UCH INSIDER

UNIVERSITY of COLORADO HEALTH

Volume 6 | Issue 5 | Through September 11, 2012

CU prof's new book says cellular triggers add pounds

'Fat Switch' May be Key to Turning off Obesity

By Todd Neff

Weighing in at just 244 pages, plus end notes, glossary, index and the like, the new book *The Fat Switch* is light for a magnum opus.

That's sweet irony for an exploration of what its author, Richard Johnson, MD, chief of the division of Renal Diseases and Hypertension at the University of Colorado School of Medicine, believes to be the hidden mechanism behind obesity, a disease that afflicts more than one-third of U.S. adults and is responsible for a host of other health problems, according to the Centers for Disease Control and Prevention.

Richard Johnson, MD, chief of the division of Renal Diseases and Hypertension at the CU School of Medicine, with his new book The Fat Switch.

Johnson is a kidney expert whose research has taken him far beyond the bounds of the typical nephrologist's sphere.

The Fat Switch ranges widely in building its case that biological survival mechanisms etched into our genes millions of years ago have at least as much say about body weight as do diet and exercise choices freely made. If Johnson is right, medical researchers may one day develop pills that help overweight and obese people get back on a healthier track. Johnson and colleagues are already working on it at CU, in fact.

From kidney to belly. Johnson came to study obesity by way of the kidney. High blood pressure, or hypertension, is associated with disease in the kidneys' small blood vessels, which robs them of their ability to get rid of salt. Uric acid, long associated with high blood pressure, drives the blood vessel disease and the development of hypertension, Johnson's lab reported in 2002. In a study published in 2008 with Dan Feig of the Baylor College of Medicine, Johnson showed that lowering uric acid could improve blood pressure in hypertensive adolescents.

Uric acid is best known for causing gout, a type of arthritis caused by the buildup of acid crystals in the joints. But as Johnson and his team looked at uric acid, they found it created even more havoc. In research pending publication, Miguel Lanaspa and Johnson have also fingered uric acid as a culprit in obesity.

Uric acid comes from the breakdown of the cellular fuel ATP (produced by mitochondria) as well as the breakdown of DNA and RNA, primarily from foods. But this breakdown doesn't have to yield uric acid, Johnson and Lanaspa found. There's a fork in the metabolic road, with only one of the paths leading to uric acid.

The path to uric acid is a rocky path. The compound leads mitochondria to boost fat synthesis while the body burns less energy, Johnson and colleagues have found. The implication is that the same amount of food builds fat into – and saps energy from – people on the uric acid pathway.

"Too much food intake plus too little exercise equals fat," Johnson writes. "However, our work suggests the interpretation is different. Obesity is not from gluttony and idleness, but rather because we have activated the same program all animals use to increase fat stores."

But who's on this program, and why?

Continued

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The answer, Johnson and colleagues say, has to do with fructose, the subject of Johnson's 2008 book, *The Sugar Fix*.

Incoming fructose – a mainstay in the corn syrup poured into sodas and many processed foods, not to mention honey, maple syrup, ripe fruit and other sources – triggers a mass mobilization of the enzyme fructokinase in cells. Fructokinase carries out the first step in the body's harvest of the four calories per gram of energy fructose carries.

But to get to that energy, fructokinase first sucks gobs of ATP, the cellular fuel, thereby activating the fat-building uric acid metabolic pathway, or switch, Johnson says.

Diet and exercise still play a role in managing weight, of course, Johnson adds.

"Fructose is the fire; high-fat diet is the firewood. Together they drive the obesity epidemic," as he described it in the book. Exercise, he adds, burns energy and predisposes the body to burn more energy over the long haul.

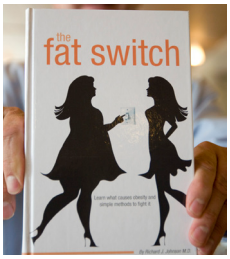
Telescopic. In writing *The Fat Switch*, Johnson didn't stop with the molecular science behind weight gain. During the year he wrote it – early mornings, late nights, weekends – he researched everything from "Norwegian fish journals to Sanskrit from 400 A.D.," as he put it.

The book incorporates discussions of emperor penguins, the art of Peter Paul Rubens; Friar Tuck; Falstaff; the Columbian World Exposition of 1893; the Yanomamö Indians of Venezuela; the Inuit; San women with steatopygy (characterized by massive behinds); the gastric brooding frog (possibly extinct); hummingbirds; the desert gerbil; the gray whale; the bar-tailed godwit; the marine calm worm; the great racehorse Secretariat; and the striped gopher – native to Minnesota, where Johnson went to medical school.

The sugar-uric acid fat switch operates in everything from whales to bears to Midwestern squirrels, Johnson found. It's what they use to fatten up before they migrate or hibernate. Mollusks, crayfish and insects similarly rely on uric acid for survival. The primates that became humans, we learn, lost their ability to process uric acid roughly 15 million years ago through a genetic mutation. Why? It helped put on fat quickly when food was bountiful, providing what became a decisive survival advantage during lean times.

Johnson described the resulting work as a "telescopic," as opposed to a microscopic, approach to science. Instead of drilling down on one molecule, as so often happens in science, his approach was to scan the horizons of human inquiry for evidence. He looked into evolutionary and molecular biology, comparative physiology, basic medicine, and even history, "and when you put it all together, the argument [for a fat switch] becomes quite compelling," Johnson said.

His fat switch hypothesis may be wrong, Johnson admits. But he says the data, published and forthcoming, is compelling.



Obesity is triggered by an ancient biological mechanism creatures that migrate and hibernate still depend on, Johnson says. The "fat switch" also gave the primates that would evolve into humans a survival advantage.

"This is going to challenge the whole field of obesity research," Johnson said. "It's identifying a mechanism for obesity and it is defended. It's going to be very exciting to see the response from the scientific community."

With the fat switch identified, Johnson's University of Colorado research group is working on finding ways to keep it turned off. Among the possibilities: fructokinase inhibitors, uric acid suppressors, and antioxidants to salve mitochondria during uric acid's onslaught. Johnson has launched a biotech startup, Polaryx Therapeutics, which is focusing on fructokinase inhibitors.

The Fat Switch is a compelling read, said James O. Hill, PhD, the Anschutz Health and Wellness Center's executive director and also director of the University of Colorado School of Medicine's Center for Human Nutrition.

"I don't think this is a magic switch at all, but he's identifying some biological pathways that might be important targets in future pharmaceuticals, diet strategies and so on," Hill said. "This is some really, really solid research, and I think it's great food for thought for anybody who's studying obesity."

Hill added that Johnson, in addition to having done his homework, "is not afraid to push a bit, which I like."

To read more about The Fat Switch and Johnson's work, visit http://articles.mercola.com/sites/articles/archive/2012/08/18/fructose-and-the-fat-switch.aspx.