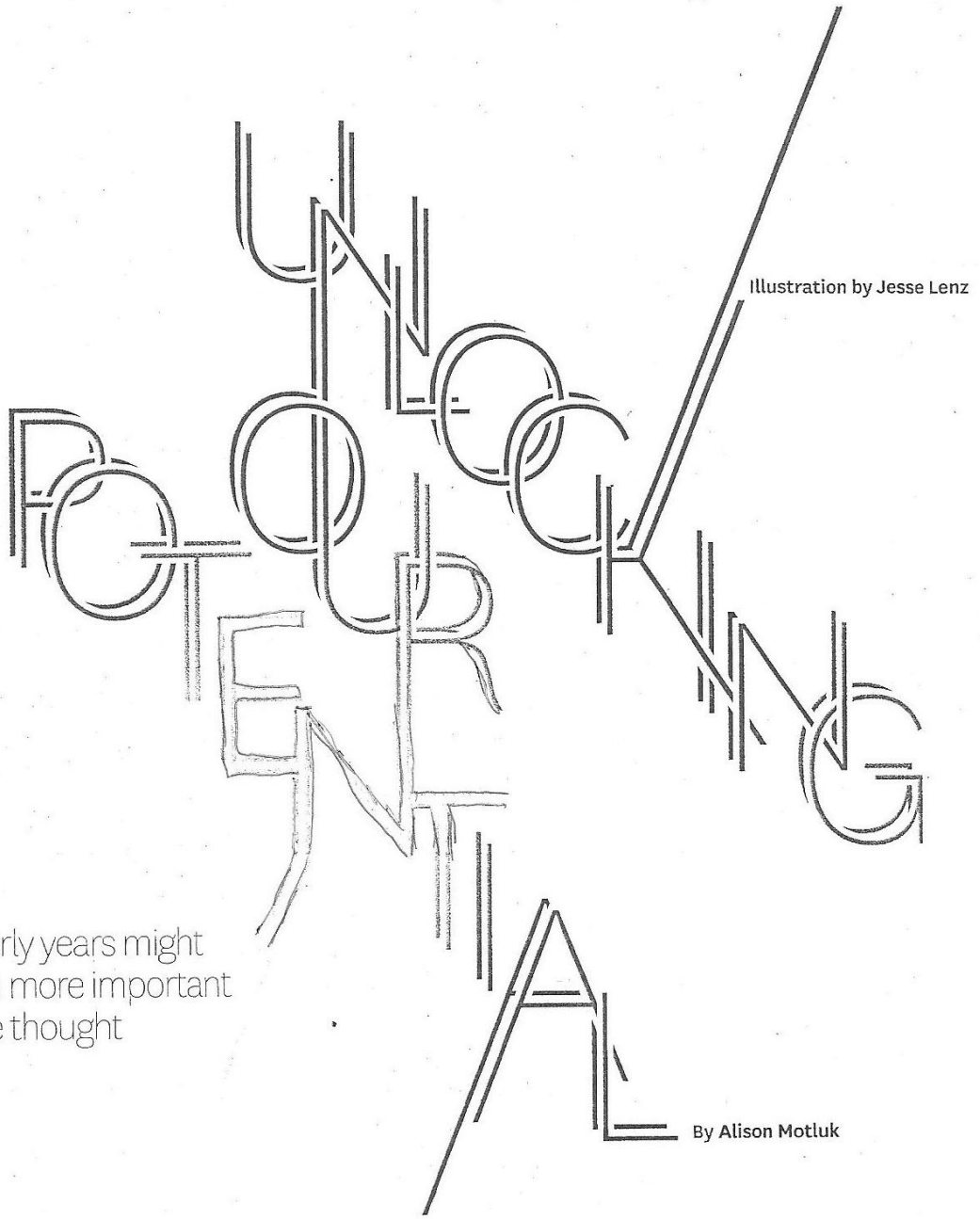

Illustration by Jesse Lenz

Unlocking potential

Life's early years might be even more important than we thought

By Alison Motluk

BY THE TIME A CHILD SETS FOOT in kindergarten, much about her future life has already been set in motion – everything from her ability to concentrate and learn, to her lifetime chances of suffering from obesity or heart disease or depression. Evidence is mounting that what happens in the first four years of life can be critical to long-term well-being. However, as a society we still don't do enough to optimize this important period, or even to stave off the biggest dangers.

Now, a group of researchers at the University of Toronto from a variety of disciplines – medicine, psychology, education and genetics – is proposing to create an Institute for Human Development. Its central mission will be to investigate how to make the most of these early years. The question, the researchers agree, is no longer whether very early life is pivotal in determining later-life health and well-being – we know it is – but rather which experiences and exposures are most important, which genes, in interaction with the early environment, put a person at the greatest risks and what practical interventions can make the most difference.

The new thinking ultimately aims to change how very young children are cared for and educated. Rather than waiting for problems to appear before taking action, these researchers advocate stepping in to prevent them from developing in the first place. This will pay off down the road

Even subtle differences in the way a parent behaves toward us in the early months of our lives can alter the way we develop emotionally, socially and cognitively

in improved health. "If we know what someone's at risk for," says Stephen Lye, a professor of obstetrics and gynecology who studies fetal health at the Samuel Lunenfeld Research Institute, "maybe we can do something early enough that we can prevent it."

Scientists have understood for decades that we inherit a complement of genes that are a combined subset of the genes of our biological parents. And while these genes give detailed instructions about how we develop, we now know they will not dictate our fate. What has become increasingly clear in recent years is that our genes are in constant conversation with our environment, and they are modified by the nutrients, pathogens and even experiences that we encounter throughout our lives.

This gene-environment dialogue starts in the womb. "About 20 years ago, there was the beginning of a new understanding," says Lye. "The period of development during pregnancy and early life is not just important for a healthy baby, but also for a person's well-being later in life." In short, the kind of experience we enjoy in utero will to a significant degree influence our health and welfare for the rest of our days.

The first strong evidence of this came in 1989 from work by David Barker, a British physician and epidemiologist. Drawing from a large population in the U.K., he looked at whether birth weight affected how likely a person was eventually to die of heart disease. As babies, all the people in the study had been in the normal weight range. But it turned out that the less they had weighed at birth, the greater at risk they were for heart disease. Exactly why this happens is still a matter of speculation – perhaps a fetus is pre-programmed in the womb to use calories sparingly, only to be born into a world of plenty, or perhaps smaller babies are less able to muster the resources to construct hearts and kidneys well.

Since that landmark study, low birth weight has been associated with other features of what has now become known as "the metabolic syndrome." These include hypertension, stroke, insulin resistance, Type 2 diabetes and a combination of high blood sugar and high cholesterol. Intriguingly, psychosocial traits such as poor concentration, anxiety and depression can also be tied back to conditions in our earliest days.

Lye admits that these big epidemiological studies, while provocative, don't provide solutions for individuals. "Population risk is not much use to parents with young children," he says. "What they really want to know is how a particular environment will affect their children's genes. We have to do research to more fully appreciate what these associations are."

Not everyone who faces adversity early in life is negatively affected by it. "The same environment can have a dramatically different effect on individuals, depending on their genetic makeup," says Marla Sokolowski, a University Professor in the department of biology at U of T Mississauga. We used to think that a trait was the product of either nature or nurture, but research on fruit flies and other organisms has made it clear that the interplay between genes and the environment is important.

For instance, in the 1980s, Sokolowski discovered the foraging gene in fruit flies, which influences several characteristics in the fly. Like most genes, this one comes in different forms, or variants. Flies with the "rover" variant of this gene produce more of a foraging enzyme in the brain. As a result, they keep moving from food patch to food patch, eat on the go, store less fat and have a stronger short-term memory. Flies with the "sitter" variant have less of the foraging enzyme, dine longer in one place, eat more overall, store more fat and have a better long-term memory.

Sokolowski points out that it's important to remember that gene expression can be mediated by circumstances. The "rover" and "sitter" characterizations describe how the flies behave when food is plentiful. When food is scarce, however, Sokolowski and her research team found that rovers turn into sitters. This is true not only in terms of behaviour, but at the molecular level of the gene as well: less of the foraging enzyme is produced in underfed rovers. In other words, the environment and genetics interact to affect what an organism is like. What researchers working in the relatively new field of epigenetics are finding is that environmental influences can turn certain genes on or off, or modify their expression up and down like a volume control.

What we also want to know, of course, is how gene-environment interactions play out in humans. For several years, Lye has been collaborating with a team in Perth, Australia, which has been following a cohort of children since before they were born. The Raine Study, as it is known, recruited 2,900 women in week 18 of their pregnancy and collected a wealth of data about what they were eating, their mental-health status and how settled things were at home in an effort to know as much as possible about the conditions of the fetuses they were carrying.

After the children were born, data collection continued. The researchers were interested both in the inputs – how well they ate, for instance, what their schooling was like and what kind of parenting they got – but also their outcomes:

how they grew, how healthy they were, how well they fared in school and in life.

As one might expect, some kids did well despite adversity and others were hampered by it. Some were healthy, others less so. To try to explain these differences, Lye and his colleagues undertook a whole genome scan of 1,800 of the children. The kids in the study are now 19 or 20 years old – too young to have full-blown cardiovascular disease or Type 2 diabetes, but old enough to be showing tendencies toward these sorts of conditions.

As part of the investigation, the research team examined a gene called FTO, a variant of which is known to be associated with obesity. In the Raine children, those who have the gene variant linked to obesity tend to have higher body mass index. But even more intriguing was what the team found when they looked specifically at the Raine girls who had this variant of the gene but who were *not* particularly overweight. Preliminary analysis has found that the girls with a near-normal body mass index all had something in common: they were more likely to have been breastfed for at least six months. It's a fairly simple intervention, but has huge implications. "If [the analysis] is confirmed, it shows that it is possible to alter the environment of the child and have a more beneficial outcome later in life," says Lye.

But altering the environment cuts both ways. Just as simple interventions can change things for the better, so too can they change things for the worse. Stephen Matthews, a professor in the department of physiology, has been studying the effects of stress hormones on the developing fetus. On the one hand we know that a short burst of the stress hormone cortisol, which happens late in gestation, is critical to the development of the lungs. It's so important, in fact, that mothers of babies at risk of being born before the natural cortisol surge receive injections of synthetic cortisol.

On the other hand, too much cortisol may do harm. Pregnant women who experience intense stress even for short periods are more likely to give birth to children who go on to have disorders such as anxiety and learning troubles. So the researchers were curious what other effects these injections of synthetic cortisol, or highly stressful maternal experiences during pregnancy, might be having. They were particularly interested in the effects on the infant's brain.

Matthews' team used guinea pigs as their model animals, because they have similar placentas to humans and give birth to similarly developed offspring. What they found was that when a pregnant guinea pig experiences stress or gets a stress hormone injection, her pups' brains can be permanently altered. The exact effect will depend on the sex of the fetus, as well as when the hormone surge happened. But the studies showed that the control centre for hormone regulation is permanently changed, as are the brain neurotransmitter systems.

Ultimately, this may be the mechanism by which stress during fetal life can affect endocrine function and behaviour throughout the rest of the animals' existence. Matthews' research and that of others has found that adversity during pregnancy is associated with offspring that tend to be more fearful, impulsive and inattentive. Perhaps most alarming of all is Matthews' discovery that sometimes these cortisol effects can last beyond the exposed generation and affect their children – and perhaps their grandchildren. "There seems to be a trans-generational memory of adversity in early life," says Matthews.

The conversation between our genes and our environment continues after we are born. Though we are no longer in our mother's womb, we are still very much affected by her interaction with us. Even subtle differences in the way a parent behaves toward us in the early months of our lives can alter the way we develop emotionally, socially and cognitively.

Landmark animal studies by Professor Michael Meaney of McGill University found that reduced maternal care affected how certain genes in the offspring expressed themselves. To find out more about how the early environment, including maternal behaviour, can affect child development, Matthews and Meaney are co-directing a large, multidisciplinary study that follows groups of mothers and children in Ontario and Quebec.

Alison Fleming, a psychology professor at U of T Mississauga who has spent her career studying parenting behaviour, is collaborating with Matthews and Meaney on the mother-and-child study. She is interested in how a new mother's own early life experiences might interact with her genes to influence her parenting style. Over the course of more than six years, Fleming and her colleagues have paid 20 home visits to each of 204 mothers, observed their parenting, and measured hormones. The study included a session in which the researchers videotaped mother-infant interactions and then measured, among other things, how attentive the mother was to her six-month-old baby.

The researchers also took a cheek swab to do genetic analysis and inquired through questionnaires about the mother's early upbringing. When they analyzed the genetic information and put it together with the mother's own background, the findings were intriguing. The mothers with at least one copy of a particular gene variant – best known for its association with depression and anxiety – turned out to be much more attentive to their babies. Mothers who both lacked this variant and had an adverse early childhood were significantly more likely to ignore their infants. Even a mother's perceived attachment to her baby seemed to be associated with interaction between her genes and her early childhood environment.

Part of what makes the findings so provocative is that the gene variant that made for more attentive mothering has long been considered a "vulnerability" variant, because it appears to put people at greater risk for depression and

Eric Jackman

Opening Doors

Gifts totalling $8 million for the newly named Dr. Eric Jackman Institute of Child Study will help position U of T as a global leader in the study of early human development

Students from the Dr. Eric Jackman Institute of Child Study

When Eric Jackman made Canada's biggest-ever private donation to early childhood development last year – a $5-million gift to the Institute of Child Study, which now bears his name – he was hoping to make a point. How we spend our early childhood, he believes, helps determine how we spend the rest of our lives. "We know more and more about the extraordinary importance of infancy and childhood to getting people off on the right start in life," he says. "I wanted to shine a spotlight on that."

Jackman has long been interested in early childhood development. He earned his undergraduate degree in economics and tried his hand in the investment business, which he describes as "not satisfying for my soul." Then, while travelling – and experiencing the cultures of Asia, the Middle East and Europe – he became fascinated with how people live. He went back to U of T for his master's in psychology, earning his degree in 1962.

But here in Canada at the time, rat mazes and pigeons pecking at dots were all the rage in psychology, he laments, and he wasn't terribly interested in that. So he set off to the University of Chicago, where, through the university's Committee on Human Development, he studied psychology, cultural anthropology, sociology and biology, becoming a "human developmentologist." He later practiced in Chicago as a clinical psychologist, both in the mental-health system and in private practice. Though Jackman eventually migrated back to the world of finance, where he currently runs Invicta Investments, he's kept his oar in psychology through philanthropy and volunteer work with organizations such as the Psychology Foundation of Canada. "That organization chose some years ago to not get involved in cures," he says. Instead it focused on prevention and health promotion, an approach championed by U of T's proposed Institute for Human Development, and by Jackman himself. "We have to start kids off as happy, resilient, energetic, motivated people, who understand their mind, their body and their soul," he says.

Jackman's own early education, and that of his siblings, began at the Institute of Child Study, which at the time was called the St. George's School of Child Study. He still remembers the tricycles, the little sidewalks and the sandboxes. "The thing I didn't like was naptime!" he laughs. "I wanted to play!"

Prof. Janette Pelletier, director of the Dr. Eric Jackman Institute of Child Study, says Jackman's gift – and a $3-million contribution from Margaret McCain and the late Wallace McCain – will support building expansion and renovation, enhance community programming, and ultimately position U of T as a global centre of excellence in early human development. (Margaret McCain, a long-time children's advocate, earned a bachelor's degree in social work from U of T in 1955. She co-wrote a report for the Ontario government in 1999 that underscored the importance of life's first three years.)

The institute's new wing – the Margaret and Wallace McCain Pavilion – will feature modern classrooms and a large auditorium-gymnasium to better serve the Jackman Institute's on-site graduate program. The addition will also allow research activities in the Dr. R.G.N. Laidlaw Centre to expand, and it will provide much-needed space to strengthen physical activity and health programming for the laboratory school students in Nursery through Grade Six. The Dr. Eric Jackman Institute is one of the few places in the world where research, graduate teacher training and an elementary laboratory school occur in one place. It is seeking another $1 million to complete its fundraising campaign. – ALISON MOTLUK

other mental-health issues. But Fleming and others now argue that rather than predisposing people to poor mental health, this gene variant may just make someone more sensitive to environmental effects. "These gene variants are not necessarily about enhancing effects of negative environments," says Viara Mileva-Seitz, a graduate student who works with Fleming and carried out the study, "but about enhancing sensitivity to any environment, be it positive or negative. You need to look at both sides of the coin. Presumably there's a reason why these genes survived. It is unlikely that they are maladaptive in all environments."

Jennifer Jenkins, a developmental psychologist with the Ontario Institute for Studies in Education, is studying how family relationships interact with various genes to affect children's development. Evidence from other labs suggests that the context in which children grow up, including the family environment, can affect not only psychosocial well-being (such as how secure a child feels) but also the propensity

to develop conditions such as diabetes or obesity. "What we know about environmental effects provides us with plenty of room for intervention," says Jenkins.

The proposed Institute for Human Development has set its sights beyond health. It will also tackle a variety of issues in learning, care and education, in particular to improve how young children self-regulate, says Carl Corter, who is another of the institute's key players and a senior researcher at OISE. This ability, which encompasses skills such as self-discipline, perseverance and emotional control, has been shown to predict later-life health, wealth and involvement in crime. Three-year-old children, for instance, who had low levels of self-control, were significantly more likely at age 32 to be drug-dependent, financially struggling or convicted of a crime.

The province and the education system acknowledge the importance of good self-regulation, says Corter. Teachers confirm that kids with limited self-regulation present huge challenges to schools, and Ontario's guidelines for child care, family support programs and kindergarten all emphasize how important it is. Newer report cards even try to measure it and suggest "next steps" for how the child can improve. "There's increasingly the view that we have to think not just about how core academic content is delivered," says Corter.

But educators have not been prepared to deal with the emerging knowledge about self-regulation in children. "Early education has long recognized the importance of creating feelings of attachment and security among children. That thinking has dominated so much of academic practice," Corter says. This is still important to do but is being supplemented by new understanding about additional processes that lead to healthy development. We're now learning that what kids really need is graded challenges, he says. This fosters self-awareness in children about their own actions. Corter would like researchers to spend time observing child-care centres and full-day kindergarten classrooms to critically examine what we are currently doing and how we could improve strategies for helping kids regulate their own behaviour and make the most of their learning experiences.

Initially, Corter says, ideas about how to foster self-regulation will be tested through the university's laboratory school at the Dr. Eric Jackman Institute of Child Study. The institute is a hub where teachers, political and educational leaders, developmental scientists and parents all meet in the interest of putting research and ideas about education into practice. "It's a mini-institute of human development," he says.

The same approach used to study how early experiences affect physical and mental health will be used to tackle problems of self-regulation. Researchers will also work hand in hand with the Ontario Birth Study, which, once launched, will recruit pregnant women from Mount Sinai Hospital. The study will follow children starting early in their gestation and will continue to track and monitor them as they grow up. It will be similar to the Raine study, but instead of being restricted to a single cohort, it will be ongoing. With the help of DNA analysis, the researchers will explore how genes and environment work together to influence each child's life course – in terms of metabolic health, mental health and self-regulation, among other things. The goal is to use the data to inform doctors and educators about how to care for and promote well-being in the next generation and how to intervene to mitigate problems and then monitor how those interventions fare.

The proposed Institute for Human Development will bring together research scientists with the people most able to deliver interventions: clinicians, social workers and educators.

In Corter's larger vision, the schools won't just be setting curriculum or determining interventions to improve kids' self-regulation. Schools will help provide parenting classes, pediatric care and social services. "We're trying to get the education system to think health," he says. "There will be more overlap in the future."

The proposed Institute for Human Development will bring together research scientists with the people most able to deliver interventions: clinicians, social workers and educators. With its scope reaching from basic scientific research into health and all the way into education, and then, uniquely, with those results channelling back into scientific research, the new institute will be unlike any other, says Sokolowski. "There's nowhere else in the world where you will find this kind of facility combining discovery and translational research on this scale," she says. The concentration of expertise is also one of a kind, she adds. Sokolowski credits the Canadian Institute for Advanced Research (CIFAR) for bringing the importance of early human development into the mainstream. Dr. Fraser Mustard, the founder of CIFAR, has also been a driving force in this area for many years, she says.

What will distinguish the institute, according to Lye, Sokolowski, Matthews and Corter, is its focus on prevention and promotion, rather than measuring or managing risk and disease after they have already begun to unfold. "We're very determined that this isn't just a research project," says Lye. "There have got to be outcomes."

Alison Motluk (BA 1989 Trinity) is a journalist in Toronto.

Read a feature article about the Dr. Eric Jackman Institute of Child Study at http://www.magazine.utoronto.ca/feature/head-of-the-class/