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When Cells Face an Energy Crisis Malfunctioning Mitochondria Cause Many Disorders

A champion swimmer, 16-year-old Joe Wise seems a healthy and happy high school junior. He enjoys time with friends, and he's looking forward to college. But take a closer look, deep into his cells, and something's not quite right. There's a malfunction in the tiny capsule-shaped structures—called **mitochondria**—that power his cells. These abnormal mitochondria cause extreme fatigue and weakness in his legs, trouble breathing and a host of other problems.

"I used to play baseball, but now I can't run so I can't do that any more. Instead, I swim," Joe says. In the past few years, he's broken several national swimming records, and in 2008 he was on the U.S. Swim Team in the Beijing Paralympic games.

Joe is 1 of tens of thousands of people nationwide who have mitochondrial diseases, although estimates vary. There are dozens of subtypes, with each affecting less than 1 in 1,500 people. There's no treatment or cure for any of these rare diseases.

Mitochondrial diseases are caused by abnormal **genes** that lead to flawed proteins or other molecules



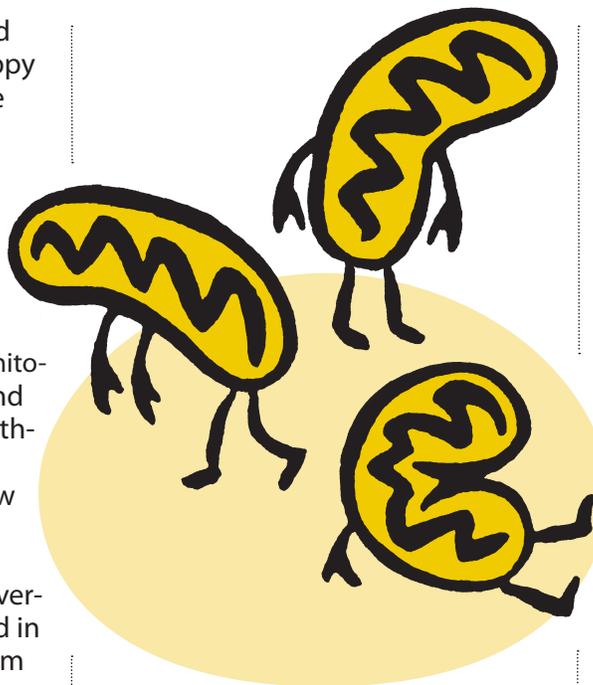
Definitions

Mitochondria

Known as the cell's "powerhouse," they convert food molecules into a form of energy your cells can use.

Genes

Stretches of DNA, a substance you inherit from your parents, that define characteristics such as how likely you are to get certain diseases.



in the mitochondria. The various subtypes are caused by alterations in different genes, leading to worn-down cells in different parts of the body. Hardest hit are organs and tissues that need a lot of energy, like muscles, brain, heart, kidneys and liver. When the energy supply slumps, cells can become damaged or destroyed.

But mitochondria have importance beyond rare diseases. Even in healthy people, researchers have found, mitochondria can gradually deteriorate as we grow older. Malfunctioning mitochondria have been linked to diabetes, heart disease, Alzheimer's disease, Parkinson's disease and even normal aging. "If we can learn more about the rare mitochondrial disorders, the findings could have implications for understanding more common diseases," says Dr. Vamsi Mootha of Harvard Medical School.

The rare mitochondrial diseases are notoriously difficult for doctors to recognize and diagnose. Depending on which cells are affected, people with mitochondrial diseases may have muscle weakness and pain, digestive problems, heart disease, seizures and many other symptoms. These diseases affect both children and adults. Some lead to early death. Because the symptoms vary widely, mitochondrial diseases are often mistaken for other conditions.

In Joe Wise's case, he was an avid baseball and football player before age 8, when his father noticed he was walking and running a little funny. He felt tired and weak. He had trouble swallowing. Joe's parents took him to see several specialists, who thought he might have juvenile arthritis, muscular dystrophy or maybe a problem with his hip. But eventually, a muscle biopsy showed that he had mitochondrial disease. His doctors didn't expect him to live beyond age 14. "It was a real shock to the family," Joe says. "It was something we suddenly had to learn a lot more about."

Joe had to make difficult adjustments—watching his diet, being careful while walking and using a ventilator twice a day and overnight to help him breathe. He finds he feels weaker over time but continues to

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swim just about every day. "Swimming has helped in a lot of different ways," Joe says. "It's kept me out of a wheelchair. It's kept me off a larger ventilator." He's now in training for the 2012 Paralympics.

Scientists don't yet know why some patients like Joe can continue to exercise, while others have more severe disabilities. Over the last decades, though, researchers have learned a lot about mitochondria.

Each cell in the body contains dozens or even hundreds of mitochondria. Mitochondria produce about 90% of the energy that cells need to function. They differ from other cell components because each contains its own tiny loops of DNA,



Wise Choices Mitochondrial Disease Symptoms

Mitochondrial disease can affect different parts of the body. Symptoms can range from mild to severe and might include:

- Poor growth
- Muscle weakness or fatigue
- Visual or hearing problems
- Mental retardation
- Heart, liver or kidney disease
- Digestive problems
- Breathing difficulties
- Diabetes
- Seizures



Web Links

For more about mitochondrial diseases, see our links online:

<http://newsinhealth.nih.gov/2010/April/feature1.htm>

called mtDNA. The circular mtDNA differs from the well-known long DNA strands that make up the chromosomes contained in the control center, or nucleus, of your cells. Your nuclear DNA comes from both your mother and your father, but mtDNA comes only from your mother.

Scientists have learned that among the genes in mtDNA are instructions for making 13 proteins that mitochondria need to produce energy.

Mutations in these genes can lead to dozens of different diseases.

But mitochondria contain much more than 13 proteins. They also contain over 1,000 proteins that come from genes in the cell's nucleus. "We now know that the vast majority of genetic mitochondrial disorders are actually due to mutations in the nuclear **genome**," says Mootha. These nuclear mutations are difficult to identify. While some research centers can now sequence the entire mtDNA and find the mutations that cause a patient's disease, that can't be done



Definitions

Mutations

Changes in a DNA sequence.

Genome

The full set of all your genes.

for most mutations in nuclear DNA.

Over the past 7 years, Mootha and his colleagues have been working to change that. They've used powerful new research tools to identify about 1,100 genes in our nuclear DNA that make proteins found in mitochondria. They're now searching for mutations in these genes in patients who have mitochondrial disease. That will help with developing diagnostics, he says. "And once we know the molecular underpinnings of these disorders, they may offer clues for completely new treatment strategies."

Several potential therapies for mitochondrial diseases are already being explored. Some patients with mtDNA mutations have a mix of normal and mutant mtDNA in their cells. Researchers are searching for ways to shift the balance toward more normal DNA. At the University of Texas Southwestern Medical School, Dr. Ronald Haller is testing to see if endurance training can safely encourage this shift, or at least improve physical health, in patients with mtDNA mutations.

"The benefits of exercise training in healthy people are well-recognized," Haller says. One benefit is to increase the number of mitochondria in your muscles. "We want to see if some of these same benefits extend to patients with mitochondrial disease."

Haller and his colleagues have already conducted small studies that suggest patients who train can improve their ability to walk and do other daily activities. He's also found evidence that mitochondrial numbers shrink once patients stop training—which also happens in healthy people. Haller has now begun a larger study of 40 patients to see how exercise training, and taking a break from exercise, affect mitochondria and exercise capacity.

"A lot of exciting new research in mitochondrial biology is taking place right now," says Mootha. "As we learn more about these disorders, we'll hopefully be able to convert this knowledge into better therapies." ■

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Dairy Dilemma

Are You Getting Enough Calcium?

You may be avoiding dairy products because of lactose intolerance. Or you might have other reasons. But dairy products are a major source of calcium, vitamin D and other nutrients that are important for your body. If you're avoiding dairy products, you need to take special care to make sure you're getting enough of these nutrients.

Our heart, muscles and nerves need calcium to work properly. Our bones need it to grow and stay strong. The body also needs vitamin D to absorb calcium. Nutrition surveys have shown that most people in the U.S. aren't getting the calcium they need. If you're avoiding milk and dairy products, you may be missing out on important sources of calcium and vitamin D.

One of the major reasons people avoid dairy products is lactose intolerance. Lactose is a natural sugar found in milk and other dairy products. You become lactose intolerant if your body doesn't have enough lactase—an **enzyme** produced in the small intestine that you need to digest lactose. Undigested lactose can cause stomach cramps, gas and diarrhea within 30 minutes to 2 hours after eating something with lactose.

Lactose intolerance isn't common in young children, but many people gradually lose their ability to digest lactose after childhood. That happens more often in some ethnic groups, such as African Americans, Native Americans, Hispanics and Asians. Most people who don't completely digest lactose have no symptoms and are entirely healthy, but some people do get those un-

comfortable symptoms.

Complicating things, some people mistake the symptoms of intestinal disorders, such as irritable bowel syndrome and inflammatory bowel disease, for lactose intolerance.

NIH recently convened a "consensus development" conference to review the scientific evidence and develop objective statements about treating lactose intolerance. The panel concluded that there isn't enough scientific evidence to answer many questions about lactose intolerance, including how many people have it, whether it causes serious health effects or how these effects should be treated. More research will be needed to answer these questions.

If you think you or your children are lactose intolerant, studies suggest you may not need to completely eliminate milk or dairy products from your diet. There are several strategies you can try to ensure you get the nutrients you need. These include spreading your dairy intake throughout the day, combining it with other foods, taking nutritional supplements and choosing reduced-lactose or non-dairy foods rich in the nutrients found in dairy products.

How much calcium and vitamin D you need depends on your age and other factors. If you're avoiding dairy products, talk to your doctor to make sure you meet your nutrient



requirements. You can also check out the Dietary Guidelines for Americans at www.health.gov/dietaryguidelines for recommendations about dietary intake, including dairy or calcium-rich foods. ■



Wise Choices Getting Enough Calcium

If you've been avoiding dairy foods, try the following strategies:

- Try low-fat or fat-free milk in servings of 1 cup or less.
- Have milk with other food, such as breakfast cereal.
- Try other dairy products, such as low-fat or fat-free cheeses or yogurt.
- Choose lactose-free milk and milk products.
- Choose other calcium-fortified foods such as orange juice, soy or rice beverages. Some non-dairy foods, such as spinach and broccoli, have calcium, too.
- Use over-the-counter pills or drops that contain lactase, which can eliminate symptoms.
- Talk to your doctor about nutritional supplements.



Definitions

Enzyme

A type of protein that does work in the body, such as helping to break down and digest food.



Web Links

For more about lactose intolerance, see our links online:

<http://newsinhealth.nih.gov/2010/April/feature2.htm>



Health Capsules

For links to more information, see these stories online:
<http://newsinhealth.nih.gov/2010/April/capsules.htm>

Resting May Boost Memory

Your memories may grow stronger when you take a break to rest, a new study suggests. The finding could have important implications for how students study and how people can best learn new things.

Long-term storage of a memory—called memory consolidation—is thought to involve interactions between different brain regions, including the hippocampus and parts of the cortex. Scientists believe that the brain “replays” memories, reactivating the same activity patterns as during the experience itself. Several studies suggest that this happens during sleep. NIH-supported researchers set out to investigate whether it can also happen when you’re awake.

The researchers used functional MRI to scan the brains of 16 people

during 2 different tasks as well as during rest periods before and after. The people were shown paired sets of images that included a human face and either an object, such as a beach ball, or a scene, such as a beach. They weren’t told their memory would be tested. They were just told to rest and think about anything they wanted, as long as they stayed awake.

As expected, correlations between the brain regions were low during the initial period of rest and high when the people were shown the pairings.

The memory for object-face pairs was much better than for scene-face pairs. Activity between the hippocampus and one region of the cortex correlated significantly during the rest period after the people saw the object-face pairs. But this didn’t

happen after people saw the scene-face pairs. The higher the correlation between the brain regions during the later rest period, the better the person remembered the pairing.

These results suggest that these brain regions coordinate to replay recent experiences during periods of rest in order to consolidate memories. “Taking a coffee break after class can actually help you retain that information you just learned,” says researcher Dr. Lila Davachi of New York University. “Your brain is working for you when you’re resting.” ■



Featured Web Site Genomic Careers

www.genome.gov/GenomicCareers/

Thinking of a career in genetics or genomics? This new site shows you the wide range of opportunities. See interviews of professionals at different points in their careers and take video tours of genomic facilities. Online tools let you rate potential career choices and play the interactive Genomics Challenge quiz.



Life Changes After Cancer

Many people who’ve survived cancer are living longer lives, thanks to better diagnostic tests and treatments. But life after cancer can bring its own challenges. “Many cancer survivors look forward to returning to a normal life after treatment ends,” says Dr. Julia Rowland of NIH’s National Cancer Institute. “But for some, this can be a stressful period.”

If you or a loved one has survived cancer, you can learn more about what to expect in “Life after Cancer,” the newest topic added to the NIH Senior Health web site for older adults. The new topic, at www.nihseniorhealth.gov/lifeaftercancer/toc.html,

has tips for managing follow-up care and making positive adjustments to your lifestyle. You’ll learn about common changes to physical and emotional health and how to cope with them. You’ll also learn how surviving cancer might affect your relationships with family and friends. The site also describes how your age and health status can affect recovery and survival.

All information on NIH Senior Health (www.nihseniorhealth.gov) is based on the latest research in cognition and aging. Upcoming topics include periodontal disease, dry eye and collecting your family health history. ■

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