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New test for mysterious metabolic diseases developed at Stanford/Packard

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Scientists at Stanford University School of Medicine have devised a much-needed way to monitor and find treatments for a mysterious and devastating group of metabolic diseases that arise from mutations in cells' fuel-burning mechanism.

Mitochondrial disorders can cause organ failure, seizures, stroke-like episodes and premature death. The diseases—more than three dozen in total—arise from genetic errors of the mitochondria, the cell structures that process oxygen and turn food molecules into useable energy. Mitochondrial disorders affect one in 4,000 kids and one in 8,500 adults. They are difficult to diagnose, and no treatments or cures exist.

But that could soon change. A team at Stanford and Lucile Packard Children's Hospital has discovered a biological marker they can use to monitor the diseases. The finding will enable researchers to hunt for treatments and help physicians check patients' status before health crises erupt. The research was published online Feb. 9 in the *Proceedings of the National Academy of Sciences.*

"When a car engine doesn't work right, it smokes," said senior study author Greg Enns, MB, ChB, who is professor of pediatrics at Stanford University School of Medicine and director of the biochemical genetics program at Packard. "What we looked for is, in essence, biochemical smoke."

Like a car engine, when mitochondria are not burning fuel cleanly, they

kick out nasty gunk. Defective mitochondria produce large quantities of oxygen free radicals—highly reactive molecules that damage DNA and cell structures. Comparing patients who have a mitochondrial disorder with healthy people in the control group, Enns' team searched for signs that free radicals overtax patients' natural antioxidant defense systems. And they found it.

"Even when these patients are coming into the clinic looking pretty healthy, they have evidence of extra metabolic stress," Enns said, noting the findings were surprising because none of the patients were in the midst of a health crisis such as organ failure when blood samples were taken. It is the first time such signs have been uniformly shown in the blood of patients across a wide range of mitochondrial disorders, he added.

The team saw that levels of glutathione, the body's primary antioxidant, were significantly reduced in white blood cells from the 20 mitochondrial disease patients in the study. The observation means patients' antioxidant defenses were indeed depleted. Glutathione was also diminished in nine patients with organic acidemias, another group of metabolic diseases that researchers think may be associated with aberrant mitochondrial function.

A second finding gave the researchers a big hint about where to hunt for treatments. Patients taking antioxidant supplements did not have depleted glutathione, they found. Scientists have long suspected antioxidants such as vitamin C and vitamin E might help patients with mitochondrial disease or organic acidemias, and doctors sometimes suggest the supplements to their patients. But no one has been able to test whether they work.

"As a clinician, one of the most frustrating things has been not being sure if supplements are doing any good," said Enns. "Now we're able to

take a baseline blood reading and see 'before' and 'after' snapshots."

William Craigen, MD, PhD, the director of the metabolic clinic at Texas Children's Hospital, called this finding "the beginning of insight into the mechanisms of mitochondrial disease." Craigen, who is also medical director for the mitochondrial diagnostic lab at Baylor College of Medicine, was not involved in the Stanford study. "This new research provides an opportunity to start treating a heterogeneous group of diseases in a single fashion, with a simple and easy-to-administer treatment, potentially improving patients' long-term outcomes," he added.

Glutathione measurements could also help diagnose patients, Enns said, by giving physicians a clear indication that something is awry in the mitochondria. Genetic and molecular tests have already led to increases in the number of diagnoses, but the diagnosis is still difficult to pin down.

The method Enns' team used to measure glutathione, called high-dimensional flow cytometry, has limitations: it requires very fresh blood samples, uses expensive equipment only available in research labs, and provides relative rather than absolute glutathione measurements. Now that the team knows what metabolic change to look for, they're working to develop a more broadly applicable measurement technique.

And glutathione measurements could help scientists unravel other disease mysteries, too. "You name the disease, you can postulate mitochondrial involvement," Enns said. "It's been proposed for everything from poor vision to hearing loss, kidney disease, liver disease, autism spectrum disorders, diabetes, Alzheimer disease, cancers. Our work could lead to research on therapies for a broad range of disorders."

Source: Stanford University Medical Center