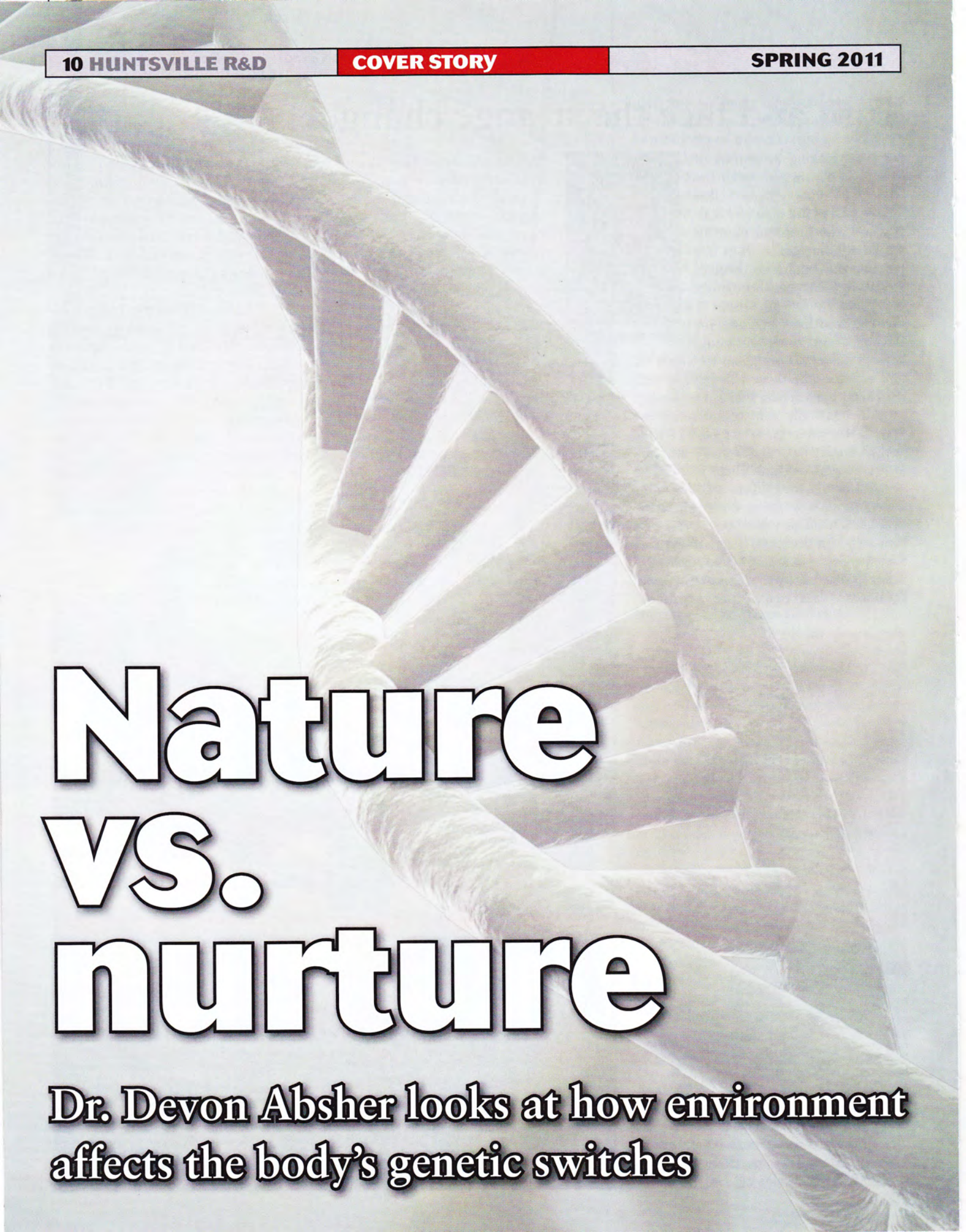

Nature vs. nurture

Dr. Devon Absher looks at how environment affects the body's genetic switches

by Diana LaChance

Over 81 million people in the U.S. have some form of cardiovascular disease, but there are 307 million Americans. So why do some people get the disease and not others? That's one of the questions Dr. Devon Absher, a geneticist at HudsonAlpha Institute for Biotechnology, is trying to answer.

Like generations of geneticists before him, Absher says his studies began by looking at "a single disease in classic genetic ways." In his case, that disease was Huntington disease, caused by a single genetic mutation and called a Mendelian inheritance disease because it follows a set of tenets about hereditary transmission that are derived from the work of pioneering 19th century geneticist Gregor Johann Mendel. Absher began where he did because of the state of the field. At the time, his choices were limited by technology to investigating one genome at a time.

As Absher completed his doctorate and was hired by the Stanford Human Genome Center, the focus on single-gene mutations began to give way to the study of more genetically complex diseases, thanks to a revolutionary scientific breakthrough known as genome-wide association studies (GWAS). GWAS examines the variation in all or most genes in different individuals of a species, in order to determine which variations are associated with different traits or diseases. Typically, a large sample of individuals is tested to determine variations and their effects. Computers are used to compare the DNA of individuals with a disease to those without disease to determine variations. "The GWAS approach allowed us to survey a lot of genetic variations in the genome, that is, hundreds of thousands of markers in the genome versus the one-at-a-time approach prior to this technology," says Absher. "So what would have taken years to do, we could now do in a matter of weeks."

The new technology gave geneticists a novel opportunity to look at diseases caused by multiple genes, like diabetes and heart disease. "When the new technology came about, it was clear we could study not just the simple diseases but also the very complex ones," says

Michael Mercier

Dr. Devon Absher works with a microarray reader to interpret human genetic data.

Absher, "so that was exciting." Unfortunately, "what the GWAS approach couldn't tell us was just how strong the effect of each gene was."

LIMITATION OPPORTUNITY

That inability to identify the impact of each gene ended up being a significant limitation. "In identifying risk profiles, GWAS technology was good for only minor components," says Absher. "Most of the variants that were discovered with GWAS technology merely increased the risk for a given disease by less than 5 percent, which ultimately isn't clinically relevant and won't impact disease management."

But for Absher, it was precisely what the GWAS approach couldn't tell geneticists that ended up saying the most. "Because we know there are things that were missed by the GWAS approach, we now know that diseases like diabetes and heart disease have a substantial heritability that can't be explained by the variants that have been discovered so far."

The search for that explanation created the field of epigenetics. "Epigenetics, which is what my lab is studying, is the modifications to the genome that occur after you've inherited your DNA sequence from your parents," says Absher. "It's basically the interpretation of your DNA sequence by the cells in your body."

A lot of that interpretation, says Absher, is developmentally driven and occurs as we age. "When we grow, all of our genes have to be switched on and off at different times to facilitate those big developmental changes. As different cell types differentiate into different tissue types, certain genes are expressed to bring about those changes." Thus, says Absher, "different parts of the body have different interpretations based on their specific purposes, all of which are controlled by the epigenome."

Another factor influencing the interpretation of DNA is the environment. "It's not clear yet how big a role those environmental factors play, but that's what we'd like to understand," say Absher. "Epigenetics not only has the potential to explain a lot of the risk factors for common diseases, but it also could potentially be a molecular read-out of your environmental exposure history. The epigenome is essentially responsive to environmental stimuli, and how it responds

may determine whether or not you get a common disease, like heart disease."

Though the term environment may suggest external factors, Absher says that personal choices like taking up smoking and what we eat can also be classified as part of our environment. "The most exciting things we're doing are looking at how diet influences our epigenome and also how the epigenome may influence our risks for getting autoimmune diseases like lupus and rheumatoid arthritis," he says.

Absher himself didn't discover these factors. "How your DNA sequence is interpreted has been known to some degree," he says. But it's only recently that geneticists have had the tools to analyze the epigenome in a comprehensive way, thanks in large part to the groundwork laid by the GWAS technology. "The GWAS technology was a huge advance. It may not have generated as many massive success stories, but it definitely changed how people thought about approaching genetic diseases, and that's continuing today with the new sequencing technology. We're reliving the GWAS revolution, but with the epigenome instead of the genome."

These advances in the field were what originally led Absher to HudsonAlpha. "When I was recruited here by Jim Hudson, it seemed like a great opportunity because HudsonAlpha was going to be an institute that was devoted to this emerging field," says Absher, "and it was just going to be exciting to start at ground level and see an institution like this develop along with this exciting field."

EPIGENETIC RISK FACTORS

Since arriving at HudsonAlpha, Absher has dedicated his time to a more complete understanding of the epigenome so that he and his colleagues "can delve into what epigenetic risk factors there might be for disease." That includes understanding the "natural epigenetic variation between people based on gender, age, ethnicity, and in response to common environmental insults like smoking or diet," he says. "Then, when we understand what the general population looks like, we can begin to compare a normal population to people who have heart disease or diabetes or bipolar disorder."

Another focus is on aging research. Age is a big influence on our DNA methylation, a process crucial to the development of normal organisms and to cellular differentiation. The effects of age on the process can contribute to disease, says Absher. "For example, if genes that were being expressed when we were younger are no longer being expressed, that can explain why certain diseases appear later in life."

Right now, Absher and his team are researching the chemical modifications that change with time that would predict an expression difference; they are not yet at the point of looking at the genetic expression itself. But Absher believes the research will progress. "The aging research we're doing," he says, "is laying the groundwork for future studies."

PERSONALIZED MEDICINE

The ultimate application of epigenetics is in personalized medicine, an emerging field in which a person's genetic and epigenetic data will be the determining factors with regard to how they are treated and medicated. And while Absher says

it's hard to say when that will happen on a large scale, he says there are already some examples of epigenetics being used in treatment today.

"Cancer is really the first testing ground for personalized genomic medicine, where the genetic makeup of your tumor can be analyzed and that information will likely influence how you're treated," says Absher. "For instance, there are known genetic markers that not only indicate your likelihood of getting breast cancer, but that can also be analyzed to determine which chemotherapies you'll respond to the best."

Even though scientists will one day be able to more reliably identify and analyze these genetic markers, Absher points out that they may never be able to manipulate the genes themselves. Personalized medicine, he says, "is probably going to be best achieved through new drugs than by actually changing the DNA sequence."

And perhaps that's for the best; gene manipulation tends to engender tricky ethical questions about privacy. "That's not my field of expertise and I don't have a lot of time to devote to that massive problem," Absher says, "but I do hope there will be systems in place to protect your genetic data from people who want to access it."

His work to focus scientific understanding of who is at risk for disease and then figure out how best to help them is the kind of real-world relevance that inspired Absher to become a geneticist. "I always wanted to be a scientist," he says, "but it seemed to me that genetics was the field that appeared to be advancing in a way that would have the biggest impact on human public health issues." Genetics is a competitive field, but it's also very collaborative, Absher says. "And genomics by nature is a collaborative science because of the expense and diversity of skills required to pull off a big study – everyone from clinicians, pathologists and epidemiologists to statisticians and molecular biologists."

And yet even with all of this collaborative expertise, there are still plenty of questions left unanswered. "I don't think you ever feel that you've achieved what you set out to achieve as a scientist. There are always new questions. Every answer you identify just generates more questions." says Absher. "It's a never-ending goal.

"I will probably retire," he says, "when they give me grant money to stop doing it!" ■