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You're only as young as your immune system

There has never been a more important time to keep your immune system fit and healthy. And as **Graham Lawton** discovers, there are now ways to keep it younger than you are

WASH your hands religiously for 20 seconds, sneeze into your elbow, avoid touching your face, stay 1 metre away from all other people and, as a last resort, self-quarantine for a week with only your emergency rations for company. If you want to avoid getting the new coronavirus, all of these are a good idea. But ultimately, one of the most important things standing between you and a deadly bout of covid-19 is your immune system.

We know that the immune system gets weaker as we age – which is a key reason why those over the age of 70 are most at risk from the disease. But what is becoming clear is that when it comes to immune health, age is just a number. Some people have an immune system that is effectively significantly older or younger than they are. “Some 60-year-olds have the immune system of a 40-year-old, some are more like an 80-year-old,” says Shai Shen-Orr, an immunologist at the Technion-Israel Institute of Technology. The good news is that there are some simple ways to turn back the immunological clock. Because even after the threat of this virus has passed – sooner or later another one is going to come along, and none of us is getting any younger.

As anyone who has studied immunology will tell you, the immune system is immensely, mind-bogglingly intricate. “It is the second-most complicated system in your body after your brain,” says Shen-Orr. It consists of hundreds of cell types and signalling molecules controlled by some 8000 genes, interacting in a network of near-infinite complexity.

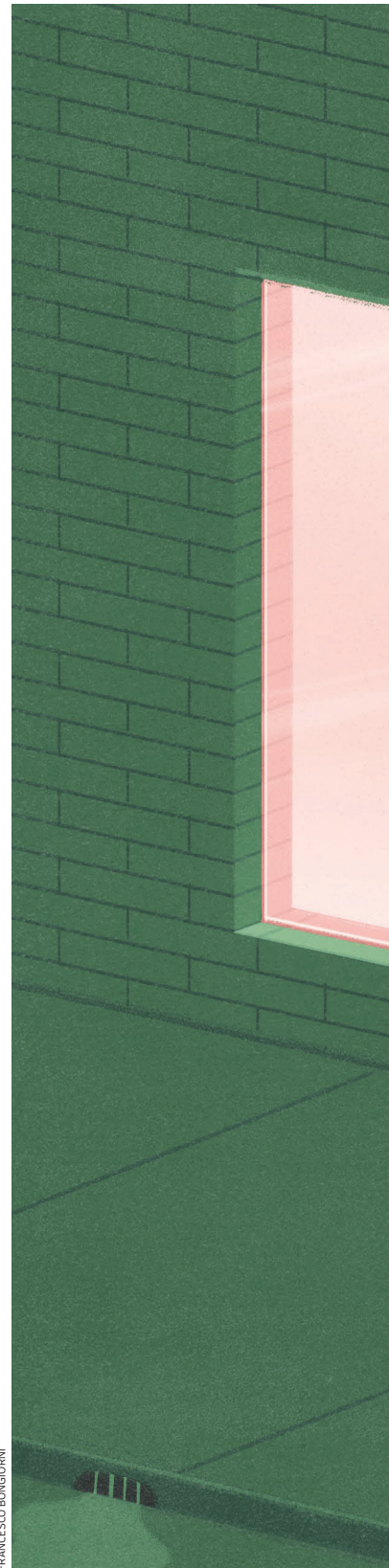
Happily, you don't need to know all of its intricacies to take advantage of the latest developments in immunology – although a little knowledge can help (see “Immunology at a glance”, page 47).

If you are younger than 60, in good health and don't have too many bad habits, then your immune system is probably functioning well enough to keep you safe from almost any infectious disease, including coronavirus.

The bad news is that as we age, our immune systems gradually deteriorate too. This “immunosenescence” starts to affect people's health at about 60, says Janet Lord at the University of Birmingham, UK. The older you get, the weaker your immune system becomes, and the more likely you are to get seriously ill or die because of it.

During a typical winter flu season, for example, very few people under the age of 65 get ill enough to be hospitalised. About 20 per cent of those aged 65 to 74 who catch the disease do, although hardly any of them die. But among the over 75s, about half of those with flu end up in hospital and 30 to 40 per cent of them die. Most of those who pull through never fully recover. Similar hospitalisation and mortality rates are being seen with the coronavirus, says Lord. As with flu, the difference for most people is down to immunosenescence.

To many, immunosenescence may sound like a far-off threat, but it is something that should concern us all. The decline starts surprisingly early in life, during puberty, and can be accelerated by all kinds of lifestyle



FRANCESCO BONGIORNI



factors. People who smoke or who are obese are particularly likely to have an immune system that is older than their chronological years. Being sedentary is another risk factor.

This has led to a new concept called immune age. It is similar to biological age, which uses chemical tags progressively added to genes throughout life to measure how far down the trajectory of ageing somebody has travelled, regardless of the number of years on the clock. Biological age and chronological age are usually quite tightly coupled, but can diverge by as much as 20 years either way. And unlike chronological age, biological age can go down as well as up, usually as a result of deliberate lifestyle changes. Both, it turns out, are also true of immunological age.

This way of thinking about the immune system has many uses. Knowing our immune age could help doctors judge how susceptible we are likely to be to illness. It might also help us all to maintain and strengthen our immune system. For instance, it could be

“At 60, some people have the immune system of a 40-year-old, others an 80-year-old”

used to validate supposed immune-boosting strategies. Does it affect immune age? If not, think twice.

Until very recently, it was impossible to measure immune age. But last year, a team led by Shen-Orr and Mark Davis of Stanford University in California revealed a way to do it. Using a “multiomics” approach – looking at a person’s genome, immune system, and protein function – the researchers audited the immune systems of 135 people in two age brackets, 20 to 31 and 60 to 96. They then repeated the measurements several times over nine years. What they discovered was that human immune systems follow a predictable trajectory. “We can give you a number which says where are you along this trajectory. That is your immune age,” says Shen-Orr. “And it is a very good predictor of all-cause mortality.”

Immune age measurement is still new and there is no commercially available test, although the team is working on one. ➤

THE IMMUNE DIET

One of the most successful anti-ageing strategies ever discovered is caloric restriction. It requires a permanent cut in energy intake of up to 60 per cent. In every experimental animal that has been put through this, from fruit flies to primates, it extends lifespan and healthspan, the number of disease-free years at the end of life.

The strategy works because it switches on an evolutionary adaptation to starvation, which prioritises repair and survival pathways over growth and reproduction. Calorie-restricted animals tend to be leaner, fitter, metabolically healthier and mentally sharper than those that eat at will. They also have a stronger immune response.

Unfortunately, caloric restriction is extremely hard to maintain voluntarily. But there are ways to mimic it without going on a permanent starvation diet. The key is to deactivate a nutrient-sensing pathway inside cells called mTOR. When calories are scarce, it switches off, initiating the metabolic cascade that transitions your system into famine mode. The pathway can also be toggled off with drugs called mTOR inhibitors, the best-known being rapamycin.

The strongest evidence that it is an immune booster comes from a clinical trial by the biotech company resTORbio, based in Massachusetts. One of its targets is immunosenescence, the gradual decline of our immune systems with age (see main story). Last year, the company ran a placebo-controlled study of a rapamycin-like mTOR inhibitor on people over the age of 65 who received a dose just before a flu vaccine. Those given the drug showed a stronger response to the injection and an uptick of their antiviral gene expression. "Some aspects of immune function are

clearly getting better," says Joan Mannick, resTORbio's chief medical officer. The drug has since failed a phase III clinical trial for reasons that are still unclear. Yet Mannick – and other researchers not involved in the work – say the principle that mTOR inhibitors can treat immunosenescence still stands.

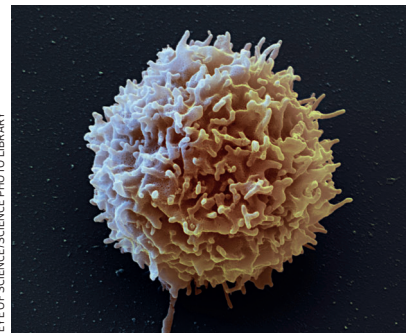
CUTTING CALORIES

Some people self-medicate with rapamycin even though it isn't officially recognised as an anti-ageing or immune-boosting drug. There are other ways to achieve mTOR inhibition though. One is intermittent fasting, a temporary state of caloric restriction that is enough to switch off mTOR for a short while and still obtain its benefits. There are various regimes including the 16:8 diet, which involves completely eschewing calories for 16 hours and only eating in an 8-hour window. Even done once a week, this is an effective way of slowing ageing and strengthening the immune system. Exercise is also a proven mTOR inhibitor.

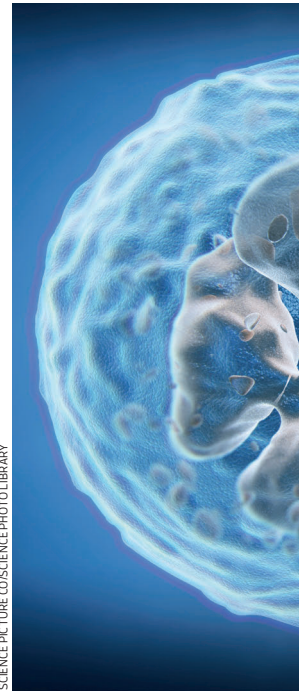
Even if a fasting diet isn't for you, simply keeping your weight down can have immune-boosting effects. According to Bonnie Blomberg at the University of Miami in Florida, being obese suppresses the immune system to a similar extent as being immunosenesced. Ageing is associated with a decline in the function of the immune system's B-cells and low production of antibodies in response to vaccines, and so is being obese. "Adipose tissue negatively impacts the antibody response," says Blomberg. "So obesity is associated with poor vaccine response, even in people who are young."



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The immune system has many defenders, including dendritic cells (top left) and a range of white blood cells that seek out and gobble up or kill invaders

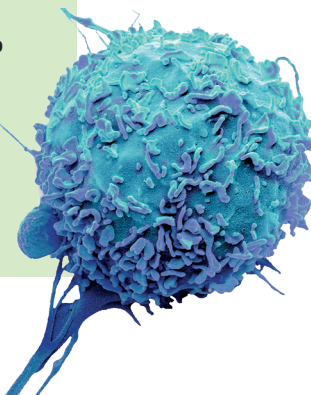
For now, probably the best way to gauge your immune age is to get your biological age tested, because the two seem to be roughly correlated.

Regardless, you don't need to know your immune age to take steps to start lowering it. And it turns out that many of the emerging anti-ageing drugs and strategies do their stuff, at least in part, by arresting or even reversing immunosenescence.

One key approach to keeping our immune age down relates to the fact that as we get older, some of our immune cells start to misbehave. This is especially problematic for a class of immune cells called neutrophils, the most common type of white blood cell. These form part of the innate immune system, the body's first line of defence against infection, and are the border force of the immune system, patrolling tirelessly through the bloodstream on the lookout for harmful bacteria. When they detect an intruder, they squeeze out of the blood vessel and barrel towards their target, then take it out in one of three ways: engulfing it like Pac-Man, spraying it with deadly chemicals or suicidally disgorging their DNA and throwing it around the invader like a net.

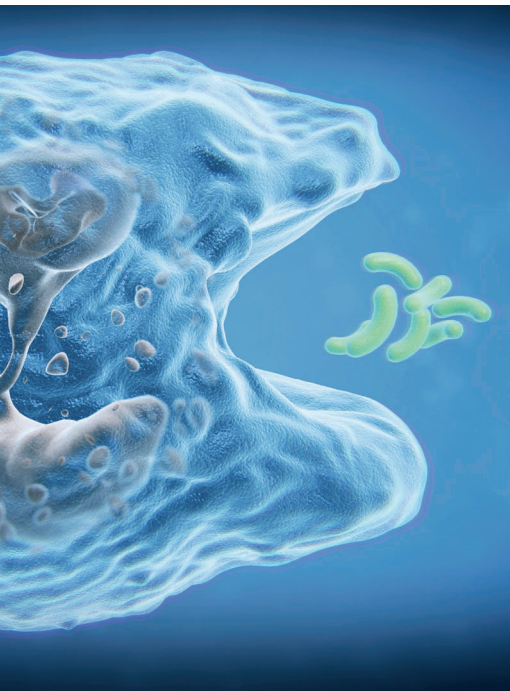
The process by which they tunnel through tissues is called chemotaxis, and it becomes increasingly erratic as we age. Older neutrophils can still detect invaders, but become much worse at hunting them down, often blundering haphazardly through tissue

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or charging off in the wrong direction. “I always say they’ve lost their satnav,” says Lord.

This is problematic for two reasons. It reduces the speed and efficiency of the defence, giving invaders more time to gain a foothold. It also causes inflammation. Lord has found that the blundering neutrophils cause between two and five times as much damage as their comrades that still know their way. Such friendly fire is a leading cause of inflammaging, the generalised low-level inflammation that creeps throughout our bodies as we age.

But the neutrophil satnav can be reset. The root of the problem is a chronically overactive enzyme involved in directional control. So Lord tracked down some existing drugs that were known to dial down this enzyme. When she gave one of these drugs to older adults, she found that it reset their satnav. “Their neutrophils are rejuvenated, they move like a young person’s neutrophils,” she says.

What are these miracle drugs? Statins, the ordinary cholesterol-lowering drugs already taken by millions of people.

Turning to real patient data from the University of Birmingham’s Queen Elizabeth hospital, Lord found that people admitted to hospital with pneumonia were much less likely to die if they were already taking statins to lower their cholesterol. This staggering result has since been confirmed in a small clinical trial. It is too early to recommend that everybody takes statins as an immune booster, says Lord – she and her team are conducting a bigger clinical trial. The drugs can also have serious side effects. But now might be a good time to have your cholesterol levels tested, once your local health system has capacity.

There is also a drug-free way to rejuvenate your neutrophils: exercise. In 2016, Lord and her colleagues measured exercise levels and neutrophil migration in 211 older adults.

“Those doing 10,000 steps on average had neutrophils as good as young adults,” she says. She emphasises that neutrophils aren’t antiviral so won’t prevent you catching coronavirus or help you beat it, but they will protect you from the real danger, which is pneumonia. “Usually what carries people away with these [viral] infections is secondary infections,” she says.

Vital vitamins

Another class of immune cells that begin to misfire as we age are T-cells. These are pivotal in the adaptive immune response – the more targeted part of the system – but are blunted in two ways by immunosenescence. As with neutrophils, their internal signalling pathways go awry, and they are also inhibited by inflammaging. But there may be a simple way to undo this damage. According to Dayong Wu, a nutritional immunologist at Tufts University in Boston, the answer is vitamin E.

In animal studies, it has long been known to enhance immune function, but the relevance of this research to humans was overshadowed by studies suggesting that vitamin E supplementation is toxic. Wu now says this is irrelevant: toxicity only arises at doses double that needed for T-cell rejuvenation. He and his colleagues tested vitamin E in older people – giving half of the 670 residents of a nursing home a small daily dose of vitamin E and the other half a placebo – and found significant differences in the rate of upper respiratory infections. A bigger clinical trial is in the pipeline, but the evidence is already strong enough that Wu recommends people over 65 routinely take 200 international units (IUs) of vitamin E. “It may help immune function. It doesn’t hurt,” he says.

Vitamin D, meanwhile, appears to do the same for the innate arm of the immune system, especially among people living at latitudes where there isn’t enough winter sunlight for their skin to synthesise the molecule. A 2017 review of the evidence for taking vitamin D supplementation concluded that it prevents upper respiratory tract infections. About 1000 to 2000 IUs should be safe and beneficial, says Wu, but people shouldn’t go higher than that because big doses actually suppress T-cell function.

A third supplement with good evidence for immune-boosting powers is zinc. “It is very effective for viral infections,” says Wu. Though he adds, “be cautious, the effective window is narrow and an overdose will suppress your immune system”.

“Taking small daily doses of vitamin E may help rejuvenate immune cells”

IMMUNOLOGY AT A GLANCE

There are two basic arms of the immune system: innate and adaptive.

Innate immunity is the first line of defence, staffed by general-purpose, pathogen-killing cells such as neutrophils and macrophages. These are the early responders to

an invasion. The adaptive side is more targeted and slower, reacting to specific pathogens with precision weapons such as T-cells, B-cells and antibodies. The adaptive arm also provides immune memory, which prevents you from getting certain diseases twice.

Cells called memory B-cells recognise the pathogen and trigger a swift and ruthless response if it invades again. Some viruses – notably flu – can mutate to evade immune memory. We don’t know yet if the new coronavirus does this.

DO SOME PEOPLE NATURALLY HAVE A STRONGER IMMUNE SYSTEM?

Even among people with a fully functioning immune system there are significant differences in how well it works. In 2018, the Milieu Intérieur Consortium based at the Pasteur Institute in France scrutinised circulating immune cells from 1000 men and women aged between 20 and 69. They found major individual differences between people of different ages, which you would expect given that the immune system declines as we get older. But they also discovered that people of the same age can have very different immune systems, beyond variation in their so-called immune age.

This is partly down to varying lifetime exposure to viruses and bacteria, which can radically alter the composition of your adaptive immune system – the wing of your defences that produces antibodies targeted to attack threats.

Genetics is also key. The Pasteur team found big disparities in the composition of people's innate immune systems, the generalised first line of defence, and these mapped onto differences in their genes. The significance of these genetic variations in immune response isn't yet known, but it may be that some people are naturally better than others at dealing with certain threats. Like a lot of things in life, immune strength is a genetic lottery.

Beyond genetics, the team found that smokers have a much older immune profile than non-smokers of the same age. It's unknown if this is reversible. But if you don't want to prematurely age your immune system, it would be best not to smoke.

Similar research on immune ageing by researchers led by Shai Shen-Orr at the Technion-Israel Institute of Technology suggests that the immune system can burn out. They tested the immune age of children living in Bangladesh, who generally have a heavy burden of infectious diseases and parasites, and found it was similar to that of young adults in California. The long-term clinical relevance of this is unclear, but it seems to undermine the adage that "what doesn't kill you only makes you stronger".

That said, an underworked immune system also seems to be problematic: people who aren't exposed to infections and parasites in childhood seem more susceptible to autoimmune disorders such as allergies later in life.

Aside from misbehaving immune cells, another big clue about the demise of our immune system with age comes from a vital but little-known organ called the thymus that is (or was) located beneath your breastbone. This heart-shaped patch of lymphatic tissue is where new T-cells mature before being released on active duty. It is very active in childhood but degenerates with age, shrinking by about 3 per cent a year from the onset of puberty. By late middle age, it has usually been reduced to a few scraps, and T-cell counts fall off a cliff.

This has consequences for the ability to fend off novel pathogens. In older people, who barely have any thymus left, the adaptive immune system is severely diminished, leaving an entire flank of their immune defences horribly exposed.

Step it up

Thymic regeneration is an active area of anti-ageing research. Some people have attempted to regenerate their own using human growth hormone. But there are non-pharmacological interventions. In 2018, Lord and her colleagues published a study of 125 amateur cyclists aged between 55 and 79. Most had been regularly riding long distances for decades. Unsurprisingly, they were leaner, fitter and stronger than average, but they also had better immune systems. Their T-cell counts were similar to those of much younger people and their thymuses were youthful. "A large part of thymic decline is down to physical inactivity," says Lord. There are strong suggestions from animal experiments that exercise might not just prevent thymic degeneration, but also reverse it, although that hasn't yet been demonstrated in humans.

Exercise has other immune-boosting effects too. "Active skeletal muscle is anti-inflammatory and stimulates macrophages," says Lord, who goes running every day. "Skeletal muscle is a profound immunoregulatory tissue in the body and keeping it going by physical activity really will have a lot of benefits for health. Exercise benefits all ages." Asked what one thing she would recommend to strengthen your immune system, she says: "Increase your step count to 10,000 per day." In the face of the new coronavirus, it is more important than ever to find ways to stay active – even in lockdown or isolation, which isn't going to be easy.

What you eat will also matter to your immune system – now is the time to look after your gut flora. There is good evidence that



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Regenerating the thymus, which wears down with age, can refresh the immune system

probiotics can enhance the immune system, that poor gut health is a cause of premature ageing and even that a healthy microbiome can reduce your immune age. In as-yet unpublished work, Lord's team analysed patients with the diarrhoea-causing gut pathogen *Clostridioides difficile*. Their immune age was off the scale, she says, 10 to 20 years higher than their chronological age. But after they were given a faecal transplant from healthy younger donors, it dropped rapidly. "The reduction is amazing, literally within a couple of weeks," says Lord.

You may not want to try that one at home. But there is plenty you can do to maintain a robust gut flora, including eating a healthy, varied diet rich in fibre, plant matter and fermented foods such as kimchi. Other dietary changes, such as fasting, are backed by good evidence too (see "The immune diet", page 46).

None of these interventions is without sacrifice. But if you want to stay alive and well for as long as possible, looking after your immune system is a no-brainer – especially now the new coronavirus is being called the biggest threat to public health since the 1918 flu. "The age of your immune system is a critical component of your lifespan," says Shen-Orr. "Think about what the system is supposed to do!" ■



Graham Lawton is a feature writer and columnist at *New Scientist* and author of *This Book Could Save Your Life*