The experimental diet that mimics a rare genetic mutation

April 12 2016, by Peter Bowes, Mosaic

With the help of a small stool, Mercy Carrion clambers onto an examination table. The obese 50-year-old woman stands just 115.6 cm (3'9.5") tall. Despite being overweight, Mercy shows no sign of developing diabetes and has remarkably low blood pressure at 100/70. "That's why they don't care much about their weight," says her doctor, Jaime Guevara-Aguirre.

Mercy, who has a rare genetic disorder, is one of his long-term patients. She and her peers know they are in some way protected from diabetes, cancer and a number of other diseases that threaten the rest of us as we age. As such, they have a happy-go-lucky attitude towards health and fitness.

Mercy giggles as she tells her doctor that dieting is not her. She enjoys a typical high-calorie Ecuadorian diet, where rice accompanies almost every meal. The next day, we visit her at home in a poor, farming community in El Oro province, a one-hour flight away. Her refrigerator is stocked with red meats, bologna and eggs. Bananas are plentiful, and usually served fried.

This high calorie-diet contributes to her excess weight. But, paradoxically, the biology that has driven her weight gain could also be what protects her from disease. I'm fascinated, partly because this woman's condition relates so much to a diet I've been trying for the past three years.

Actually, it is somewhat misleading to call it a 'diet'. It certainly leads to short-term weight loss, but researchers prefer to see it as an investment in the future. It could, they say, start a regenerative process that will lead to improved health and longer life. If the theory stands, I could enjoy a lower risk of cancer, a strengthened immune system, improved cognitive ability and little to no chance of contracting diabetes.

I signed up to it three years ago as part of an intriguing clinical trial at the University of Southern California, Los Angeles. It involved reducing my calories by up to two-thirds, over five consecutive days, once a month for three months. The rest of the time I ate normally, without restrictions. Three years on, I have just completed my tenth Fasting Mimicking Diet.

The science is based on years of experimentation with yeast, worms, flies, mice – and studies of Ecuadorians with a form of dwarfism.

An Israeli researcher, working with people who had stunted growth, first identified the condition in the late 1950s. But it took Zvi Laron a further two decades to unravel the mechanism behind Laron syndrome, as it later became known.

Laron found that his patients had the body's primary growth hormone (GH) in abundance in their bloodstream, an observation that seemed to defy logic, since they had stunted growth. He eventually concluded that their dwarfism was caused by damage to GH receptors in the liver. It results in extremely low levels of another growth hormone, known as insulin-like growth factor-1 (IGF-1).

In the normal sequence of events, GH, secreted by the pituitary gland, locks on to GH receptors, initiating the production of IGF-1 in the liver. But if a mutation has caused the receptors to be faulty, there are two major effects: the body is unable to generate IGF-1 and the individual is

more sensitive to the hormone insulin, which helps regulate the amount of sugar in the bloodstream.

Because IGF-1 stimulates cells to grow and divide, lack of it is linked to a lower risk of cancer – uncontrolled cell division. Meanwhile, a greater sensitivity to insulin helps to prevent diabetes.

There are about 350 people in the world living with Laron syndrome. Laron himself identified cases in the Middle East, Europe and Asia, but about a third of those with the condition live in Loja, a remote, mountainous province of southern Ecuador. Known colloquially as Larons, they grow to about a metre in height and experience delayed puberty. Men do not reach full maturity until they are at least 22. For women it is between 16 and 19.

They do not like being short and hate being described as dwarfs, but the recessive gene behind their stunted growth could prove to be an immensely valuable accident of nature, for they appear to have what most people want: an ability to stave off debilitating diseases.

Historians think that Ecuador's Larons descended from conversos, Sephardi Jews who converted to Christianity and fled to South America at the time of the Spanish inquisition in the 16th century. At first there may have been just one person who had no outward symptoms but who passed on a recessive gene. It is assumed that, over generations, inbreeding in the small, isolated Ecuadorian community led to children being born with copies of this gene inherited from both parents – which causes Laron syndrome.

It was Jaime Guevara-Aguirre, Mercy's doctor, who in 1988 began studying the people with Laron syndrome living in Ecuador. With a dogged determination to unravel the mechanisms behind their condition, Guevara-Aguirre has been caring for about 100 Laron patients for the

past three decades. He visits them at home, takes samples, tests their blood and meets with their families.

During this time, Guevara-Aguirre has had only one Laron patient die of cancer and none from diabetes. This is in stark contrast to their relatives without Laron syndrome, who have a death rate from cancer of 17 per cent and 5 per cent from diabetes. Despite higher body fat, Larons have a lower resistance to insulin and a much lower incidence of diabetes. And they do not need to fast to achieve this. They eat what they like and are often obese. Because the mutation in their GH receptors blocks the production of IGF-1 in their bodies, they can get fat and still not develop diabetes.

"They're really the human version of what the research of many groups has shown in simple organisms," says Valter Longo, biogerontologist and director of the University of Southern California Longevity Institute. Longo and others have shown that you can significantly extend the life of yeast, nematode worms, flies and rhesus monkeys by introducing mutations that affect growth. For instance, a mutation in a single gene can give yeast – the simplest of organisms – a lifespan three times longer than normal. Scientists have also found that mice, when genetically modified so that their GH receptors are impaired, enjoy lives 40 per cent longer than normal. What's more, their longer lives are also free of major diseases.

"It's a remarkable increase in what's called health span, in addition to longevity," says Longo. And, he believes, the same could apply to humans. The ageing process appears to be controlled, in distantly related organisms, by similar genes and mechanisms. There are a whole range of studies that support the view that growth-control pathways are involved in promoting the diseases of old age, says David Gems, Professor of Biogerontology at the Institute of Healthy Ageing, University College London. "The thing about the Laron dwarfs in Ecuador," he says, "is that

they provide some tantalising evidence that this control of ageing extends from the animal models up to humans."

The food is called ProLon. It comes in small, neatly organised, white boxes. They contain vegetable-based soups, tiny energy bars, kale biscuits, herbal teas and an energy drink, together with a warning that the Fasting Mimicking Diet (FMD) is "not intended to diagnose, treat, cure, or prevent any disease".

The meals were first supplied to me in 2013, free of charge as part of the clinical trial, by researchers at the University of Southern California. They are made by L-Nutra, a Los Angeles-based company founded by Longo. ProLon is not commercially available, although L-Nutra has plans to start selling it sometime in 2016. (For the purposes of full disclosure, Longo says he has no financial interest in the product. He has started a non-profit foundation called Create Cures, which, he says, will focus on providing fast interventions, "similar to fasting", to treat conditions like cancer, Alzheimer's disease and multiple sclerosis, for which there are currently no cures. Longo plans to donate all of his shares in L-Nutra to the foundation.)

The clinical trial was set up by Longo's group to see whether people could cope with such a strict dietary regime. The laboratory-formulated food is designed to deliver maximum nutrition through minimum calories. Based on two decades of research, the idea is to produce the benefits of fasting without actually fasting.

The practice of fasting is an age-old tradition in many societies and religions. It leads to a vast array of changes, at a cellular level – including a drop in levels of IGF-1. In other words, it has a similar effect on my body to that of the genetic mutation that causes Laron syndrome.

But very few people are prepared to endure an extended period of time

with little food, even if it is beneficial to their health. For most people, even a five-day regime is a daunting prospect. The FMD aims to lessen the burden of a complete fast while still promoting the positive aspects of food deprivation.

Longo and his team of nutritionists believe it is necessary only to do the diet three or four times a year to reap the benefits, although there is no 'one size fits all' and the recommended frequency will depend on an individual's health and general eating habits. Longo favours a low-protein (preferably plant-based) diet, in between stints of FMD, to optimise its effects. Those who default to a typical Western high-calorie diet, rich in red meats and processed foods, may, Longo says, need more frequent interventions to have a lasting impact on their health.

Longo's team of researchers refer to it as a "periodic fasting regime". Each cycle brings a rollercoaster of emotions and physical challenges, as I found out as one of their first human guinea pigs.

The regime requires 100 per cent adherence. My first instinct was to binge-eat in the days before it all started. This, as I soon learned, is futile and counter-productive. The best preparation is to gradually ease into the five-day plan. It is far easier to eat smaller meals in the run-up and cut out snacking and caffeinated drinks (which also come with high calories) altogether, over a period of days before the FMD, than to suddenly and extremely change your food intake.

On paper, the first day should be the easiest, with ProLon meals containing 1,090 calories (10 per cent protein, 56 per cent fat, 34 per cent carbohydrates) – more than the four remaining days, which only have 725 calories (9 per cent protein, 44 per cent fat, 47 per cent carbohydrates). Yet I found it could be the most challenging.

Some volunteers complain of pounding headaches, which can be caused by dehydration as cutting down on food also reduces your water intake (the FMD does allow for unlimited drinking water). Headaches can also occur as the brain gets used to burning fat instead of glucose for fuel. And for heavy coffee drinkers, the sudden drop in consumption can play havoc. With the researchers' permission, though, I continued to drink one cup of black coffee per day. They allowed it for trial subjects like me who felt that their daily espresso was so important that they might not be able to complete the diet without it (a single cup, with no milk or sugar, did not significantly affect my daily intake of calories).

The headaches normally ease after a few hours and, after a number of cycles, were not a problem at all for me. It is as if the body learns what to expect and quickly adapts to the temporary state of caloric restriction. Hunger pangs come and go. After enduring the first few waves of discomfort, stomach rumbles give way to a Zen-like state of mind and body.

This makes some sense – a feeling of being cognitively sharper is a commonly reported effect of ketosis, the process by which the body burns ketone bodies, an alternative fuel produced by breaking down fat when glucose stores in the body are depleted. A majority of participants in the trial also said they felt more clear-minded but others reported that they were mentally fatigued during the five-day cycle. I experienced both. Sheer exhaustion set in some days but at other times my brain was buzzing.

What was remarkable was that 95 per cent of the participants stuck to the regime without cheating. This is a key issue: those who found the diet the most difficult tended to be people who live on convenience food – microwave meals and the like – and ate mostly meat-based meals rich in animal protein. Arguably this is also the group that would benefit the most from the diet.

"The people who came from a very poor diet, where they were eating lots of processed foods, lots of sweets and fast food and such, they found it really challenging," says Dr Felice Gersh, an unpaid medical adviser to L-Nutra, who says she has overseen 48 patients on the FMD. For people on a "terrible diet" Gersh recommends a four-week detox from their regular eating pattern before the FMD, "otherwise it can be a little bit overwhelming."

I talk with Sandra, another dieter, who has completed one round of FMD and plans to do more. She describes herself as a "typical American – I like to eat". "If I could do it, anybody could do it," she says. Her goal was weight loss. The 55-year-old lost just under 2 kg, which is on the low side of what most people achieve – with each fasting cycle I lost approximately 3–4 kg.

Sandra speaks enthusiastically of FMD. She, like many others on the trial, says she would do it again. I try to be dispassionate, but to be honest I felt the same. So after completing the 2013 trial, I decided to continue. I did it four times in 2014 and twice in 2015.

The biggest tangible benefit was weight control. Although I inevitably regained some weight once I start eating normally again, I, like Sandra, found it reduced my tendency to snack, even when not on the regime. Longo's group have reported a significant drop in the amount of IGF-1 in the bodies of their study participants after a five-day round of FMD. Once we returned to a normal diet, IGF-1 increased, but not to its original level. Subsequent rounds of the diet followed a similar pattern.

It is possible that all this good feeling is simply selection bias – that people who volunteer for a diet trial are more inclined to react enthusiastically than those in a real-world setting. But immediately after each five-day intervention, I felt reinvigorated. I felt stronger at the gym, though whether this can be directly linked to the diet is unclear. After

all, this isn't much different from how others say they feel after following any other diet or detox fad. And I still get sick. But the potential rewards for my life down the road continue to pique my interest.

§

I join Longo on a field trip to Ecuador. As we bounce around in the back of an SUV, he recalls the first time he made the journey, when the mountain lanes were far bumpier.

He first heard about the Larons around a decade ago, stunned that there existed an isolated human population with the same mutation as his mice, and seemingly enjoying the same benefits. It was a unique opportunity to study a group of people, spanning several generations, known to lack IGF-1. "For me, I think 10 years ago was like winning the lottery," he says. "Suddenly, you have 100 years of observation."

The Institute of Endocrinology, Metabolism, and Reproduction was founded by Jaime Guevara-Aguirre in Quito, Ecuador, in 1987. In a nondescript building in the bustling city centre, he sees his patients and maintains their health records, forming an extensive database of people known to have Laron syndrome. When Longo first arrived, he was impressed that Guevara-Aguirre knew them all by name.

One by one, in outlying villages, Guevara-Aguirre identified people with the distinctive characteristics of Laron syndrome. As well as being short they tend to have a protruding forehead, a flat nasal bridge and a high-pitched voice.

The Larons are known to be sensitive to insulin, which protects them from diabetes. One theory is that they have less fat deposited in the liver because it is redistributed subcutaneously, leading to a gain in body

weight. Being fat could therefore be a positive sign that the liver is in a healthy state. MRI scans on the livers of a group of Larons, including Mercy, found no problems, and nor did ultrasound examinations. Mercy's liver was in perfect condition – no sign of the fatty liver condition normally associated with insulin resistance and diabetes.

To Longo, the parallels with his laboratory mice – genetically modified to block the action of their GH receptor – were striking. Like humans with Laron syndrome, these mice also have healthy livers and accumulate fat subcutaneously. "The similarities between the mouse and the human being are unbelievable," says John Kopchick, a molecular biologist at the University of Ohio.

Kopchick's laboratory has discovered a compound that can treat people with acromegaly, a rare condition that is, in a sense, the anti-Laron syndrome. These people have too much GH circulating in their blood, and develop unusually large hands and feet, as well as pronounced facial features such as thick lips. Kopchick's compound, pegvisomant – now marketed as the drug Somavert – blocks GH at the receptor, lowering the overall level of IGF-1 in the body.

When normal mice were given the drug, they were significantly healthier than ones that weren't. Kopchick says they were less likely to develop diabetes, breast cancer and prostate cancer. To test this further, he and his colleagues genetically modified mice to deactivate their GH receptor. The result? Overweight dwarf mice with low IGF-1 levels and a resistance to disease. To be precise, there was a 49 per cent reduction in deaths from neoplastic disease – or abnormal cell growth – which includes cancer. The mice were also long-lived, a discovery that was made accidentally when a lab technician asked Kopchick what he should do with their elderly mice. Some were four years old – 18 months older than they are supposed to live. It turns out that they are the longest-lived laboratory mice in the world.

"Valter and I and Jaime believe lowering IGF-1 levels is one of the keys to increasing lifespan but more important, in my mind, health span," says Kopchick. For instance, IGF-1 does not cause cancer but will promote the growth of a cancer cell once it's been transformed into a cancerous form itself. Lowering IGF-1, therefore, seems to make it harder for cancer to get a foothold, something that bears out in laboratory tests. When human (non-Laron) mammary cells were mixed with Laron blood serum (low IGF-1) and exposed to hydrogen peroxide to mimic cell damage from oxidation, they were protected from damage. And when the stress became too great they self-destructed, which in a body would prevent the spread of cancer any further.

Says Longo, "You have multiple papers now showing that [people with Laron syndrome] rarely get cancer, they rarely get diabetes – these are in at least two continents. And you have the mouse data that is very supportive of the human data."

It is impossible to extrapolate from one clinical trial to estimate anyone else's chances of developing cancer or diabetes. Nevertheless, Longo says the improvement seen in so-called biomarkers linked to these diseases (such as the levels of protein or signalling molecules in the blood) was immediately apparent. For example, a marker known as C-reactive protein, levels of which rise when there is inflammation in the body, were reduced after the FMD. This, Longo suggests, means the diet could help lower the risk for cardiovascular disease.

§

Freddy Salazar, a 43-year-old Laron, lives with his parents in a house nestled into the scenic hillside above the town of Piñas. It is a region of breathtaking natural beauty. We visited on a sultry winter's morning, with a deep layer of mist shrouding the Salazars' homestead. They live a simple life, growing their own food. The outbuildings house a healthy

stock of pigs, while chickens rummage in the yard.

Guevara-Aguirre and Longo are keen to interview the family elders about their health and that of their extended family. That's not easy. Piñas is extremely remote – it can take hours of driving through the mountains just to reach one person with Laron syndrome. Some have spent much of their lives away from wider society, apparently ashamed or shy about the way they look. Guevara-Aguirre and Longo are working on a theory that GH receptor deficiency may play a role in preventing not only cancer, diabetes and cardiovascular disease but Alzheimer's disease too. But medical records, especially those of older generations, can be hard to track down.

The Salazars huddle around the kitchen table. Freddy, the only Laron member of the family, has seven siblings. His parents, aged 83 and 75, are carriers of the condition. They also come from large families. Their health histories are a goldmine of information. Uncles and aunts have died early from a range of conditions, especially cancer. Guevara-Aguirre quizzes them about their ancestors and takes careful notes. He will later cross-reference their stories with local hospital records and death certificates. It is a painstaking and ongoing process.

Guevara-Aguirre is aware that he is working with a relatively small sample of people – epidemiological studies usually involve thousands. But, he says, it doesn't matter how small this cohort is. "They are an amazing model of humans that have a mutation that knocks out their growth hormone receptor, so that must mean something."

His dream is to find an affordable treatment for the dwarfism caused by the mutation but still keep its health benefits.

"This is a tragedy for the patients, you know, their size is a big handicap from every standpoint that you look at it. I have talked to them. They

don't like their height, that simple. And it's very obvious."

Guevara-Aguirre also believes that there are "limits" to his patients' protection from disease. Subject to further studies, he says he may have identified two of them who do have diabetes. He believes the Ecuadorian diet, which is becoming increasingly Westernised with foods rich in refined sugars, will lead to more diseases for the Larons. "They will still be protected, but not as much as before."

"Let me give you the perfect human," he says. "That would be a Laron patient that has been treated with IGF-1 to final height." Giving this extra growth hormone in childhood could help Larons reach a normal height. Then, he says, the treatment could be withdrawn and they would still have their "impressive protection" against metabolic disease.

It sounds like a miracle, but such a drug already exists. It is IGF-1 in a synthetic form, but is very expensive – Guevara-Aguirre estimates that it would cost up to US$20,000 a year to treat one person. He believes drug companies should step up to provide the medication, considering how much they and medical science have benefited from studying his patients' condition. "They gave us their clinical data, they gave us their blood," he says, arguing that it would also produce a unique research opportunity to compare IGF-1-treated Laron children with relatives who do not have the condition.

Meanwhile, Longo and Kopchick are developing a drug similar to Somavert, something that mimics the Larons' genetic mutation and could extend the same health benefits to non-Larons, much like Kopchick's mice. A form of it is already in clinical use, as a daily injection to treat acromegaly. What they need to do now is to come up with a longer-acting drug that could be swallowed and taken less frequently. And less expensively – Somavert costs thousands of dollars a month. Crucially, although Somavert is licensed as a treatment (for acromegaly), Kopchick

believes the US Food and Drug Administration would be unlikely to green-light such a drug as a preventative medicine to promote healthy ageing.

And then there is FMD, the IGF-1-reducing diet. It's biscuits, soups and energy bars. David Gems says the concept is clever because it is something people can try immediately. Pills might work better, he adds, but because of the investment required and the need to make sure that they are safe, bringing them to the market would be a difficult process. With a diet, users simply have to eat everything – while resisting other food or drink – with minimal instruction.

Longo, who skips lunch every day as part of his own calorie restriction regime, says his goal is to give doctors "tools that they never had before": a diet that is clinically tested and has been proven to produce results.

Since the initial findings were published, homemade versions of the FMD have appeared online, attempting to replicate ProLon recipes with foods people can buy at a shop. Longo stresses that people should take medical advice and not undergo any kind of fasting diet alone – individuals with diabetes, anorexia or other metabolic disorders could be killed. He says the regime is "complicated", with ProLon's boxes made from a delicate balance of clinically tested ingredients.

Some researchers I spoke to, such as Joao Pedro De Magalhaes, who studies the genomics of ageing at the University of Liverpool, voiced concerns that the FMD could, over long periods, have side-effects. Others, such as Gems, are cautious as to whether the regime will work in the long term.

Conceptually, though, the idea seems to have merit. Guevara-Aguirre believes the Ecuadorian Larons prove it. "That's why I'm so certain that

it's good to have low IGF-1." But being a lover of food, and especially meat, he isn't convinced that a diet based on fasting will find many takers. "Everybody agrees that fasting is good. The problem is in doing it… so far I have been unsuccessful."

And here's the kicker: the Larons of Ecuador, on average, live to about the same ages as their neighbours and family members, no longer, although the causes of death are different. People with Laron syndrome have a higher than usual mortality rate from non-age-related causes, such as accidents. Being small, they are more prone to being knocked over in the road. They also have a tendency to suffer from alcoholism and psychological problems, and have a higher rate of suicide. It is a surprising and rather sobering fact that, despite their remarkable protection against disease, the Larons of Ecuador do not enjoy exceptionally long lives.