It's All in the Epigenes

Daniel Tencer, The Ottawa Citizen
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Arturas Petronis and Moshe Szyf know a little something about the fads of science. As pioneers in the budding field of study known as epigenetics, they took their share of abuse for supporting scientific theories that, for many years, were considered heresy among most scientists.

Mr. Petronis, head of epigenetics at the University of Toronto's Centre for Addiction and Mental Health, once applied for a research grant, and received the following anonymous written comment: "This is shit."

Mr. Szyf, a professor of pharmacology at McGill University in Montreal, had a proposed research article of his described as "a misguided attempt at scientific humour."

"What they do is crush any opinion that doesn't fit theirs," Mr. Szyf says. "I was told not to work on (epigenetics) if I ever wanted a career."

But what a difference a few years makes. Mr. Petronis and Mr. Szyf are now both mini-celebrities in the increasingly accepted field of epigenetics, which postulates that there is a "second code" of programming on top of our DNA, a code that -- unlike DNA -- can change during our lifetimes. In the past half decade, epigenetics researchers have theorized that our diet, the chemicals we are exposed to and even our behaviour towards one another can cause changes in the way that our genes are expressed -- and some of those changes may even be passed on to future generations.

That, in turn, has caused many scientists to rethink almost everything we know about how genetic information is passed on from parent to child. The traditional view of genetics has been almost deterministic: We are born with a code that dictates everything we are, physiologically. Our genes work the same way from the day we are born to the day we die. Our destiny, geneticists said, was written in our DNA. But now scientists are beginning to think that people aren't just shells to carry on DNA, but rather the "caretakers" of our genetic code. How we live, epigenetics researchers say, changes the way our genes function, and some of those changes can be passed on to our children and grandchildren.

This is a seismic shift in our view of heredity, but to understand how we got to epigenetics, first we have to look at genetics.

Remember the Human Genome Project? A decade ago, it was the darling of molecular biologists everywhere. Thousands of scientists in hundreds of labs deciphering every gene in the human body, creating a comprehensive map of human DNA structure. Once completed, proponents said, it would clue us in to almost everything that happens with humans: The likelihood of contracting a particular disease, the effectiveness of a particular treatment, even our propensity towards violent or criminal behaviour, would be read like an open book by geneticists.

But as genetics-mania swept the world through the 1990s and the Human Genome Project came to fruition, it slowly became clear that DNA would not answer all the questions scientists had believed it would. Researchers expected to find at least 100,000 genes in the human body, but found only a fraction of that -- less than 30,000. Diseases that were obviously hereditary, such as diabetes, did not seem to have a gene that determined if a person would develop the disease -- only genes that suggested a predisposition to the disease. Scientists cloned animals that, though identical in DNA to the original, had different physical traits from the original and suffered rare and inexplicable diseases.

Slowly, one of the fundamental tenets of genetics began to implode, and scientists had to start looking seriously at the idea that people inherit more than just genes.

"The scientific community thought that the Human Genome Project was going to be the complete story," says Jeffrey Besterman, chief scientific officer at the Montreal-based firm MethylGene. "People thought that just knowing the sequence of DNA in humans was going to be adequate. But it turns out that that's actually just the beginning."

Enter epigenetics. The basic science behind it had been theorized for some time. As much as 30 years ago, researchers proposed that there are chemicals that attach themselves to our DNA and change the way the genes function.

The idea was meant to answer some fundamental questions that genetics could not. One of those was the problem of identical twins. Even though twins carry the exact same DNA, it has been known for decades that one twin can develop hereditary diseases the other one does not.

This was the problem Mr. Petronis set off to explore about eight years ago. He noticed that in about half of the cases of schizophrenia found in twins, only one twin developed the condition, even though schizophrenia is widely considered to be genetic.

"After 50 or 60 years of study, there was no specific explanation of twin discordance," Mr. Petronis says. "Ninety-nine per cent of geneticists still believe environmental factors play a role, but when you ask for specifics, they can offer nothing."

By studying sets of twins where one twin had a psychiatric disorder and the other didn't, Mr. Petronis found the psychiatric patients had more in common with each other, epigenetically, than they did with their own twins.

"Any two random people share 99.7 per cent of their DNA, but at the epigenetic level, people are very, very different," Mr. Petronis says.

(This may also help to explain why recent attempts at cloning animals have met with less than total success. Scientists may be properly cloning the genetic sequence, but not the epigenetic sequence, giving rise to errors in replication.)

But the more controversial and eyebrow-raising aspect of epigenetics has to do with heredity. Evidence is beginning to mount that the epigenetic code, or at least parts of it, can be passed down from parents to their children.

One of the most prominent backers of this idea is Marcus Pembrey, a geneticist at University College London in the U.K. who studied the unusually detailed historical medical records of the isolated northern Swedish city of Overkalix. What Pembrey and his colleagues found was astonishing: The grandsons of men who experienced famine during mid-childhood went through puberty earlier and had longer lifespans, while the grandsons of men who were well fed in early childhood had an increased likelihood of diabetes. For females, the effect was similar but it was tied to the grandmother, rather than the grandfather.

"This is not a 'trickle-through' (of genetic material), this is clearly an evolved response," Mr. Pembrey says. He speculates that the purpose of such a response "would be to adjust early growth and reproduction to accommodate unpredictable or adverse environments."

Mr. Pembrey then looked at a contemporary study of two generations of families living in Bristol, England. He found that fathers who had started smoking before age 11 had sons who were significantly fatter than average. There was no similar effect on daughters.

For the first time, it seemed there was a scientific basis for that old adage that the sins of the father are visited upon the son.

Mr. Pembrey points out that his research is not the first evidence of genes having the ability to "remember" experiences. He cites a 1913 book by A.T. Swain, *The Earth, Its Genesis and Evolution Considered in the Light of the Most Recent Scientific Research*, which describes an obscure discovery by the famed 19th-century psychologist and physician Ivan Pavlov. In experiments on mice, Pavlov found that the children of mice who had learned to navigate a maze had an easier time learning the maze than their parents had -- and the grandchildren were able to learn the maze even faster than the children.

Other research in recent years has backed up Mr. Pembrey's hypothesis. Michael Skinner, director of Washington State University's Center for Reproductive Biology, exposed a group of pregnant rats to methoxychlor, an insecticide, and vinclozolin, a fungicide, both believed to cause infertility. He found that not only did the rats' offspring suffer from an increased infertility rate, so did the next three generations of descendants, without any further exposure to the toxins. His research identified two genes that appeared to have undergone epigenetic changes.

Mr. Skinner told the press: "This is a new paradigm for medicine and explains how our environment could impact our health, and generations to come."

Yet the idea that what we are exposed to can be recorded in our genes and passed on to our descendants is still controversial, even within the field of epigenetics itself.

"You ask five people to interpret these findings, you get five different answers," Mr. Petronis says, adding that the interpretation of cross-generational data is "very speculative."

"There could be lots of compounding factors."

That's something Mr. Pembrey and other epigenetics researchers concede.

"We have observed trans-generational responses, but of course that doesn't prove that they're (caused by) epigenetic inheritances," Mr. Pembrey says. "This is purely speculative. But not entirely wild speculation."

The major problem with epigenetics is that researchers still know so little about it. According to Mr. Szyf, we have yet to learn 90 per cent of what there is to know about how these processes work, and figuring it all out will be "much more complicated than reading genes," he says.

"Epigenetic codes are moving targets. They could change at any time. And the same gene, one gene, could have 700 epigenetic programs. So that complicates things."

Mr. Szyf, who is editor-in-chief of the newly-launched scientific journal Epigenetics, the first publication devoted to the field, has done research linking epigenetic changes to social interaction -- yes, even the way we behave toward one another can apparently change the way our genes work.

With his colleague Michael Meaney, a researcher at Montreal's Douglas Hospital, Mr. Szyf showed that rats whose mothers groom and lick them when they are young grow up to be much calmer than rats whose mothers neglected them.

Nothing surprising about that -- we all understand the importance of good child-rearing. But what was surprising was that Mr. Szyf and Mr. Meaney found epigenetic changes to be the cause. By nurturing their young, the rat mothers activated a gene that suppressed the creation of cortisol, a stress hormone. The neglected pups did not have that gene activated, produced more cortisol, and therefore were more stressed out.

Perhaps most interestingly, Mr. Szyf and Mr. Meaney were able to increase the well-nurtured rats' stress by injecting them with methionine, an amino acid commonly found in food supplements. Although in this case the treatment was negative (it caused the rats to have more stress), Mr. Szyf and Mr. Meaney demonstrated that something as simple as a chemical in our diet can cause fundamental changes in the way our genes work -- in this case, changing the individual's emotions and state of mind.

Of course, researchers are still many years away from developing drugs that could therapeutically alter the function of our DNA, but that doesn't mean they're not trying. Montreal-based MethylGene is one of the first pharmaceutical companies in the world to focus exclusively on epigenetic drugs.

Founded a decade ago, the company has developed two kidney cancer-fighting compounds, designed to "turn on" a gene that suppresses tumours. If it proves successful in trials, it would be one of the first medical treatments in the world built on the science of epigenetics.

Because cancer is a disease of the genes -- it is essentially the uncontrolled and unregulated reproduction of DNA -- it is an obvious first target for epigenetic medicine. But MethylGene CEO Don Corcoran says altered versions of the drugs could potentially work on other, non-cancer diseases.

By targeting different enzymes, MethylGene hopes to develop drugs that would aid in the fight against Huntington's disease, for which there are currently very few therapies, as well as fungal infections and diabetes.

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"So even though the diseases are completely different, you might be able to fix them with a similar process," Mr. Corcoran says.

But if serious progress is to be made in understanding epigenetics, it will require a thorough map of how the epigenetic code works. In 2003, a consortium of public and private firms in Europe began the first Human Epigenome Project, which aims to have 10 per cent of the human epigenetic structure mapped by this fall.

Just last month, the group released its first major findings, comprehensively mapping the epigenetics of three human chromosomes. The researchers found that about one-fifth of the genes in those chromosomes can have their behaviour changed.

But the European epigenome project is relatively small, with only three participating organizations. Last December, a group of 40 prominent cancer researchers called for the creation of a wide-scale Human Epigenome Project, one they expect would take at least a decade to sift through the complex data. With new research papers on epigenetics now coming out at a frenzied pace, the full-scale project seems increasingly likely to become reality soon.

So what can we glean from all this? We have reason to believe that the food we eat, the chemicals we ingest and even our parents' behaviour towards us can all change the way our genes function. But what can and should we be doing to protect ourselves -- and our descendants -- from harm? Few are willing to say just yet.

But Mr. Pembrey doesn't beat around the bush. "Childcare has a whole new meaning," he says. "Given that we have shown exposure-sensitive periods in mid-childhood and fetal life, the responsibility would appear to fall on the parents and those charged with the care and protection of children."

Mr. Szyf agrees that what we know about epigenetics adds a whole new moral dimension to our own behaviour, but he cautions against jumping to any conclusions about what parents should be doing, until we know more about how it all works.

"We shouldn't walk around worried that everything we do will affect our grandchildren," he says. "It will, but we can't do anything about it except to do the things we were taught to do through evolution or social evolution.

And we should be careful about changing things without knowing what we're doing. Because they may have consequences we never thought of."

Questions on Epigenetics

1. What is epigenetics? Give an example.

2. What were three clues that began to emerge in the 1990's suggesting the picture of DNA may not be complete.

3. What is the more controversial side of epigenetics ?

4. Very briefly discuss the two studies by Marcus Pembey.

5. What did the super famous Ivan Pavlov discover about rats?

6. Find three limitations or problems of knowledge with this new paradigm of epigenetics.

7. How could morality link with the science of epigentics?

Don't blame your genes

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They may simply be getting bad instructions—from you

GENES are acquired at conception and carried to the grave. But the same gene can be expressed differently in different people—or at different times during an individual's life. The differences are the result of what are known as epigenetic marks, chemicals such as methyl groups that are sometimes attached to a gene to tell it to turn out more of a vital protein, or to stop making that protein altogether.

Many researchers believe epigenetic marks hold the key to understanding, and eventually preventing, a number of diseases—and one whose epigenetic origins they are particularly interested in is type 2, or late-onset, diabetes. Juleen Zierath and her colleagues at the Karolinska Institute in Stockholm, Sweden, are trying to find out how people develop insulin resistance, the underlying cause of type 2 diabetes.

Insulin is a hormone produced by the pancreas. When all is going well, it lets cells know when they need to mop up glucose from the blood, usually just after a person has eaten. If the hormone is absent or is produced in insufficient quantities because of damage to the pancreatic cells that secrete it, the result is classical (or type 1) diabetes. But people with insulin resistance—and thus the late-onset version of the disease—do produce insulin. Their problem is that their glucose-absorbing cells cannot heed its advice. The sugar stays in their bloodstreams, where it damages the vessels, leading to ailments such as heart disease, kidney failure and blindness.

As they report in *Cell Metabolism* , Dr Zierath and her team decided to look at one of the main consumers of glucose: muscle tissue. They took muscle biopsies from 17 healthy people, 17 people with type 2 diabetes and eight people with early signs of insulin resistance, so-called "pre-diabetics". They then compared the patterns of the methyl groups attached to the genes of the healthy volunteers with those of the diabetic and pre-diabetic ones.

As it turned out, they found hundreds of genes in which the patterns differed systematically, so to whittle the problem down they concentrated on those involved in the function of the mitochondria. These are the components of a cell that extract energy from glucose and use it to manufacture a chemical called ATP, which is the universal fuel of biological processes. Having fewer or less effective mitochondria causes a drop in demand for glucose, and might thus cause a cell to become insulin resistant.

Even narrowing the question down like this, though, left 44 genes to look at. Of these, Dr Zierath and her team picked one called PGC-1 alpha for further study. This gene is involved in the development of mitochondria, and the extra epigenetic marks the researchers found on it in diabetics and pre-diabetics had the effect of instructing the cells the marked genes were located in to produce fewer and smaller mitochondria than is normal.

The next question was how those marks got there. It is well known that poor diet and lack of exercise make insulin resistance more likely, so one hypothesis is that these things change the epigenetic marks on genes such as PGC-1 alpha. To test that idea, the researchers bathed cells in glucose and fats (chosen as surrogates for bad diet and lack of exercise for obvious reasons) and also in inflammation-producing proteins called cytokines. These proteins, they knew, are produced abundantly in the obese. And obesity, the consequence of bad diet and lack of exercise, is another risk factor for type 2 diabetes. Lo and behold, doses of both fats and cytokines caused PGC-1 alpha to be methylated.

Next, Dr Zierath wanted to know if she could prevent that. So, this time, before bathing the healthy cells in fats or cytokines, the team added a chemical that blocks the activity of DNMT3B, an enzyme which they found methylates PGC-1 alpha. When that was done, no extra methyl groups appeared.

These findings have two interesting implications. First, the fact the team was able to stop PGC-1 alpha being methylated suggests that a drug might be developed to do the same. Second, they show that bodily abuse can stretch all the way down to the genetic level. As Dr Zierath puts it, “we are not victims of our genes. If anything, our genes are victims of us.”