this, in part to make final arrangements for her body to be shipped to the NIH for further study. Even at the end of her quest for a diagnosis, she wanted to help.

Aurelius, in Santa Fe, is still anxiously awaiting news. Nesterova contacted him in July to tell him that she wished to publish an abstract about the *CYP24A1* microdeletion for a meeting on metabolic disorders in San Diego, California, this month. She suspects that it is responsible for his symptoms; if it is, it could mean the identification of an entirely new genetic disease. Although excited by this possibility, Nesterova is reluctant to become too confident until she can do more follow-up work to show definitively that the mutation affects the function or levels of the protein it encodes. Her colleagues have been sequencing the gene in 100 healthy controls to see whether the deletion is simply a harmless variant. "She's cautious and thorough," Aurelius says.

Despite being happy that someone is still working on his case, Aurelius says the pace still feels slow. "At the end of the day what I want to stop is the kidney stones because I don't want to have renal failure," he says. Another stone is currently growing in his left kidney. Aurelius and his wife are preparing for the birth of their child in late October, and he continues with his sculptures — large, craggy, organic-looking pieces in bronze and wood that unmistakably evoke the calcium phosphate stones that have caused him so much pain. He is even planning a show for the Clinical Center starting in November. He's promised that a portion of the proceeds from any sales will go to a patients' fund at the NIH. "It's rare in life when you feel like someone gives so much to you — taking me out there for a week, getting all these doctors together. It's important to give back to that."

And Gahl, like the other doctors in the programme, continues to wrestle with his dual motivations for it. "The physician in me is interested in helping people," he says. "The scientific part of us goes after the new disease areas. That's very stimulating — to be the first to discover something. I think all of us feel that way". Even if they don't find either diagnosis or new disease, the Undiagnosed Diseases Program offers at least an extension of hope for those who enter it.

"I'm astounded at how appreciative they are of our failed efforts," says Gahl. ■

Brendan Maher is *Nature*'s biology features editor.

(Episode #613)

Imagine having a condition that cannot be diagnosed for months or years. How do doctors find the answer to an elusive disease, and what role does the patient play in finding the cause?

This episode takes the expert diagnosticians through a case of a patient whose diagnosis is far from clear. See first hand how doctors work together, and with the patient, to find the cause of the symptoms, and an appropriate treatment.

Read full Art of Diagnosis episode **transcript**.

Conduct an off-site search for Art of Diagnosis from MedlinePlus. These up-to-date search results are based on search terms specific to *Second Opinion* Key Points.

- **Talking With Your Doctor** main page – all aspects. Includes overviews, latest news, related issues, tutorials and videos, dictionaries and glossaries, and guides related to children, teenagers, and seniors, etc.
- **Rare Diseases** main page – all aspects. Includes treatment, related issues, dictionaries and glossaries, organizations, etc.
- **Laboratory Tests** main page – all aspects. Includes overviews, latest news, related issues, dictionaries and glossaries, and guides related to children, teenagers, women, and seniors, etc.
- **Diagnostic Imaging** main page – all aspects. Includes overviews, latest news, related issues, dictionaries and glossaries, etc.

PBS

Second Opinion Art of Diagnosis

Partial Transcript

(Peter)
I want to sum up what we've been discussing. The end point of any elusive diagnosis may not necessarily be finding a name for it, but perhaps finding an effective treatment is a good thing. Six years have gone by since her initial visit with her PCP and she's got a diagnosis. She's had a muscle biopsy, I can tell you that much, and that's where they made the diagnosis. Anybody want to make the diagnosis here?

(William)
I would guess she might have ragged red fiber based on her muscle biopsy.

(Lisa)
Or muscular dystrophy.

(Bilal)
Yes, that's what I would say.

(Peter)
Holy smokes! How about I read you want the muscle biopsy showed? Somebody gets a gold star. She has ragged red fibers. Additional testing showed the muscle ((cox)) activity was only 30 percent of normal and her mother, who was presumed to have had ALS, was now presumed to have mitochondrial myopathy.

(William)
So that really points out –

(Peter)
By the way, before you even say anymore, great work. This is what docs live for – making diagnoses.

(William)
Well, we sometimes are successful but particularly this is my area. What this points out is there are experts in different areas, and what the world of medicine needs are people who are experts in certain rare diseases. This is one of those examples.

TODAY MSNBC

Jan 14, 2010

Doctors puzzle over woman's mystery ailment

After eight years, they still don't know what's wrong with Kelly Klodzinski

By Michael Inbar
TODAYshow.com contributor
updated 10:09 a.m. ET, Thurs., Jan. 14, 2010

For eight years, Kelly Klodzinski has lived through a medical hell. Her jaw clenches so tightly that she can't eat a peanut butter sandwich; she has an inflamed heart that often makes it difficult to breathe, much less walk; and she spends so much time in hospital beds that she's on a first-name basis with staff at seven or eight clinics.

Thankfully, though, Klodzinski is now part of a groundbreaking **new** program: At a clinic in Bethesda, Md., she is examined by some of the leading minds in medicine, who aren't rushed because they only see three or four patients a week. And the charge to Klodzinski for such acute care? Not one red cent.

TODAY

Baffling ailments go undiagnosed
Jan. 14: NBC's chief medical editor Dr. Nancy Snyderman reports on a new program from the National Institutes of Health that aims to solve what some patients call medical mysteries. Today show

There is a catch, however: Patients like Kelly have to be sick, really sick, to be admitted. And what's more, those patients have already had to suffer through years of medical maladies that don't even have a name.

That's the mission of the Undiagnosed Diseases Program, created by the National Institutes of Health in May 2008. And even though it sounds a bit like the medical-mystery TV show "House," the doctors caution their work can't be tied into a neat bow in the space of a one-hour episode.

Mysterious symptoms

Still, for Klodzinski, being treated at the UDP clinic is the first light of hope she's seen after eight years of medical darkness. The young Louisiana wife — focus of the first of a two-part series examining medical mysteries on TODAY — has seen her body steadily break down in many ways, with doctors unable even to give her a diagnosis, much less cure her.

Appearing live on TODAY Thursday, Klodzinski told Matt Lauer she feels like a medical orphan: Concerned friends don't understand that she suffers from maladies that have no name.

"It's very, very frustrating," she told Lauer. "People ask me every day, 'What's wrong with you, what do you have?' And I don't have an answer; I just tell them it's undiagnosed. And they will say, 'Well, what do they call it?' And I say, 'I don't know, they've don't have anything TO call it.'"

Klodzinski's health began deteriorating at age 15, when a small sore in her mouth grew so large it made it impossible to open her jaw more than a fraction of an inch. It was followed by serious but seemingly unrelated health issues: inflammation in her heart that left her struggling to walk, nodules forming on her lungs and an enlargement of her right kidney.

She's been in and out of hospitals ever since, and she sometimes has as many as four doctor's appointments in a week. She's been looked at by pulmonologists, cardiologists, hematologists and oncologists. Klodzinski has undergone multiple surgeries, one of which she barely survived. But all the while, well-trained doctors have been unable to pinpoint the root cause of her health dilemma.

Now, with treatment at the UDP clinic, Klodzinski told TODAY she can finally see some progress in turning her health crisis around, even if she's been down the road with doctors too many times to be totally confident.

TODAY

A growth on Kelly Klodzinski's jaw was the first of a series of apparently unrelated symptoms to plague her.

"It would be a pretty big deal to get a diagnosis after eight years," she said. "I would be in shock if [they] told me, 'This is what you have.' If I could just get some treatment options, how to keep it under control, how to keep it from flaring up again, that would be great."

Not like 'House'

The novel program undertaken by NIH can be called forward-thinking; just don't call it "House" in the presence of Dr. William A. Gahl, one of its founders. "That's entertainment — we're not here for entertainment in any respect," Gahl told TODAY. "That program essentially solves that problem, that story, within an hour. The whole premise is completely unrealistic and completely off track, and it's intended to be drama. I think also, someone who has Dr. House's personality characteristics would never be permitted to handle patients or would have his license taken away."

Klodzinski told TODAY she knows she's in better hands with the experts at the UDP clinic, and counts herself lucky she was accepted into the program. Since opening, the clinic has sifted through some 2,100 inquiries and accepted only 140 patients thus far.

Klodzinski feared she wouldn't be accepted, believing "there were probably a lot weirder cases," but says she feels like she's finally found the right place for treatment.

"It's weird because it's like, 'Do I really have the disease that nobody knows what it is?' Klodzinski told TODAY. "I go to the hospital and there are so many sick people there and they all know what's wrong with them. What's so weird about my **condition** that they don't know what it is or what doctor to send me to?"

Unrelated ailments

Gahl said the intriguing mystery with Klodzinski is that she suffers from multiple maladies, with one not necessarily being related to the other. She shows signs of ascites (free fluid in her abdomen), pericarditis (inflammation of her heart covering) and hydroneophrosis (enlargement of her kidney), along with mouth cysts that cause her jaw to become inflamed.

"It's possible [she] has a genetic disorder," Gahl said, and if "we could find the gene that is responsible and relate mutations in that gene to her symptomatology, [it would be] a great outcome for us and for the profession, too."

Another one of Klodzinski's physicians at UDP, pulmonologist Dr. Bernadette Gochuico, said, "Kelly is very unusual, and she's challenging. We are doing some detective work in that Kelly has something that has not been described before, and we're trying to identify for the first time what may be causing her disease."

Klodzinski told Lauer she's taken steroids and morphine for years, but the UDP clinic has put her on a new drug normally used to treat rheumatoid arthritis, lupus and malaria. She began taking the drug in December, and is due back at the clinic in March to see if it's helping.

Symptoms first, diagnosis later

Appearing with Klodzinski on TODAY, medical correspondent Dr. Nancy Snyderman says it is good medicine to try to make Kelly feel better first, then figure out the root cause for all that ails her. "When a patient has real symptoms, sometimes doctors are better off to treat the symptoms, then wait for the diagnosis," she said.

Snyderman also lauded the NIH program for bringing together experts from various fields. "Not everything fits into a neat package; sometimes Mother Nature has a sort of different plan, and the constellation of symptoms don't fall into one package," she said.

Klodzinski told TODAY her spirits are somewhat buoyed by visiting the UDP clinic, but she still has her dark days. Recurrence of severe symptoms forced her into a hospital bed last year and made her have to plan her wedding while lying on her back.

"It's kind of scary," she said, "especially when it first started happening. I'm never really happy that I have to take steroids to live, basically. I don't like knowing that without a little pill every day there's a possibility I might die. I feel pretty helpless, and it is hard knowing that no one has really gone through the same disease process as I have."

Still, getting accepted into the UDP clinic allows her to see doctors she would never have been able to afford otherwise. "I don't have **insurance**; we don't have the money to fly around the world," she explained. "When I found out someone was interested in finding out what was wrong with me, I was so excited."

DISCOVERY HEALTH **VIDEO**

Feb 28, 2010

DISCOVERY HEALTH'S *DISEASE DETECTIVES* FOLLOWS A REAL-LIFE "DR. HOUSE" INSIDE THE NIH'S UNDIAGNOSED DISEASE PROGRAM

--World Premiere Special Airs on Rare Disease Day, Sunday, February 28, at 8 PM (ET/PT)—

(Silver Spring, Md.)—More than 30 million Americans suffer from rare or undiagnosed medical disorders—and for many, these mysterious conditions are life-threatening. When physicians and medical experts are left baffled, there is one last place to send the most puzzling and dire cases—the Undiagnosed Disease Program (UDP) at the National Institutes for Health (NIH). On **Sunday, February 28, at 8 PM (ET/PT)**, Discovery Health brings viewers inside the UDP for the first time with **DISEASE DETECTIVES**, an hour-long special following a real-life "Dr. House" and his team of experts as they attempt to solve real medical mysteries and help desperate patients in just five days.

DISEASE DETECTIVES profiles Dr. William Gahl, the head of the UDP, and his multidisciplinary team of dedicated experts as they attempt to solve riddles that have perplexed other medical researchers for years. Though thousands of cases are submitted to the UDP each year, only a fraction can be accepted for examination. Admitted patients journey to NIH headquarters in Bethesda, Md., for five full days of round-the-clock testing and analysis by Dr. Gahl and his team in what often represents their last hope for a resolution.

In the special, Dr. Gahl and his team take on two extremely different but equally perplexing cases. The first involves Jayden, a 7-year-old boy who travels to the UDP with his young parents. Jayden's developmental delays have led some doctors to believe that he could be autistic, but the fear also exists that he could be suffering from a potentially life-threatening condition. **DISEASE DETECTIVES** also follows Jon Page, 52, whose life has been severely disrupted by a strange condition involving a constellation of symptoms—from shaking, to muscle weakness, to chronic gastrointestinal issues. Working against the clock, Dr. Gahl and the UDP team struggle to find real answers for both Jon and Jayden's perplexing conditions.

"You see 'racing for a cure' plotlines every day on scripted TV and in major motion pictures, but with **DISEASE DETECTIVES**, you're seeing the genuine article." said Alon Orstein, executive producer for Discovery Health. "This is an extremely dedicated and talented team of medical professionals whose mission is to find answers to questions that have haunted patients for years."

DISEASE DETECTIVES premieres on February 28, which also is Rare Disease Day 2010, a global event aimed at raising awareness of the millions around the world living with rare and undiagnosed conditions. In the United States, Rare Disease Day 2010 is presented by NORD, the National Organization for Rare Disorders. Discovery Health is serving as media partner for the event for the second consecutive year. More information on Rare Disease Day and NORD can be found at www.rarediseases.org.

DISEASE DETECTIVES is produced for Discovery Health by Discovery Studios. For Discovery Health, Alon Orstein is executive producer, and for Discovery Studios, Robin Sestero is executive producer.

About Discovery Health: Discovery Health Media includes the Discovery Health and FitTV television networks and online assets including www.discoveryhealth.com, as well as its Continuing Medical Education (CME) business and Discovery's first stand-alone VOD service, Discovery Health On-Call. Discovery Health Media is part of Discovery Communications (NASDAQ: DISAD, DISBD, DISCK), the world's number one nonfiction media company, reaching more than 1.5 billion cumulative subscribers in over 170 countries. Discovery empowers people to explore their world and satisfy their curiosity through 100-plus worldwide networks, led by Discovery Channel, TLC, Animal Planet, Science Channel, Planet Green, Investigation Discovery and HD Theater, as well as leading consumer and educational products and services, and a diversified portfolio of digital media services including HowStuffWorks.com. For more information, please visit www.discoverycommunications.com.