The pursuit of happiness

Researchers have struggled to identify how certain states of mind influence physical health. One biologist thinks he has an answer.

BY JO MARCHANT

When Steve Cole was a postdoc, he had an unusual hobby: matching art buyers with artists that they might like. The task made looking at art, something he had always loved, even more enjoyable. "There was an extra layer of purpose. I loved the ability to help artists I thought were great to find an appreciative audience," he says.

At the time, it was nothing more than a quirky sideline. But his latest findings have caused Cole — now a professor at the Cousins Center for Psychoneuroimmunology at the University of California, Los Angeles — to wonder whether the exhilaration and sense of purpose that he felt during that period might have done more than help him to find homes for unloved pieces of art. It might have benefited his immune system too.

At one time, most self-respecting molecular biologists would have scoffed at the idea. Today, evidence from many studies suggests that mental states such as stress can influence health. Still, it has proved difficult to explain how this happens at the molecular level — how subjective moods connect with the vastly complex physiology of the nervous and immune systems. The field that searches for these explanations, known as psychoneuroimmunology (PNI), is often criticized as lacking rigour. Cole's stated aim is to fix that, and his tool of choice is genome-wide transcriptional analysis: looking at broad patterns of gene expression in cells. "My job is to be a hard-core tracker," he says. "How do these mental states get out into the rest of the body?"

With his colleagues, Cole has published a string of studies suggesting that negative mental states such as stress and loneliness guide immune responses by driving broad programs of gene expression, shaping our ability to fight disease. If he is right, the way people see the world could affect everything from their risk of chronic illnesses such as diabetes and heart disease to the progression of conditions such as HIV and cancer. Now Cole has switched tack, moving from negative moods into the even more murky territory of happiness. It is a risky strategy; his work has already been criticized as wishful thinking and moralizing. But the pay-off is nothing less than finding a healthier way to live.

"If you talk to any high-quality neurobiologist or immunologist about PNI, it will invariably generate a little snicker," says Stephen Smale, an immunologist at the University of California, Los Angeles, who is not affiliated with the Cousins Center. "But this doesn't mean the topic should be ignored forever. Someday we need to confront it and try to understand how the immune system and nervous system interact."

THE BEST MEDICINE?

In 1964, magazine editor Norman Cousins was diagnosed with ankylosing spondylitis, a life-threatening autoimmune disease, and given a 1 in 500 chance of recovery. Cousins rejected his doctors' prognosis and embarked on his own programme of happiness therapy, including regular doses of Marx Brothers films, and credited it with triggering a dramatic recovery. He later established the Cousins Center, which is dedicated to investigating whether psychological factors really can keep people healthy.

At the time, mainstream science rejected the idea that any psychological state, positive or negative, could affect physical well-being. But studies during the 1980s and early 1990s revealed that the brain is directly wired to the immune system — portions of the nervous system connect with immune-related organs such as the thymus and bone marrow, and immune cells have receptors for neurotransmitters, suggesting that there is crosstalk.

"Mood matters. If we change the psychology, physiological changes do parallel that."

These connections seem to have clinical relevance, at least in the case of stress. One of the first researchers to show this was virologist Ronald Glaser, now director of the Institute for Behavioral Medicine Research at the Ohio State University in Columbus. "When I started working on this in the 1980s, nobody believed what stress could do, including me," he recalls. He and his colleagues sampled blood from medical students, and found that during a stressful exam period, they had lower activity from virus-fighting immune cells[1], and higher levels of antibodies for the common virus Epstein–Barr[2], suggesting that stress had compromised their immune systems and allowed the normally latent virus to become reactivated.

The field of PNI has grown hugely since then, with medical schools worldwide boasting their own departments of mind–body medicine, of which PNI is just one component. It is now accepted that the body's response to stress can suppress parts of the immune system and, over the long term, lead to damaging levels of inflammation. Large epidemiological studies — including the Whitehall studies, which have been following thousands of British civil servants since 1967 — suggest[3] that chronic work stress increases the risk of coronary heart disease and type 2 diabetes, for example. Low socio-economic status increases susceptibility to a wide range of infectious diseases, and there is considerable evidence that stress increases the rate of progression of HIV/AIDS. But researchers have a long way to go before they will understand exactly how signals from the brain feed into physical health.

WORRIED SICK

PNI studies have mostly tended to look at levels of individual immune-cell types or molecular messengers — such as the stress hormone cortisol and the immune messenger proteins called cytokines — or the expression of individual genes. But Cole wanted to get a sense of how the whole system was working.

His first foray, published in 2007, looked at loneliness[4]. Social isolation is one of the most powerful known psychological risk factors for poor health, but it is never certain whether it causes the health problems, or whether a third factor is involved: lonely people might be less likely than others to eat well, for example, or to visit their doctor regularly.

Cole and his colleagues looked at gene expression in the white blood cells of six chronically lonely people — people who had said consistently over several years that they felt lonely or isolated, and were fearful of other people — and eight people who said that they had great friends and social support. Out of the roughly 22,000 genes in the human genome, the researchers identified 209 that distinguished the lonely people from the sociable ones: they were either regulated up to produce

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A volunteer helps to bag meals for the homeless at Cathedral Kitchen in Camden, New Jersey.

more of an individual protein or regulated down to produce less. Any individual gene could easily look different by chance, but Cole was struck by the overall pattern. A particularly large proportion of the upregulated genes in the lonely group turned out to be involved in the inflammatory response, whereas many of the downregulated genes had antiviral roles. In sociable people, the reverse was true. It was a small study, but one of the first to link a psychological risk factor with a broad underlying change in gene expression.

The researchers have since replicated that result in a group of 93 people[5]. Cole says that he has also seen a similar shift in gene expression in individuals exposed to various types of social adversity, from imminent bereavement to low socio-economic status.

The results make evolutionary sense, he says. Early humans in close-knit social groups would have faced increased risk of viral infections, so they would have benefited from revved-up antiviral genes. By contrast, people who were isolated and under stress faced greater risk of injuries that could cause bacterial infection — and thus would need to respond by ramping up genes associated with inflammation, to help heal wounds and fight off those infections. But modern stresses lead to chronic and unhelpful inflammation, which over time damages the body's tissues, increasing the risk of chronic diseases such as atherosclerosis, cancer and diabetes.

To a classical immunologist such as Smale, Cole's results are "intriguing, wonderful observations", but not yet completely convincing. In future work, he wants to see the rest of the physiological pathway nailed down. "Until you put together a full understanding of that mechanism, you have this level of uncertainty and scepticism," he says. That sentiment is echoed by Alexander Tarakhovsky, an immunologist at the Rockefeller University in New York City. Pinning down precise mechanisms — for example, which neurotransmitters cause which specific effects — is extremely difficult, he says, because the brain and the immune system are both so complex. Cole's research "makes you think about what the consequences of social hardship could be, but it doesn't really tell you how it works".

Greg Gibson, director of the Center for Integrative Genomics at the Georgia Institute of Technology in Atlanta, wants to see larger studies but argues that the big-picture "genetic architecture" that Cole is uncovering is worth studying, even if not every detail of the mechanism is yet understood. "A lot of people are taking a whole-genome approach, but they focus only on a handful of 'top hits'. They are missing the wood for the trees."

DON'T WORRY, BE HAPPY

In 2010, Cole received an e-mail from Barbara Fredrickson, a friend from graduate school who was now studying emotional well-being at the University of North Carolina in Chapel Hill. "Remember me?" she said. She was interested in the biological correlates of happiness and other positive emotional states, and suggested that the pair collaborate. After years of looking at stress and adversity, Cole loved the idea. "I was bored as hell with misery," he says.

If PNI as a whole has credibility issues, studying well-being is even trickier. It is more slippery to measure than stress — there is no biological marker such as cortisol to fall back on and no simple way to induce it in the lab, and mainstream biologists tend to look down on fuzzy methods of data collection such as questionnaires.

One approach is to test whether it is possible to reverse the adverse effects on gene expression caused by stress. Cole has collaborated in three small, randomized, controlled trials that attempt to do this. Studies involving 45 stressed caregivers[6] and 40 lonely adults[7] respectively found that courses in meditation shifted gene-expression profiles in the participants' white blood cells away from inflammatory genes and towards antiviral genes. A third trial[8], led by psycho-oncologist Michael Antoni at the University of Miami, Florida, involved 200 women with early-stage breast cancer. In those who completed a ten-week stress-management programme, genes associated with inflammation and metastasis were downregulated compared with those of women in the control group, who attended a one-day educational seminar. Meanwhile, genes involved in the type I interferon response

NOAH BERGER

Psychoneuroimmunologist Steve Cole studies how stress and happiness affect health.

(which fights tumours as well as viruses) were upregulated in the women who took the stress-management course. "Our conclusion was that mood matters," says Antoni. "If we change the psychology, physiological changes do parallel that."

Cole and Fredrickson aspired to go further. Instead of looking at the benefits of blocking stress, they wanted to investigate what happens in the body when people are happy. To that end, they asked 80 participants 14 questions, such as how often in the past week they had felt happy or satisfied, and how often they felt that their life had a sense of meaning[9]. The questions were designed to distinguish between the two forms of happiness recognized by psychologists: hedonic well-being (characterized by material or bodily pleasures such as eating well or having sex) and eudaimonic well-being (deeper satisfaction from activities with a greater meaning or purpose, such as intellectual pursuits, social relationships or charity work).

The researchers were surprised to find that the two types of happiness influenced gene expression in different ways. People with a meaning-based or purpose-based outlook had favourable gene-expression profiles, whereas hedonic well-being, when it occurred on its own, was associated with profiles similar to those seen in individuals facing adversity.

One interpretation is that eudaimonic well-being benefits immune function directly. But Cole prefers to explain it in terms of response to stress. If someone is driven purely by hollow consumption, he argues, all of their happiness depends on their personal circumstances. If they run into adversity, they may become very stressed. But if they care about things beyond themselves — community, politics, art — then everyday stresses will perhaps be of less concern. Eudaimonia, in other words, may help to buffer our sense of threat or uncertainty, potentially improving our health. "It's fine to invest in yourself," says Cole, "as long as you invest in lots of other things as well."

PERILS OF POSITIVE THINKING

This is just the kind of advice that attracts some of the most vociferous criticisms of Cole's work. James Coyne, a health psychologist and emeritus professor at the University of Pennsylvania in Philadelphia, says that Cole and Fredrickson's well-being study is simply too small to show anything useful. He also argues that the measures of eudaimonic and hedonic happiness are so highly correlated in the study as to be essentially the same thing. Coyne says that early results are being vastly over-sold. "They claim that if you make the right choices, you'll be healthy. And if you don't, you'll die."

Coyne wants researchers across the field of PNI to stop publicizing claims about health benefits until the science is more solid. "They're turning it into books and workshops, telling people how to live their lives."

Fredrickson, for example, is the author of two popular books, including *Positivity* (Crown Archetype, 2009), which posits that a specific ratio of positive to negative emotions (2.9013, to be precise) is linked to good health. The book has been praised by eminent psychologists such as Daniel Goleman and Martin Seligman, but the set of equations behind the ratio was criticized this year[10] by Alan Sokal, a physicist at New York University (who famously published a deliberately nonsensical paper in the journal *Social Text* in 1996, intended to expose the lack of rigour in the field of cultural studies). He pointed out that the equations are based on parameters from a 1962 paper on air flow, with no connection to psychological data at all. Fredrickson acknowledges problems with the maths, which she based on a peer-reviewed paper on the complex dynamics of teams[11], but says that she stands by the fundamental principles described in the book. "There seems good enough evidence to suggest that emotions contribute to health."

Cole and Fredrickson agree that their study is small and needs to be repeated. But they say that extensive previous research has validated the questionnaire they used and confirmed that it measures two distinct, albeit highly correlated, emotional states. They also note that correlation does not necessarily mean that two states are the same: height and weight are also highly correlated, for example, yet describe different things. Each type of happiness tends to encourage the other, says Fredrickson, "but we can try to understand which is leading the way towards health".

The researchers are not the first from the PNI community to face accusations of wishful thinking. Indeed, the story of the field's founder — hailed in the press as proof of the power of positive emotions — has been questioned. Immunologists have suggested that Cousins was not suffering from ankylosing spondylitis at all, but from polymyalgia rheumatica, which often clears up on its own. His "health probably coincidentally remitted", says Cole.

Despite the criticisms, and the fact that his work is in its early days, Cole says that he is struck by the evidence that positive emotions can override the biological effects of adversity — enough to make changes in his own life. Although he no longer has time to engage in the art trade, he has embraced the ways that his hobby helped him. "I have spent most of my career and personal life trying to avoid or overcome bad things," he says. "I spend a lot more time now thinking about what I really want to do with my life, and where I'd like to go with whatever years remain." ■

Jo Marchant *is a freelance science journalist based in London.*

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