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**Abstract:** The article discusses mitochondrial disease, a mysterious disease affecting both children and adults. It describes the case of Asher Gould, who was diagnosed with the disease by Dr. John Shoffner. The disease afflicts at least 2 million Americans and is a suspect in other diseases including Alzheimer's and Parkinson's. Mitochondria are also implicated in diabetes, hypertension, and ageing, but no cure for mitochondrial diseases is available.

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### When Cells Stop Working

#### Children keep dying from mysterious illnesses that have been traced to tiny structures called mitochondria

Nothing worries parents more than a sick infant--especially when nobody can figure out what's wrong. For Asher Gould's parents, the uncertainty lasted for the first three years of their son's life. Asher's older brother Sam, now 10, has always been pretty healthy. But a couple of months after he was born, Asher started having trouble feeding and was spotting his diapers with blood. The pediatrician decided he had an allergy to milk. Then, at 9 months, he couldn't crawl or sit up. The diagnosis this time was hypotonia, a vague term that basically means "poor muscle tone." With physical therapy, Asher walked at 17 months, but then a month later he caught a cold--and overnight lost half his vocabulary. Nobody could figure out what was going on.

Asher was almost 3 when he began preschool, and that's when the phone started ringing. He was falling down at school. He became weaker and weaker. And after a mild flu, he stopped eating. By Christmas he was emaciated, but with a big, distended belly. His intestines had all but stopped working, and nobody could figure out why. Maybe it was myopathy (a muscle disease) or some sort of nerve-wasting disorder. "Don't try to figure it out," advised a doctor. "Just put in a feeding tube."

But Asher's parents--Anne Reckling, a child psychologist, and David Gould, an administrator at a private school in Columbus, Ohio--were determined to get to the

bottom of it. On the urging of someone on a myopathy e-mail discussion list, they went to see Dr. John Shoffner, a neurologist and geneticist at Horizon Molecular Medicine, a private group in Atlanta. A few weeks later, a fax arrived with Shoffner's diagnosis. Asher was suffering from a type of mitochondrial disease.

If the term is unfamiliar, that's no surprise. "When I began working on mitochondrial disease back in the '80s," says Shoffner, "people were still arguing over whether it even existed." Nobody is arguing about that anymore. In fact, doctors have now identified hundreds of different subtypes of the disorder. What they all have in common is a malfunction of the mitochondria--tiny substructures, or organelles, found inside every cell in the body. Their job is to convert food into a chemical called ATP that cells use for energy. When they go bad, all sorts of havoc is wreaked on the body. Depending on which types of cells are affected, mitochondrial disease can cause muscle wasting, nerve damage, seizures, stroke, blindness, deafness and more.

Officially, as many as 2 million Americans suffer from mitochondrial disease. But because defects in the mitochondria may underlie an astonishing range of very familiar illnesses, researchers are beginning to suspect that the real number is vastly higher. In the past few weeks alone, reports have come out in *Cell*, *Nature* and the *Journal of Neuroscience* implicating the mitochondria as factors in diseases such as Alzheimer's and Parkinson's. Indeed, says Dr. Vamsi Mootha, a Harvard Medical School researcher who won a MacArthur Foundation "genius" grant in 2004 for his work on mitochondria, "it looks like they're really important in diabetes, hypertension and many other common diseases--even in the aging process itself."

Exactly what role mitochondria play in these illnesses is still unclear. It's not even certain whether mitochondrial breakdowns are the cause or the effect of disease--although researchers suspect it's often a little of both. As mitochondria process food into energy, they create free radicals--highly reactive oxygen ions that can cause damage to proteins. Many experts believe that as cells age, this damage accumulates, weakening the mitochondria irrevocably and doing harm to specific organs--or, more generally, to the whole body. There's no smoking gun yet, says Mootha, but there's some tantalizing evidence. "We do know," he says, "that exercise can help slow the damage from diabetes and other disorders and also that exercise boosts the function of mitochondria."

In the known mitochondrial diseases, though, it's clearly a genetic abnormality that almost always sets things off. Mitochondria are different from the rest of the cell in that they have their own DNA, inherited directly from the mother (with no input from the father) that's entirely separate from the DNA in the nucleus. Evolutionary biologists suspect, in fact, that these organelles started out as independent bacteria that were absorbed long ago into cells and harnessed as energy factories.

By the mid-1980s, says Mootha, the mitochondrial genome--with only about 16,000 genetic "letters," compared with 3 billion in the nuclear genome--had been sequenced. That let researchers link specific, rare disorders to specific mitochondrial mutations, always passed from mother to child. But by the time the Human Genome Project was completed in 2000, it was clear that mutations in the nucleus could cause problems in the mitochondria as well. "We now estimate," says Mootha, "that while mitochondrial DNA encodes just 13 proteins, another 1,500 or so proteins used by mitochondria are encoded by the nucleus."

This helps explain why mitochondrial disease occurs in such bewildering variety and why

it can be so difficult to diagnose. Even now that it's better understood, parents sometimes face doctors' accusations of deliberately poisoning children to draw attention to themselves.

There's no cure yet for mitochondrial disease, nor even a surefire treatment. Sufferers are usually given vitamin and nutritional supplements, which can help slow the progress of the illness, but they aren't always effective. "If you'd asked me a year ago," says Shoffner, "I would have said that's the only option." Since then, however, some promising drugs have been developed, and will soon go into clinical trials. And a new company called Edison Pharmaceuticals, of San Jose, Calif., was founded last year for the sole purpose of coming up with drugs for mitochondrial disease.

Still, supplements have made a big difference for Asher. He tires easily and has to conserve energy--he uses a wheelchair if he has to travel long distances. He still needs a feeding tube. And he has damage to his optic and auditory nerves, along with some cognitive impairment. Nevertheless, says his mother, "he's a really positive, upbeat boy." Now 5, Asher is in kindergarten. He takes karate lessons and is learning to play tennis. But his family is well aware that he may not survive childhood, so they're always vigilant--sometimes to a fault. One morning last week, says Reckling, "he told me his legs were tingling. I don't know if it's new nerve damage--or if his feet were just asleep."

### **OUT OF WHACK**

Mitochondria are structures within cells that carry their own set of DNA, inherited from the mother. Their job is to convert food into a form of energy the cell can use

## **Symptoms**

When mitochondrial genes are damaged--or when damage occurs to genes in the nucleus that affect mitochondrial function--victims can suffer from symptoms including muscle weakness, blindness, deafness, neurological damage and more

DIAGRAM: OUT OF WHACK

PHOTO (COLOR): FEELING BETTER: Asher still needs a feeding tube, but he can play tennis and do karate

PHOTO (COLOR)

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By Michael D. Lemonick

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