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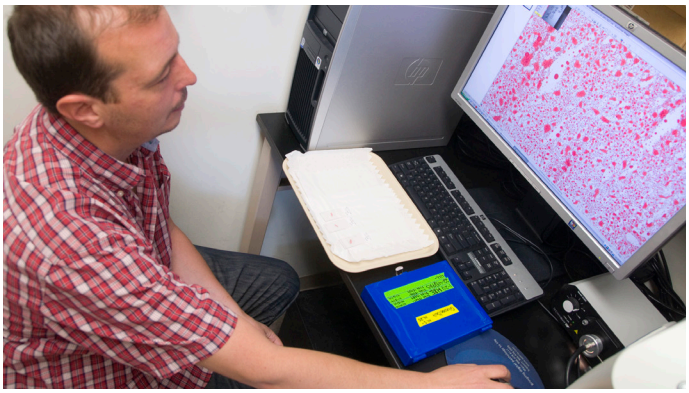
Once fringe idea moving toward the middle

'Fat Switch' Work Is Full-Speed Ahead

By Todd Neff

In his 2012 book "The Fat Switch," Richard Johnson, MD, described his team's work to illuminate why we get fat. He evoked everything from the enzyme AMP deaminase to the hibernation habits of thirteen-lined ground squirrels to do it.

Two years later, he alluded to Thomas Kuhn, author of the 1962 classic "The Structure of Scientific Revolutions," to describe his team's role in the broader realms of obesity and diabetes research.



Miguel Lanaspa-Garcia, DVM, PhD, a faculty researcher in the Johnson Lab at the CU School of Medicine, takes a magnified look at a thin slice of a mouse liver. The mouse, fed a rich fructose mix, developed a fatty liver (the fat pockets are stained red in this image).

"Kuhn said paradigm shifts require someone new to come in or an established scientist from another discipline to enter the field," said Johnson, a renal specialist who sees patients at University of Colorado Hospital. "We're coming in more from the side."

The side looks to be moving quickly to the center. A growing chorus (including a recent review in the journal *Nature; a National Geographic* cover story on sugar; a May 16 commentary in the Journal of the American Medical Association and an accompanying *New York Times* Sunday Review piece) is all singing more or less the same tune: it's seems that we get fat not just because of calories, but because of the kind of calories we take in. Sugar – in particular fructose, which is everywhere in the American diet – appears to be a major problem.

Which is what Johnson has been saying for years.

Not just talk. His conclusions are based on thousands of hours of lab work and described in many scientific papers. The gist is that the prevailing wisdom of weight gain boiling down simply to calories consumed exceeding calories burned may be wrong. Rather, he said, the metabolic roads in our cells have natural forks – in part plowed into our DNA 15 million years ago when we were 20-pound apes. These alternate pathways, Johnson believes, lead to either burning fat or accumulating it.

Johnson fits Kuhn's bill of an established scientist from another field. He is chief of the Division of Renal Diseases and Hypertension at the University of Colorado School of Medicine. He came into the world of metabolic syndrome – characterized by high blood pressure, high blood sugar, fat around the middle, and high cholesterol levels, all of which boost risk of heart disease, stroke, and diabetes – via study of the kidneys, which suffer when blood pressure rises. In particular, he is known as a uric acid guru. Best known for triggering gout, uric acid also messes with cellular switching as well as mitochondria, the power plants for cells.

Johnson and colleagues like Miguel Lanaspa-Garcia, DVM, PhD, can now tell a very complicated story they say helps to explain the much-discussed rise in obesity rates in the United States. Distilled to its essence, it goes roughly like this.

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Back in the day. Fifteen million years ago, an ape was born with a mutation. She couldn't produce the enzyme uricase, which breaks down uric acid, so she was prone to having more uric acid in her system than her uricase-producing proto-human compadres. They all ate fruit, which has lots of fructose.

The mutant's body broke down fructose using an enzyme called fructokinase. Fructokinase accomplished this breakdown by stealing a phosphate from the cellular fuel ATP. As the ATP degraded, her levels of adenosine monophosphate (AMP) shot up. Normally, the increase might have triggered a corresponding increase of an enzyme called AMP kinase, which would have told her cells to burn fat and sugar to replace the ATP she was using.

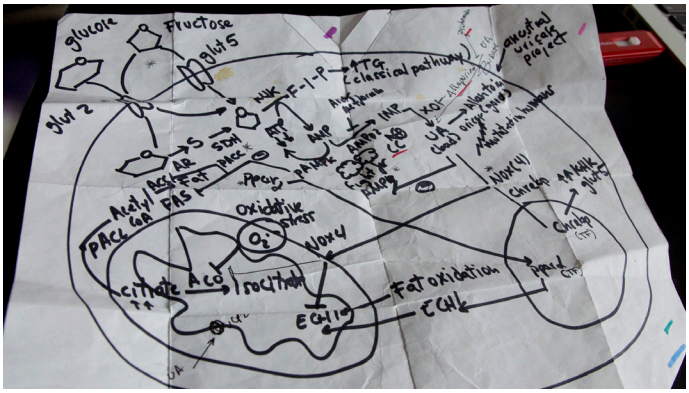
But in her case, the process triggered an increase of an enzyme called AMP deaminase, or AMPD, which *decreases* AMP kinase levels, and in the end produces uric acid, a trigger for storing fat. So her cells, rather than burning fat and sugar to replenish the ATP fuel as they might normally, accumulated fat.

This ape, whose offspring would, 9 million years later, diverge from chimps and become us, was unconcerned with any of this. But she survived when others starved because her cells were, for purely cellular-mechanical reasons, preferentially piling on fat and sugar rather than burning it. Uric acid further came into play in that it stressed her cells' mitochondria in ways that triggered fat production by different means. Human cells do the same thing, which is, Johnson and others contend, why we get fat like thirteen-lined ground squirrels preparing for hibernation – although we're obviously not headed off to sleep for months at a time. Nor do we benefit any longer from piling on fat, as our ape ancestor did.

Student assistant Juan Martinez washes off secondary antibodies in the Johnson Lab at the CU School of Medicine.

Lanaspa-Garcia, who had filled a whiteboard to describe this process, summarized: "Nobody ever said it was easy."

Skinny pills? He and Johnson think they've untangled much of the mystery. Lanaspa has found that mice engineered to produce no fructokinase don't get fat on fructose water like normal mice. He also genetically modified liver cells with high and low levels of AMPD. Liver cells high in AMPD were high in uric acid and accumulated more fat; cutting the AMPD levels sharply slowed the fat accumulation.



If fat switches were light switches, many of us would be in the dark. It's hard for professionals, even. Here's Johnson Lab Professional Research Assistant Christina Cicerchi's cheat sheet.

Johnson, Lanaspa-Garcia and colleagues Gabriela Garcia, MD, and Christopher Rivard, PhD, were recently granted a patent covering cellular targets for inhibitors of the second isoform of AMP deaminase (AMPD2) in the liver. Metformin, the type-2 diabetes drug, also happens to work by inhibiting AMPD, Lanaspa said.

"We believe we've identified a central mechanism to fat and glucose accumulation," Johnson said.

There's much work to be done, both he and Lanaspa-Garcia said. Their research to date has shown that turning off the "fat switch" can keep a thin mouse thin, but it's less clear whether it can help a fat mouse slim down, for example. And whether the switch can in fact keep humans slim remains an open question.

A range of other studies, though, suggests that fructose may not be the only – or even the most important – factor in the development of obesity or its treatment. Dan Bessesen, MD, a CU School of Medicine specialist in endocrinology, diabetes and metabolism, said clinical data on reducing fructose as a weight-reduction

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strategy has only a "modest" positive effect. Reducing total calories and getting more exercise have greater impacts, he said.

Bottles of sugary (and salty) compounds stand at the ready for mouse consumption in the Johnson Lab.

Studies have shown that everything from air conditioner adoption to smoking status to sleep hours to the concentrations of PBDE-based flame retardants to the average age of mothers at giving birth are correlated with (though not necessarily the cause of) rising obesity rates. Sorting out what is most important – and then understanding how each unique person responds to so many dietary and other variables at the molecular level – is an enormous task, Bessesen said.

He said Johnson's work could be very important in describing some "very specific molecular and cellular steps in metabolism," but added that "you could say the same thing about a number of other areas."

Johnson's team is forging ahead. They're researching plant extracts and other compounds from dandelions, strawberries, parsley, and hundreds of other sources and testing them in test tubes and on cell cultures. The goal is to identify chemicals that might one day find their way into pills that could, in our sugar-rich world, turn off the fat switch. It may have once saved us from starvation, but it may be killing us now.