Medical Detectives Find Their First New Disease

By **GINA KOLATA**

Louise Benge's medical problems started when she was 25. Walking became excruciating. Her calves got hard as rocks, and every step was agony. Her hands started hurting too. And the condition, whatever it was, only got worse over the next two decades.

Ms. Benge's family doctor in Mount Vernon, Ky., was at a loss, as were a vascular specialist, a hand specialist and a kidney specialist. Her two sisters and two brothers had the problem too, but no doctor could figure out why.

It was clear from X-rays why Ms. Benge could barely walk: The blood vessels in her legs, feet and hands were accumulating calcium deposits like the scale that sometimes forms inside water pipes. The deposits had grown so thick that blood could hardly squeeze through. But calcium was only in those blood vessels of her legs and hands; her heart's vessels were spared, so she was not in immediate danger of dying.

A doctor prescribed weekly infusions of a drug, sodium thiosulfate, Ms. Benge said, thinking it might bind to the calcium so her body could flush it out. But the drug did not work — it only made her vomit.

Finally, Ms. Benge's family doctor sent her medical history to a detective agency of sorts, the Undiagnosed Diseases Program at the National Institutes of Health. Set up in the spring of 2008, the program relies on teams of specialists who use the most advanced tools of medicine and genomics to try to figure out the causes of diseases that have baffled doctors.

The idea was that understanding rare diseases can give insights into more common ones, said Dr. William A. Gahl, director of the program.

And, he said, there was another reason.

"Patients who have rare diseases are often abandoned by the medical community," Dr. Gahl said. "We don't know how to treat if we don't have a diagnosis. The way our society treats abandoned individuals is a measure of our society. It speaks to how our society treats the poorest among us."

With Ms. Benge and her siblings, the researchers have their first newly discovered disease. It is caused, they report on Thursday in The New England Journal of Medicine, by a mutation in a gene that prevents calcium from depositing in blood vessels.

Now that they know the cause of the disease, the researchers have ideas for how to treat it. And the discovery also has implications for more common diseases, like heart disease and osteoporosis, in which calcium is deposited inappropriately.

The unraveling of Ms. Benge's mystery disease began the week of May 11, 2009, when Ms. Benge, who is 56, and her sister Paula Allen, who is 51, arrived at the tall red-brick clinical center on the campus of the National Institutes of Health.

The Office of Undiagnosed Diseases had been hearing from thousands of patients, Dr. Gahl said, 1,700 of whom sent their medical records. "Many had been to Hopkins, the Mayo Clinic and the Cleveland Clinic, and some had been to all three and been there more than once," he said.

Dr. Gahl and his colleagues were looking for people with unusual symptoms or unusual clues to what might be wrong. For example, they are now investigating a mystery disease in a young girl with uncontrollable muscle contractions that make it hard for her to talk, walk and use her hands; one that gave a young boy symptoms that look like Parkinson's disease; and one that gives a middle-aged woman shards of keratin, a hair protein, coming out of her hair follicles.

Ms. Benge and her sister had symptoms like no one had ever seen before. X-rays and M.R.I. images of their legs, hands and feet showed blood vessels so clogged with calcium that blood could get through only by squeezing into tiny vessels that had sprouted to circumvent the blockages. And those tiny vessels just were not able to supply enough blood.

Because there were five affected siblings, the researchers decided to take a genetic approach, using techniques not available at most major medical centers. The parents were fine, and that indicated the disease might be caused by a recessive gene — each parent would have one copy of the mutated gene and one copy of the intact gene, and each child with the disease would have two copies of the mutated gene, one inherited from each parent.

That led the investigators to a stretch of DNA with 92 genes. From there, the researchers zoomed in on the gene that was the culprit. A mutation had stopped it from functioning.

Cells use the gene to make extracellular adenosine, a common compound that, in this case, was needed to suppress calcification. No one had known about this metabolic pathway, said Dr. Manfred Boehm, a vascular biologist at the National Heart, Lung and Blood Institute.

The discovery is very important, said Dr. Dwight Towler, a bone endocrinologist at Washington University in St. Louis who was not part of the study, because it can help researchers understand signals for calcification in different parts of the body.

"You notice they don't have problems everywhere," he said of Ms. Benge and her siblings. That is because bone calcification and blood vessel formation are exquisitely coordinated, and different parts of the body use similar, yet subtly distinct, mechanisms.

The disease also fits in with a growing understanding of the close relationship between blood vessel cells and bone cells. Researchers say it could lead to new insights into heart disease, in which calcium deposits in coronary arteries, and heart valve disease, in which calcium can deposit in heart valves. Sometimes, said Dr. Towler, actual bone, with marrow, forms in valves.

It also could help illuminate the relationship between osteoporosis, in which bone is lost, and heart disease. In osteoporosis, as people lose bone, calcium often accumulates in arteries. It is as if the calcium that is not being deposited in bones is going into blood vessels instead.

“I think it has to do with the fact that the cells that make up our blood vessels are of the same origin as the cells that make up bone,” said Dr. Gahl, who is also clinical director of the National Human Genome Research Institute.

The researchers have now identified nine people from three families who have the newly discovered disease: Ms. Benge’s family, a patient in San Francisco and a family in Italy. Now they are working on treatments. The simplest might be to give a bisphosphonate, an osteoporosis drug. With the gene mutation and decreased levels of adenosine, patients end up with high levels of an enzyme, alkaline phosphatase, needed to make calcium deposits. Bisphosphonates bring down levels of that enzyme.

The investigators are putting together plans to test bisphosphonates and submitting them to ethics boards for approval.

“We hope to know in three or four months whether we can go forward,” Dr. Gahl said.