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Jeremy Nicholson's Gut Instincts: Researching Intestinal Bacteria

The body and its intestinal flora produce chemicals with hidden health information, Jeremy Nicholson has found. Someday treating disease may mean treating those bacteria

By Melinda Wenner

Editor's Note: The extended Q&A with Jeremy Nicholson mentioned in the July magazine can be found here.

Jeremy Nicholson was only trying to be thorough. It was 1981, and the young biochemist was using a technique called nuclear magnetic resonance spectroscopy, which can identify chemicals based on the magnetic properties of atomic nuclei. In particular, Nicholson wanted to study how red blood cells absorb cadmium, a metal that causes cancer. Realizing that he would achieve the best results if he could mimic the cells' natural environment, he added a few drops of blood to the cells and ran the test.

"Suddenly there was a huge variety of signals that we hadn't seen before—there were these amazing sets of spectra coming out," Nicholson recalls. A sample of blood or urine contains thousands of metabolites—signatures of all the chemical reactions occurring in the body at a given time. If he could find a way to identify those chemical signatures and their significance, he reasoned, he would be able not only to better understand different diseases—based on chemical reactions that had gone awry—but also to identify early warning signs and potential interventions. That kind of science, he decided, was his kind of science.

Today the 51-year-old Nicholson is one of the world's foremost experts on the so-called metabolome, the collection of chemicals produced by human metabolism. Whereas the genome provides detailed information about a person's genetic makeup, the metabolome is a few steps down the line—it reveals how genes interact with the environment, providing a complete snapshot of a person's physical health. "The genome is really like a telephone directory without any of the names or addresses filled in. On a very basic level, it's got a lot of numbers," explains Nicholson, who now heads the department of biomolecular medicine at Imperial College London. The metabolome "helps to give value to genome information and put it in perspective."

But first it has to be deciphered, and that is no easy task. The job requires the analysis of blood, urine, breath and feces within large populations. For instance, to find potential chemical signatures, or biomarkers, for high blood pressure, Nicholson and his colleagues analyzed the urine of 4,630 individuals from the U.K., the U.S. and Asia and compared the urinary metabolites with blood pressure data to determine if any consistent metabolic differences exist between individuals with hypertension and those without it.

It is kind of like doing science backward: instead of making hypotheses and then devising experiments to test them, he performs experiments first and tries to decipher his results later. He must sift through the range of chemicals produced by the genes people have, the food they eat, the drugs they take, the diseases they suffer from and the intestinal bacteria they harbor.

Those bacteria in particular have become Nicholson's prime focus. They influence how our bodies break down food and drugs and may explain why food affects people differently. For instance, some people cannot derive

benefit from one of soy's components because they lack the gut microbes necessary to process it. Although deciphering which metabolites come directly from our gut microbes can be difficult, in some cases it is easy—they are the chemicals that are not produced by cells or ingested in food.

Nicholson focuses on these chemicals both because little is known about them and because they appear to be highly relevant: recent research suggests that gut microbes play a crucial role in human health and disease. They help us absorb nutrients and fight off viruses and "bad" bacteria; disrupting intestinal colonies, such as with a course of antibiotics, often leads to digestive sickness. In fact, Nicholson says, "almost every sort of disease has a gut bug connection somewhere."

Perhaps the most well-known disease-causing gut organism is the bacterium *Helicobacter pylori*, which can trigger peptic ulcer. In the past few years, scientists have linked obesity to the relative abundance of two dominant intestinal bacterial phyla and found that dysfunctional intestinal bacteria are associated with nonalcoholic fatty liver disease, inflammatory bowel disease and some types of cancer. Nicholson even speculates that the organisms could play a role in neurological disorders, such as attention-deficit hyperactivity disorder, Tourette's syndrome and autism. "We have some evidence now that shows that if you mess around with the gut microbes, you mess around with brain chemistry in major ways," Nicholson remarks. He currently collaborates with microbiologists to match metabolites with specific bacteria—there are thought to be 1,000 species and more than 10 trillion bacterial cells inside us at any given time.

This identification process has only recently become possible. Although scientists have been able to extract gut bacteria from fecal samples for many years, it has been next to impossible to culture the samples afterward because they survive only in highly acidic, oxygen-free environments. Thanks to new DNA-sequencing technologies, scientists can now identify gut bacteria fairly easily, and there is growing interest in doing so: the National Institutes of Health launched its Human Microbiome Project last December with the goal of fully characterizing the human gut flora.

Once investigators can correlate metabolites with health, it may one day be possible, Nicholson says, to make urine sticks similar to those used in pregnancy tests to regularly check the fitness of our gut flora. Some companies have already begun selling food products to help keep these populations in line—with live beneficial bacteria (probiotics) or compounds that help these species grow (prebiotics), or combinations of the two (synbiotics). Unfortunately, these medications typically fall into the category of "functional foods," which means they are rarely tested in clinical trials. One exception is VSL #3, a combination of eight bacterial species sold in packet form by the Gaithersburg, Md.–based VSL Pharmaceuticals. In double-blind, placebo-controlled trials, the colonies effectively treated ulcerative colitis and irritable bowel syndrome.

Many possibilities exist for bug-based drugs, and there is a strong need for them, Nicholson maintains. According to a study published by scientists at the pharmaceutical giant Pfizer, the human genome offers only about 3,000 potential drug targets, because just a subset of genes produces proteins that can be bound and modified by druglike molecules. But "there are 100 times as many genes in the microbial pool," says Nicholson, who regularly works with drug companies to better elucidate how people metabolize medicines. He is "one of a few academics I've met who's interested in the pharmaceutical industry for its problems rather than just for its cash," comments Ian Wilson, a scientist working in England for the pharmaceutical company AstraZeneca. Wilson adds that Nicholson is always full of potential solutions, referring to him as "a bubbling mass of ideas."

Because genes provide only limited information about a person's risk for disease, Nicholson dreams of a time when physicians can provide personalized health care on the metabolome. Simple blood or urine tests would detect the risk of cancer or heart disease early enough to begin preventive therapy; drugs would be tailored to each person's metabolic profile—and in many cases, they would not target our organs but our bacteria. "It opens up visions of a future that we would never have suspected even a few years ago," Nicholson says. "Many microbiologists might argue this is fanciful, but you only make huge progress in science by thinking almost the unthinkable."

This story was originally printed with the title, "Going with His Gut Bacteria".

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