ORIGIN STORY: DEEPTIME PLATYPUSES AND AUSTRALIA'S MONOTREME MYSTERY

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THE SCIENCE OF EVERYTHING

Issue 95

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Does loneliness affect our cells and genes?

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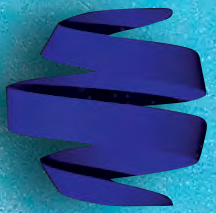

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From the Editors

PEOPLE SEEM TO LOVE CHANGE or to hate it – it's a quality that most definitely lacks middle ground. We're declaring ourselves value-neutral on the matter in introducing this issue as one themed on change – after all, not every change is for the better.

The impact of one change – the re-measurement of the W boson – may not be certain for years, but as particle physicist Martin White points out, it's the strongest shake yet to the Standard Model and holds tantalising promise of a future change to what we know about physics.

Wouldn't it be great if you could change the outcome for species that are threatened with extinction? Well, if your method involves synthetic biology, it's not as easy an answer as it seems. What are the ethics of re-introducing a gene-engineered plant or animal to a wild that has, for better or worse, already marked the organism as an evolutionary dead end?

Some changes aren't so great, as Paul Biegler's story about isolation reveals. Research is drilling down to the physiological changes wrought by loneliness – important work when one considers the separation we've all suffered since COVID jumped into our lives.

Also this issue, Annamaria Talas reveals the science of success; Ken Eastwood looks at the changed landscape of monotreme origins; Robyn Arianrhod considers the importance of logic to the rise of computers; and Bron Willis takes us inside the new HumanISE lab at Monash University, which aims to change how and why we make software.

It isn't necessarily science's role to create change, but change is sometimes the result of scientific investigation. If you believe that a world built on evidence derived from patient research is far, far better than one with much shakier foundations, it would seem to follow that you at least have to *embrace* change – whether you love it or not.

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Loneliness: we all know the feeling of it, but it's hard to pin down precisely its causes and effects. Now, as **PAUL BIEGLER** reports, a growing field of study shows that this subjective feeling has objective effects – right to a cellular level.

ISOLA

On a cool night in the suburbs of Los Angeles in December, 1978, Jack Morris was at a house party. It was one o'clock in the morning and things were getting tense. Morris was 18 years old and hadn't long been released from juvenile detention.

"We were all drinking," he remembers. "Two guys went out into the back yard to fight, that fight ensued, and then the guy that was fighting said he didn't want to fight no more, and he ran into me, and he ran into another guy."

Morris is seated at his desk at the St John's Community Health Clinic in a squat brick building south of downtown LA, where he helps people who've left prison get jobs, housing, manage drug problems and avoid re-entering the prison system. He's spruce, with thick greying hair cut to a medium crew and he's wearing a dark shirt, and smart, tinted reading glasses. Morris speaks confidently, but when he recalls what happened, his voice fades.

"And then I pulled out a knife and stabbed him. He died right there."

Morris graduated to adult prison. He went to San Quentin, Corcoran then Tehachapi, doing solitary confinement in each. But out in the general population there was human contact. A handshake, a conversation, a gaze being met. In August 1991, however, all that changed. Morris was transferred to

HARA TAKETO/GETTY IMAGES

Pelican Bay, a supermax prison in northern California where the inmates were housed in windowless, poured concrete cells that measured 2.4 x 3.0 metres, around half the size of a standard car parking space.

"When the door is closed, even though it is perforated plate steel, you could feel your soul being sucked out," he recalls. "You're standing there naked with what they handed you and you're just looking at the cell and you realise there is nothing in here but a concrete box, stainless steel sink, a toilet. You're standing there ... barefoot on cold cement, and you're saying, 'well, this is it'."

What Morris didn't realise was that a sentence to solitary came with hidden extras. Soon, like hundreds of fellow prisoners, he would get high blood pressure. His risk of heart disease would go up. He would get symptoms of anxiety, sleeplessness, and depression. His knees and back would ache and he'd be taking anti-inflammatory medication. But few people cared about the plight of hardened criminals doing time.

Then the pandemic hit, and much of the world was forced into its own brand of lockdown isolation. Rates of depression and anxiety skyrocketed. The American Academy of Paediatrics declared a national emergency in children's mental health. Now everyone was interested in the very same question: what does isolation do to bodies and minds? Scientists tackling that question have come up with some

disturbing answers. Isolation, it seems, changes us down to our core, right down to the level of our genes.

Blue genes?

These days Steve Cole is a professor of medicine at the University of California, Los Angeles, but in the late nineties he was a virologist studying HIV. And he was perplexed. Something odd was happening with a subset of the gay men who were getting the virus. Their immune system was declining faster, and they were dying earlier.

"The ones that were most vulnerable were those who were most socially marginalised, especially the guys who were in the closet," Cole recalls.

"How was it that the HIV genome operated differently in the body of a person who was living in the closet, and constantly afraid of being discovered and losing his job, or his family, or his friends?"

Cole embarked on a series of studies to find out, and unearthed something astonishing. Gay men with a "socially inhibited" temperament were switching on their "fight and flight" sympathetic nervous system. They were pumping out stress hormones, including one called noradrenalin, which binds to a white blood cell that's key in the fight against HIV, the T lymphocyte. Those lymphocytes were then winding back production of proteins called interferons, critical defenders against viruses.

"There was a set of programs that were built into the human immune system, that caused threatened people to throttle back on their antiviral immune responses," says Cole.

Gay men with a "socially inhibited" temperament, it turned out, were switching on the "fight and flight" sympathetic nervous system.

Incredibly, the social truth of sexual orientation was playing out at the level of these men's infection-fighting cells. Cole presented his findings at a thinktank and, afterwards, was approached by a man with an unusual request. His name was John Cacioppo and he was a pioneer in the scientific study of loneliness, whose links to physical diseases such as heart disease, Alzheimer's and high blood pressure were only just being teased out.

Cacioppo wanted to know if the stress of social isolation could do similar things to the immune system and might somehow, be elevating the risk of chronic disease. Cole jumped at the chance to work with him.

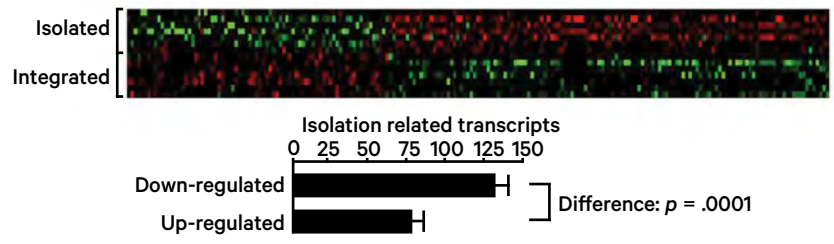
"We did this initial study. It was painfully small, like, 14 people. A really small number of chronically lonely individuals, and another complementarily small number of chronically, socially integrated individuals. And we just took some white blood cells that John had stored in freezers and did this RNA profile on them," Cole remembers.

That profile homed in on the activity of genes in the white blood cells. It was a small study, but the results were emphatic.

"If you look at the genes that were most reduced in activity in lonely people, a surprisingly high proportion of them were the genes that were involved in type one interferon responses, these basic, innate antiviral responses," says Cole.

"That was really stomped down in these lonely people in a way that looked a lot like the gay men in the closet."

CAN LONELINESS BE SEEN IN YOUR DNA?



A study by medical researcher Steve Cole explored the relationship between subjective social isolation (or loneliness) and gene expression in leukocyte cells in a group of chronically lonely and socially integrated people. Analysis identified 209 genes with a greater than 30% difference in average expression levels between the lonely and non-lonely groups. In the lonely group, significantly more genes were downregulated (red) than upregulated (green): 131 to 78.

The stress of loneliness – the subjective, unpleasant experience of social isolation – was doing similar things to the stress of hiding one's sexuality. Something, however, didn't gel. How could a stunted response to viruses put lonely people at risk of illnesses, such as coronary heart disease, that seemingly had nothing to do with a virus?

Cole's study had picked up a clue. If lonely people were making less interferon, genes linked to production of something else were in overdrive.

Lonely people were churning out more proteins, known as cytokines, that ramp up inflammation. And inflammation is central to heart disease and increasingly thought to play a role in cancer and Alzheimer's, the very diseases Cacioppo was interested in.

"It was pretty clear that there was this teeter totter regulation where the human immune system, which is generally pretty heavy on antiviral capacity and kind of stomps down on inflammation, was recalibrating in the opposite direction in these lonely people," says Cole.

According to Cole there are sound evolutionary reasons the body would do this. Our default mode is to be prepared for the infectious threat we see all the time – socially transmissible viruses. A rarer event is a wound which, if it gets infected with bacteria, can kill us quickly. It is the inflammatory response, and the mobilisation of different types of white cells, such as monocytes, that mop up these bacterial invaders.

The upshot, says Cole, is that we need to be able to pivot, rapidly, from an antiviral to an antibacterial footing, something the stress response achieves well.

"Loneliness is just a surprisingly good way of being threatened. The primary safety signal for most humans is being a member of some kind of supportive community, a family, a tribe." The body, then, sees loneliness as a cue that injury, and bacterial infection, are just one predator away.

When the pandemic began, Cole was a go-to guy for the media, who were desperate to uncover what the science showed about millions of people in enforced isolation. Cole realised he could only make inferences from previous studies. Then he realised he might have the answer right in front of him.

For many years Cole has worked closely with primate researcher John Capitanio, a psychologist at the University of California, Davis. Around 2016 the pair, in a team that included John Cacioppo, began a study of rhesus macaque monkeys at the California National Primate Research Centre. It's a sprawling facility on the outskirts of Sacramento, where scores of monkeys cohabit in half-acre field cages equipped with play gyms, mini-Ferris wheels and tree branches.

The team wanted to catalogue the behaviour of lonely and non-lonely monkeys during two weeks isolation in a smaller cage. When the media queries started pouring in 2020, Cole realised the experiment was a near-perfect model to study the effects of lockdown. So the team switched tack. What would the mere fact of being separated from its friends do to the monkey's immune system, they wondered? A lot, as it happened.

The results, published in *Proceedings of the National Academy of Sciences* in 2021, found the monkeys dialled up, by around 9%, production of white

DIMITRI OTIS/GETTY IMAGES

blood cells, called classical monocytes, responsible for inflammation. Cells that make interferon and fight viruses, such as lymphocytes, plummeted by up to 50%. How soon did it all start? Within 48 hours of the animals entering the cage. It was a dramatic demonstration of the biological force of isolation.

Not everyone, of course, experiences lockdown alone. Parents, for example, have to care for children. The researchers knew older primates are predisposed to care for juveniles, so they tried something else. A month after each monkey was released they put it back into isolation, this time caged with a young monkey.

"That made a huge difference in terms of how the adult monkey's biology responded to lockdown," says Cole. "The monkey that goes into the same setting, with an infant there, doesn't show any material ramp up in inflammatory cell, monocyte production, and doesn't show any material ramp down in antiviral biology."

Put a monkey in lockdown with caregiving, they had found, and all those stress-related changes in immunity seem to melt away. The reason why the mere presence of a needy child could taper the adult monkey's stress response may well come from a curious study that Cole and colleagues published in 2013.

They analysed gene expression in the white blood cells of 80 healthy adults and, at the same time, asked them how, on balance, their lives were going. Some people scored higher on scales that measure a sense of purpose and meaning in life, so-called "eudaimonic" well-being (in the writings of Aristotle eudaimonia refers to "human flourishing"). Those people, the team found, were turning down the threat-related immune response.

Cole has since gathered evidence that being connected to a deeper purpose activates brain areas linked to motivation and "wanting", including the ventral striatum and nucleus accumbens. Those areas can quell the effects of the brain's anxiety centre, the amygdala, whose job is to put the body on a threat footing.

"When those monkeys engage in caregiving, and when humans engage in this kind of virtuous and striving and generative activity, what you're getting is a lot of activity in this seeking, hoping, wanting section of your brain that essentially vetoes some degree of threat-related biology," says Cole.

It is a facility, Cole believes, that likely arose to push parents to face danger for the sake of their children. If a parent is to run inside a burning building and save a child, for example, they must put the risk of self-harm to one side.

Closing time

No animal study maps perfectly onto the human condition. But it's hard to avoid speculating that aches in Jack Morris's back and knees were manifesting a change in his inflammatory biology.

Inflammation has also been linked to high blood

But something else was happening too. The hunger for human contact, so familiar to people who've spent time alone, was ebbing away.

MARTIN BARRAUD/GETTY IMAGES

REMOTE CONTROL: THE ZOOM EFFECT

Dr Louise Hawkley is a principal research scientist at NORC at the University of Chicago and has studied loneliness for more than two decades. When the pandemic hit, Hawkley was on a team that had been surveying a group of older adults as part of the National Social Life, Health, and Aging Project.

"There was all this hype around video calls," says Hawkley. "That's your answer, you better learn how to do video calls because then you're going to get your best quality interaction with other people."

Hawkley convened a new team to survey around 2500 people from the cohort, all aged 55 and up. They asked respondents to rate their levels of happiness, depression and loneliness, which could be compared with ratings from the same group taken in 2015, pre-pandemic. People also reported their level of contact with family and friends, how much was in-person, how much was via video and phone calls, email and messaging, and how it all tracked over the pandemic. Hawkley's findings, published in the *Journal of the American Geriatrics Society* in 2021, showed that around 40% of people had reduced in-person contact.

The effects, too, are unsurprising. "The more you stayed at home and didn't have contact, the more lonely you became, the more depressed symptoms you had, the less happy you were," says Hawkley.

Most worrying, though, was the impact of remote contact. "Could they improve that by having more virtual interactions? The take-home seems to be 'no'," she says. Hawkley's team found that between 16% and 26% of respondents increased their levels of remote contact during the pandemic.

"It seemed to make no difference," says Hawkley. "It did not alleviate loneliness to any significant degree. It did not alleviate depressive symptoms or improve happiness."

There is little data why this is the case, so Hawkley can only offer her intuition, albeit drawn from decades of research.

"It's the whole sensory experience. It's not just what we see and hear but all the subtle cues we get from, call it body odour, pheromones, whatever. ... And there are subtleties in body posture, physiognomy, that essentially change with emotions. That is very hard to detect accurately on a virtual platform.

"We all have that need for assurance, for security, and we don't give it to babies by having them watch a screen. It requires this very immediate detection of signals, eye to eye, hand to hand, chest to chest, just to round us out as what we are as people. Because we aren't islands. We are not sufficient for ourselves."

pressure, but it's likely the stress of isolation, and a rise in stress hormones like cortisol, contributed too.

Morris also seemed driven to find a higher purpose. He studied maths. He took legal training and helped fellow inmates lodge writs. He read thousands of books on everything from quantum physics to the migration patterns of the peregrine falcon.

"You have to figure out a way to exist. You can't sit there and stare at the wall because then the wall is going to start moving on you. I didn't know how to draw. I learned it, because it gave me something to do eight to ten hours of that day."

There were pencils, but no colour. Morris drew a bird, with intricate feathers and strange, cord-like appendages in red, blue and green. He made the colours from Skittles and M&M's. Somehow, in that prison within a prison, Morris was impelled to find meaning. But something else was happening too. The hunger for human contact, so familiar to people who've spent time alone, was ebbing away. Morris could yell to the eight other people in his "pod" through the dime-shaped holes in the steel door. But, as the years passed, he stopped.

"You don't even want to communicate no more. Your world becomes smaller and smaller and smaller. Somebody calls up to you saying, 'what are you doing? I haven't heard from you in two days.' And we're in the same pod. And my cell is next door to him."

In pursuit of happiness

A bit over a decade ago Gillian Matthews was elbow deep in her PhD at Imperial College London. She was researching addiction, specifically, the effects of cocaine on an enigmatic structure in the mouse brain called the dorsal raphe nucleus or DRN. But when you inject cocaine into mice things can get, well, interesting.

"Typically the mouse on cocaine is quite excitable," says Matthews. "You'll put them in a separate cage overnight for 24 hours, so that they don't interrupt their cage mates."

Matthews had a control group of mice getting salt water injections so, to keep conditions equal, they were also isolated for 24 hours. When Matthews examined the mice brains afterwards she found a major change in the cocaine group – connections in neurons that feed into the DRN, and drive its activity, had grown way stronger. But something weird was going on. The mice that got salt water had an almost identical muscling up of those same neurons.

"My initial reaction was that I'd probably mixed up the syringes, given the saline mice the cocaine," Matthews remembers. She repeated the experiment. Same result. The effect was real. The simple fact of isolation looked to be pumping up neurons that drive activity in the DRN. But why?

Until now, Matthews had been recording DRN

activity in brain slices from euthanised mice, whose neurons can remain active for 12–14 hours. To get a better handle on the DRN meant studying live mice using different techniques. So, in 2013, Matthews crossed the Atlantic to take up a post-doc role in the lab of Professor Kay Tye, then at MIT.

They began experiments in animals bred so that fluorescent indicators could track the influx of calcium into their neurons, which happens when the neurons are firing. It's called calcium imaging – brighter neurons mean more activity. For 24 hours the mice were either held in isolation or caged with a bunch of other mice. When the time was up they had each mouse say hi to an unfamiliar young mouse.

The mice that had been group-housed had a bit more activity in the DRN neurons. But in the mice that had done solo time, it was something else again.

"These neurons go crazy," said Tye, shortly after the experiment's publication in 2016.

DRN neurons looked to be tracking the social state of the mouse, firing up in isolated animals when they finally reconnected with others. But could those brain cells be doing even more? Were they actually driving behaviour? To find out Matthews and Tye turned to optogenetics, a technique that introduces light-sensitive proteins into neurons, which can then be activated by a given wavelength of light. The team engineered things so the DRN could, effectively, be turned on at the flick of a switch. They put the mouse in a cage with a mesh wall at one end, behind which another mouse was going about its business. And flicked the DRN switch. The effect was immediate, and dramatic.

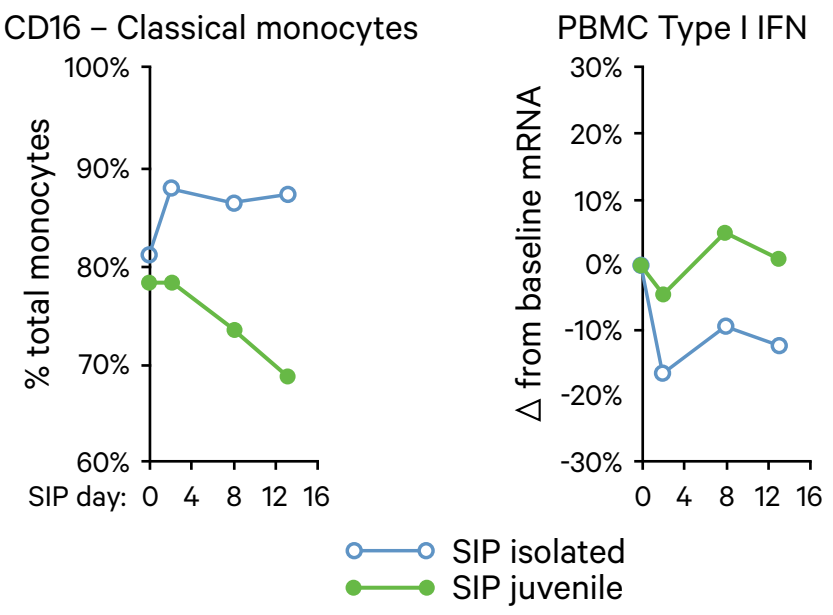
"The primary safety signal for most humans is being a member of some kind of supportive community, a family, a tribe." The body, then, sees loneliness as a cue that injury, and bacterial infection, are just one predator away.

"We found that they increased the amount of time that they wanted to spend with another mouse," says Matthews. "They increased their social preference, so they spent more time on that social side of the chamber." It was a stunning finding. The DRN was, almost single-handedly, deciding whether mice would be shrinking violets, or party animals.

Matthews had another tool at her disposal. Optogenetics can also silence neurons. When mice go into isolation for short periods they get convivial on release, as if to make up for the social deficit. The team put mice into lockdown for 24 hours, and then used optogenetics to turn off the DRN neurons. "When we silenced these neurons after animals had gone through 24 hours of isolation, we found that it suppressed that rebound social contact," says Matthews.

The DRN, they had discovered, was crucial to the process of reconnecting after brief isolation. Matthews, Tye and other researchers at the Salk

MONKEY BUSINESS



In 2020, Cole tested the health effects of social isolation in a group of macaque monkeys, who spent 14 days isolated in smaller cages (blue), and, later, 14 days isolated in a space with a juvenile macaque (green). Changes in the immune system, such as an increase in inflammation-related classical monocytes (A) and downregulation of the type I interferon response (B), were significantly reversed in monkeys when they were paired with a juvenile.

Institute in California, where Tye is now based, have set out what they think happens over longer periods of isolation when many people become socially withdrawn.

In two key papers, published in 2019 and 2021, they describe the DRN as part of a system that works like a thermostat. Reduce your contacts and the system will prompt you to mingle and get your social "temperature" back to the set point. Matthews and Tye call this "social homeostasis".

But deprive someone of social contact for months on end and they can get antisocial, content with the new normal of fewer entanglements. Matthews and Tye think this is a "set point adaptation", a reset of the thermostat that winds down our social needs. You might feel fine in the trackie-daks and slippers of lockdown, but emerge into your former social milieu and things get uncomfortable. It now feels overcrowded and people can react with avoidance, aggression or social anxiety. So, what should people do to keep things steady in lockdown, and to re-adapt when they come out?

In lockdown with caregiving, they had found, all those stress-related changes in immunity seem to melt away.

KOHEI HARA/GETTY IMAGES

Hearts and minds

In December 2016 Jack Morris was told, after 30 years of continuous solitary confinement, that he would be transferred to general population in a prison downstate.

"I spent Christmas staring out of a window. Out of a window. And I saw snowflakes falling from the sky and that's after living in a cell for decades and not seeing no night sky, or no sun, or no clouds," he says. "For weeks I had headaches. I was seeing colours. I'd see the colour of dirt. I'd see the colour of grass. Because in there it's strictly concrete, you don't see colour. You walk on concrete, you sleep on concrete, you eat on concrete. You stare at concrete."

Re-connecting with people came with a distinct set of challenges. "I didn't know how to socialise. How can I go up to somebody and talk to them? What am I going to do, look at 'em and talk to 'em? Shake a hand? You don't do that. That's foreign to you. It's no longer something you know about. It's something you have to learn all over again."

The process wasn't helped by the profound anxiety Morris felt being around people again. "Your heart, you could literally hear it pounding in your chest. Somebody would just run by. You're turning around, you're jumpy, you're jittery. You can't sit down. You can't get any relaxation."

Released from prison in 2017, Morris has slowly inched his way back into society. Millions of people around the world are recovering from their own, less extreme struggles with isolation.

"You do need to be conscious that there are long term changes that could have impacted how long it will take people to change their behaviour and to feel comfortable and to feel less anxious," says Matthews.

But deep in all that neuroscience there is also a message of hope. "If we have learnt anything about the brain it is that it's really good at adapting. I think people will adapt back, and I think the brain will adapt too." ◉

PAUL BIEGLER is a bio-ethicist based in Melbourne. His last story for the magazine, on mindsharing, was in Issue 91.