THE AGE

Good Weekend

The silent killer: Why medical research is fired up about inflammation

From long COVID to Alzheimer's, all manner of health woes are increasingly thought to have one thing in common: inflammation. But there's an ongoing mystery: why does it go rogue in some people and not others? Great medical minds are on the case.

By Greg Callaghan

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Thanks to the focus on inflammation research over the past decade or so, we have a much richer understanding of how it behaves in our bodies. GETTY IMAGES

Pinned to the noticeboard behind Dr Sarah Coombes' desk at the bunker-like Sydney Ambulance Centre in Eveleigh is a dramatic aerial photograph of a medical emergency helicopter winching a patient up to safety. Before she stepped into a management role in 2018, Coombes spent her days in a chopper just like this one, flying to confronting scenes of road crashes, accidents, stabbings and shootings, delivering critical care, hour by hour, minute by life-saving minute.

One memorable time, as an air ambulance doctor in London (originally from Yorkshire, Coombes settled in Australia in 2004), she effectively performed open-heart surgery on a stabbing victim in the middle of a crowded pub after her chopper set down in the adjacent car park.

You need to be made of sturdy stuff for such pressurised work, which demands military-like precision honed by years of training, not just in emergency medicine, but winching, underwater escape and on-board safety. Even after becoming executive director of NSW Ambulance's Aeromedical Operations in 2018, Coombes was turning up for weekly shifts in the emergency department of St George Hospital in southern Sydney's Kogarah ("I'm a clinician at heart; the interaction with patients is what I find rewarding"). She was also impressively fit – training three times a week with a personal trainer, running and swimming, and skiing during her holidays.

But Coombes faced a tough new reality after she returned from a business trip to Switzerland in March 2020, where she'd been assessing a prospective purchase of a new fixed-wing jet for the medical fleet. While she was away, the COVID-19 outbreak was declared a pandemic by the World Health Organisation. "I returned to Australia only a couple of days before the borders shut," the 55-year-old recalls. "We were met at the airport by healthcare workers in full PPE."

On at least three occasions during the conversation that follows, as she reveals the chain reaction of inflammatory symptoms that led to her diagnosis of long COVID, Coombes becomes tearful, so much has it affected her quality of life. At first, she says, she dismissed the feelings of sluggishness and a sore throat as the simple result of a long flight. “But I soon developed a cracking headache, nausea, chest pain and a persistent cough, so I took myself off to a COVID-19 testing facility.”

The following day, NSW Health called Coombes to inform her that she’d tested positive. “Like many people in the early days of the pandemic, I thought this would be a mild, flu-like illness that would pass after a couple of weeks. But just as the headache and nausea faded, I began to get this really intense pain in my ankles, hips and sacroiliac joints [linking the pelvis and lower spine], which I put down to a reactive inflammation from the virus.” No position – sitting, standing, or lying down – felt comfortable. “If you want a blunt medical diagnosis: I felt like shit.”

On day 30 (ever the medic, she has a record-keeping mind), her fatigue came back with a vengeance, along with shortness of breath and a skyrocketing heart rate (a resting pulse rate of 120 beats per minute would sometimes jump to 130 or 150 at the slightest exertion). On day 37, after two people in full PPE gear had arrived on her doorstep to administer a test, she received news she was free of coronavirus. When the inflammatory symptoms persisted, Coombes began to suspect she might have long COVID, the name given to those still suffering long after testing negative.

In that pre-vaccine year of 2020, experts estimated that between 10 and 30 per cent of those who fell ill with COVID had a lingering array of symptoms months after the initial infection (there is still no internationally-agreed timeline on long COVID: the NHS in the UK defines it when symptoms persist for 12 weeks after the initial illness, the Mayo Clinic in the US puts it at four weeks). A person’s susceptibility to inflammation was also emerging as a key factor in their vulnerability to the lung damage caused by severe COVID and the continued breathlessness associated with long COVID.

The isolation of the pandemic was no picnic for Coombes, who lives alone. After a few months, she developed a return-to-work plan, beginning with two or three hours a day until she felt stronger (“If I got tired, the first thing I noticed was that my resting heart rate would increase, so I learnt to pace myself”). What baffled her, however, was the persisting merry-go-round of symptoms.

The three most common symptoms of long COVID – fatigue, shortness of breath and chest pain – would come and go with frustrating unpredictability over the next year, some triggered by bouts of pleurisy, a condition in which the large, thin layers of tissue lining your lungs and chest cavity become inflamed. “Some of these appeared to be classic post-viral symptoms, others not,” she says. “I’d have shoulder pain for a month or so, and then elbow pain, then knee pain, before it would return to my ankles again.”

As a healthcare worker, Coombes was among the first wave of people to be vaccinated in NSW last year, which couldn’t come soon enough as by then, her body had zero antibodies to the disease, and was at real risk of reinfection. In late 2020, she signed up to be a participant in a study of COVID patients by a team of researchers from the Kirby Institute at the University of NSW and Sydney’s St Vincent’s Hospital, which involved regular blood tests, physical examinations and cognitive testing. Last month, this research grabbed international headlines after it identified a clear biological marker of long COVID, which University of Michigan research last year estimated to affect as many as 100 million people worldwide.

This fingerprint, if you like, of long COVID showed a biological basis for an illness some had dismissed as psychosomatic. “We found there is a significant and sustained inflammation that indicates prolonged activation of the immune-system response detectable for at least eight months following initial infection,” notes Dr Chan Phetsouphanh, senior research associate at the Kirby Institute.

“One possible hypothesis is that viruses are still present in tissues of [long-COVID] patients and may be driving production of inflammatory interferons.”

Another study by researchers in South Africa found long COVID patients were suffering from an overabundance of inflammatory molecules trapped inside microscopic blood clots, triggering a range of lingering symptoms.

“The dilemma with long COVID is with the percentage of individuals, up to 30 per cent, who never really get over these clotting abnormalities … when they are not infective any more,” Professor Resia Pretorius, head of physiological sciences at Stellenbosch University, who led the study, told America’s National Public Radio.

Interestingly, studies suggest no cause and effect between the risk of getting long COVID and the severity of the initial infection – even some of those suffering only a moderate initial illness, like Coombes, went on to develop long COVID. In the Kirby Institute study, two pro-inflammatory cytokines (inflammation messengers) were identified as being elevated in long COVID patients. The sheer scale of the pandemic has also brought to light other inflammatory rarities, beginning in 2020 with a rare complaint in children that mimicked Kawasaki disease, involving a “cytokine storm” of uncontrolled hyperinflammation leading to widespread tissue damage, organ failure and a high risk of death.

Dr Sarah Coombes. “I hope COVID doesn’t leave me with ongoing symptoms or vulnerable to infections for the rest of my life.” LOUISE KENNERLEY

Coombes returned to full-time work this year but has never regained the energy levels she once took for granted, and has ruled out returning to hands-on emergency care in the immediate future. “Wearing full PPE all day is incredibly tiring: you get hot and sweaty and you can’t even get a drink in the clinical areas. I don’t know if I will ever be able to return to emergency-department work.”

Still, she considers herself one of the lucky ones because she never lost her sense of taste or smell, nor did she suffer from the “brain fog” so many long-COVID patients complain of. Even now, she has an occasional but persistent cough, a legacy from a bout of pneumonia (non-COVID) she suffered last December after making an urgent trip back to the UK following the death of her grandfather. “I just hope COVID doesn’t leave me with ongoing symptoms or vulnerable to infections for the rest of my life.”

Long COVID is merely the latest in a big, mixed bag of diseases in which inflammation has been found to play a key role. Over the past 20 years, study after study has revealed inflammation’s contribution to heart disease, respiratory diseases like asthma, rheumatoid arthritis, Alzheimer’s disease, and autoimmune diseases like type 1 diabetes, lupus and inflammatory bowel disease, which encompasses Crohn’s disease and ulcerative colitis.

Inflammation has been shown to loosen cholesterol deposits in coronary arteries, leading to heart attacks; it’s the mechanism that wears down large and small joints in rheumatoid arthritis; it’s the engine behind the ulceration of the gastrointestinal tract in inflammatory bowel disease; it’s at the centre of the immune system attacking its own tissues in lupus sufferers; it’s at the heart of the process of T-cells attacking insulin-producing cells in the pancreas in type 1 diabetes; it’s behind the chronic pain of endometriosis; in Alzheimer’s, prolonged neuroinflammation can trigger onset of the disease.

The word *inflammation* might sit a little flat on the page beside dramatic words like cancer and heart disease, but because it’s an underlying dynamic in a host of diseases, it’s now a focus of cutting-edge medical research across the globe.

“There’s been a growing realisation among scientists and clinicians in recent years of the importance of inflammation, and now it’s a rapidly evolving field,” says Professor Philip Hansbro, director of the Centenary UTS Centre for Inflammation in Sydney, Australia’s first research centre dedicated exclusively to studying the mechanisms underlying inflammation. “Because inflammation is implicated in so many diseases, the better we understand it, the better we’ll be able to widen our arsenal of treatments.”

Professor Elizabeth Hartland, director and CEO of Melbourne’s Hudson Institute of Medical Research, which houses the largest number of inflammation researchers – 150 – in Australia, contends that inflammation contributes to more than 50 per cent of deaths worldwide, and is the single biggest cause of death from COVID. “We’re not designed to withstand constant bouts of inflammation,” Hartland tells me via video from her Melbourne office. “That’s why when it becomes overblown or chronic, it can have such lasting, damaging effects on the

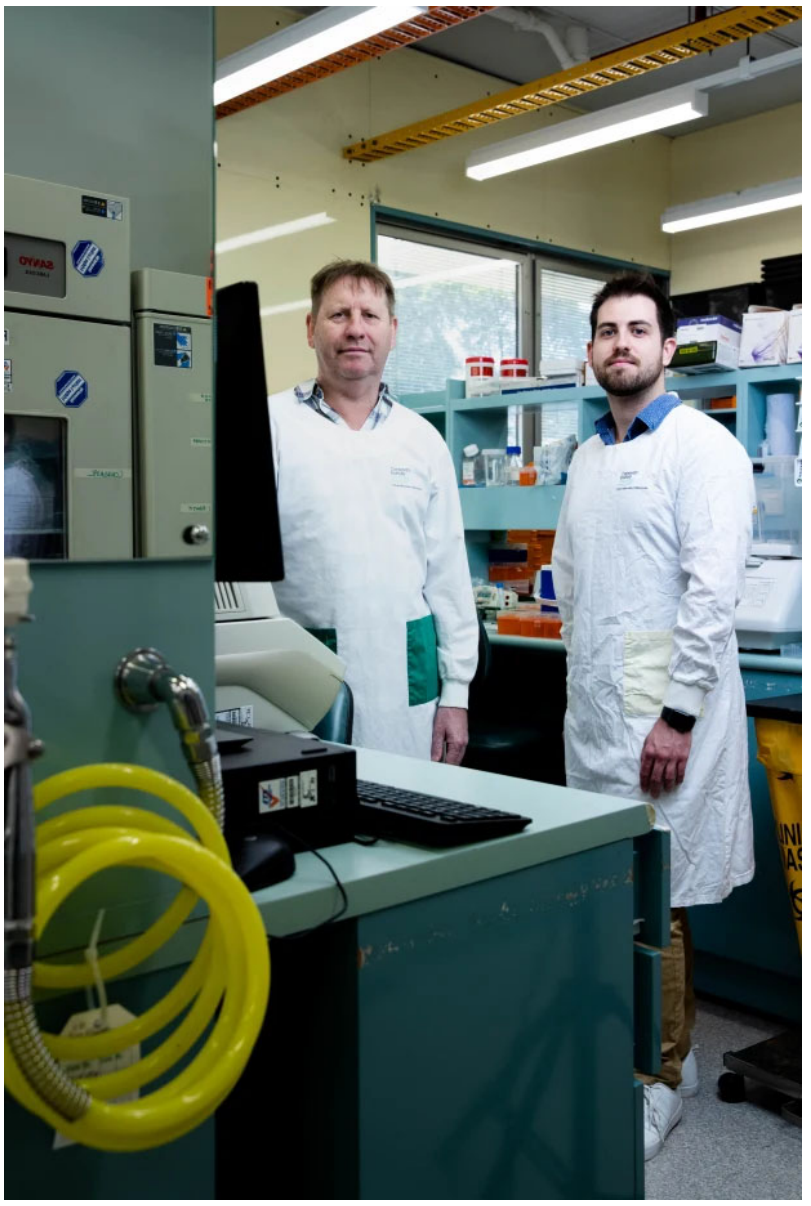
body. Overwhelmingly, we need access to a better range of therapies that targets inflammation when it becomes harmful."

Scientists are now talking about an "inflammation clock", Hartland later explains in the *Good Weekend* podcast chat, *GW Talks*. "People who have less inflammation are predicted to live longer, and people with chronic inflammation to age faster."

Trying to sum up the many facets of inflammation is a little like trying to describe a moon landing. But it's safe to say that without inflammation, our lives, to quote Thomas Hobbes, would be nasty, brutish and short. Once a foreign invader – a bacterium, virus or parasite – enters your body, your immune system immediately dispatches white blood cells to the injury or entry site, slowing down the march of the intruder, until wave after wave of reinforcements arrive to launch a counter-attack against its spread.

The infection-fighting cells release proteins called cytokines that fuel inflammation, the trademark signs of which are heat, swelling and redness. This is the process that turns the tissue around a splinter in your finger red and hot – and it's essential to healing.

Inflammation is indeed a lifesaver – until it's not. Occasionally, even after the unwelcome pathogen has been destroyed and the healing process is over, the inflammatory fires continue to burn away, fuelled by an immune system in overdrive. "Inflammation is a frontline system, it needs to be activated quickly but then should switch off when the job is done," explains Hartland. Over time, this chronic inflammation can lead to lasting collateral damage to organs such as the lungs, heart, bowels and joints.



Professor Philip Hansbro, left, director of the Centenary UTS Centre for Inflammation in Sydney, and his colleague Matt Johansen. Hansbro says "the better we understand inflammation, the better we'll be able to widen our arsenal of treatments." JANIE BARRETT

"Inflammation is a frontline system, it needs to be activated quickly but then should switch off when the job is done."

The big question about inflammation is this: why does it turn rogue in some people and not others? Why do some COVID patients fall victim to severe respiratory disease while others escape unscathed? What is it that makes a person's digestive tract susceptible to the inflammatory ulcers of ulcerative colitis? Do we become more susceptible to chronic inflammation as we age? (Yes.) And can suffering one inflammatory disease make us more vulnerable to another? (Yes again.) Inflammation's tangled involvement in so many diseases explains why it's now one of the hottest (no pun intended) areas of medical research.

When Michael Gantier was 11, growing up in the town of Cholet in France's picturesque Loire Valley, having his appendix removed didn't seem like such a big deal. Then again, he had no idea of what was in store. "Unfortunately, it was a Friday afternoon, probably the worst time to get an operation," the 41-year-old father of two says half-jokingly of the minor medical horror story he's about to share. "After the operation, I had a temperature of 40-41 degrees and a high count of white blood cells."

While the doctors initially dismissed this as part of his recovery from the operation, his parents, both teachers of biology in school, suspected otherwise.

Associate professor Michael Gantier, who is working on anti-inflammatory treatments for COVID, also suffers from an inflammatory disease. “I still get weird symptoms a few times a year,” he says. PENNY STEPHENS

“The pain was excruciating, I wasn’t eating and was on an IV drip for seven days,” he recalls. An X-ray revealed his intestine to be misshapen, which prompted emergency surgery that revealed a huge build-up of infected fluid in his peritoneal cavity that had to be drained. Suffering sepsis, a life-threatening infection of the blood, he was critically ill. “When the appendix is removed, surgeons have to be careful that bacteria from the gut don’t
leak out into the peritoneal cavity,” explains Gantier. “And unfortunately, that’s exactly what happened. The surgeon later said I was only hours away from death.”

In the years afterwards, Gantier was plagued by stomach problems, which resulted in a diagnosis in his mid-20s of Crohn’s disease, a debilitating condition characterised by diarrhoea, abdominal cramping, fatigue and weight loss. In the meantime, his experience as a child inspired him to become a doctor and scientist, and he is now an associate professor and research group leader at the Hudson Institute, where he is working on anti-inflammatory treatments for COVID.

Both Crohn’s disease and ulcerative colitis fall under the umbrella of inflammatory bowel disease. Both are notorious for flare-ups, which can last for days or weeks depending on the severity of the attack and, if not swiftly controlled by medication, can result in hospitalisation. Gantier is on lifelong immunosuppressant drugs, which make him especially vulnerable to being infected with COVID, resulting in him working from home and avoiding unnecessary social contact in 2020 and 2021. Although people with Crohn’s and ulcerative colitis usually learn to identify possible triggers – Gantier, for example, avoids dairy – flare-ups can be frustratingly unpredictable.

Like many people living with inflammatory bowel disease, Gantier has suffered his share of lower back and joint problems. “Pretty much all the autoimmune diseases overlap around joint inflammation; we don’t know exactly why that is,” he says. The joint pain can be like arthritis (pain with inflammation) or arthralgia (pain without inflammation). “My disease has been much more stable since I started taking immunosuppressants, but I still get weird symptoms like back pain, reflux, diarrhoea a few times a year.”

Gantier, a warm and self-deprecating man, has my sympathy. I was diagnosed with a mild form of ulcerative colitis, which causes inflammation and ulcers in your digestive tract, more than 20 years ago. In the wake of a minor flare-up in 2020, I was struck with a range of mystifying symptoms not dissimilar to Gantier’s. First a frozen shoulder, then a nasty inflammation in one eyelid, followed by excruciating lower back pain that lasted for more than six weeks, which led to a battery of medical tests with frustratingly inconclusive results.

Like most sufferers of ulcerative colitis, non-steroidal anti-inflammatory drugs like Ibuprofen and Naprosyn are a big no-no because they worsen bleeding and even bring people out of remission (after years of no flare-ups, a single tablet of Naprosyn back in 2011 triggered my nastiest attack) and I now even avoid the grandfather of anti-inflammatories, aspirin.

Treatment varies according to the severity of the inflammation, and can involve a combination of drugs, including corticosteroids (steroidal anti-inflammatories like prednisone) which are immunosuppressive. If medications are administered early enough before the ulcerative process takes hold, most sufferers go into remission, avoiding too much disruption to their social and working lives, or hospitalisation. Regardless, it’s the unpredictability of inflammatory bowel disease that can lead to anxiety and depression in some people.

We are also at higher risk of colon cancer and ankylosing spondylitis, another inflammatory disease that over time can cause bones in the spine to fuse. The gut microbiome, which refers to the billions of bacteria colonised inside your digestive tract, has become a particular focus of inflammation research over the past decade. “The microbiome is something we really focus on now,” says Philip Hansbro, his cluttered

desk piled high with research papers. “Advances in technology have enabled high throughput sequencing of microbiomes, which means anyone can get their biome sequenced for a reasonable cost.”

Any imbalance in the microbiome can influence pro-inflammatory processes in the body, explains Michael Gantier, whose research in the past has involved trying to define how immune sensors distinguish good from bad bacteria, such as salmonella. A colleague at the Hudson, Dr Sam Forster, who leads the Microbiota and Systems Biology Laboratory, compares a healthy gut biome to a pristine forest bursting with a rich variety of trees, shrubs and flowers; an unhealthy biome to a partly cleared one, lacking in biodiversity and riddled with invasive pests and weeds. “If you have an inflammatory response from the gut, you’ll likely have an inflammatory response in other parts of the body, because our systems are interlinked,” says Forster.

Microbiome tests, which reveal the current state of your gut, have become quite popular in recent years, and there is some evidence they can help predict those at risk of inflammatory bowel disease, but it’s a technology still in its infancy. “There are something like 100 trillion bacteria in your gut and about 6000 species,” explains Hansbro.

Diet plays a role, although how big a role depends on which expert you speak to. Inflammatory bowel diseases, which are increasing across the globe, were rare in Asian countries like Japan before they switched to a Western diet. My gastroenterologist once told me that when he started practising in the mid-1980s, he had very few patients of Asian heritage with inflammatory bowel disease; now they represent up to half of his patients. Forster says our microbiomes have typically become less complex with a Western diet and lifestyle. “There is a lot of association between changes in bacteria and the modification of the immune response,” he says.

One treatment that has taken off over the past decade is – ugh alert – faecal microbiota transplantation, in which faecal matter is transplanted from a healthy donor into the body of someone suffering from a gut disorder. Faecal transfers have become much more common in the past five years, particularly in the US. “Faecal transfers have been found to be 90 per cent effective in treating inflammatory bowel disease caused by the bacterium *Clostridium difficile*,” says Hansbro. Hansbro and his team have also recently shown that the transfers may benefit people suffering the chronic inflammatory lung disease, COPD.

But Hansbro cautions against over-optimism: this is a procedure that still has many unknowns. “There have been two recent fatalities in the US, where the faeces that were transferred contained a virus. And there was the case where a person was treated with faeces from an obese person, and they became obese themselves.”

Look at Charlotte Bachali – dewy-skinned, with a warm smile and a dynamic manner (she’s a children’s book editor, a marriage celebrant and has also been a teacher) – and you’d never guess she’s been plagued by rheumatoid arthritis (RA) for most of her life. “That’s the thing with an invisible disease like RA,” she says. “I can be smiling and enjoying myself at a party or other social situation, but I’m also in pain at the same time.”

Arthritis entered her life as an aching, swollen right thumb when she was studying for her HSC. She wasn’t too worried at the time – the family doctor had initially dismissed the symptoms as RSI or perhaps carpal tunnel syndrome, from all the handwriting she’d been doing. “It would start hurting when I woke up each morning,” the now 35-year-old recalls. “I’d hang my hand over the side of the bed, because something about doing that made it feel better.”

Within a year the aching had spread to the knuckles and wrist of both hands, which sent her to the Sydney Hospital Hand Unit, where she was diagnosed with seronegative RA (a form that doesn’t show up in blood tests). In the years that followed, the pain and inflammation spread to her feet and ankles and later the knees, elbows and shoulders during particularly bad attacks.

Charlotte Bachali. “It’s quite disconcerting to wake up and look at a hand that I don’t recognise as my own.” DOMINIC LORRIMER

“That’s the thing with an invisible disease like rheumatoid arthritis. I can be smiling and enjoying myself at a party, but I’m also in pain.”

“Being diagnosed with arthritis as a teenager wasn’t something I was expecting,” says Bachali. “At first, I was against taking medication because I was worried about side effects and the prospect of taking it for the rest of my life, which was overwhelming. But then one doctor

warned me that if I didn't start taking the medication, I'd be in a wheelchair in five years, based on the level of inflammation occurring in my joints."

The lack of a cure – facing a lifetime of drug treatment – "was the most shattering part of my diagnosis", Bachali reflects. (Rheumatoid arthritis is a totally different disease from osteoarthritis, with which it's often confused. Osteoarthritis results from wear and tear, tends to be concentrated in a particular joint and happen among the over-40s; RA is a systemic auto-immune disease and can happen at any age.)

Arthritis has affected every area of Bachali's life ("work, relationships, hobbies and financially"). "I've learnt to make adjustments. Knowing I can't walk for more than 10 minutes, that I can't sit long either. My hands, wrists, feet and ankles have always been the most problematic joints for me. If my hands become inflamed, all my fingers will puff up like sausages. It's quite disconcerting to wake up and look at a hand that I don't recognise as my own. The pain is difficult to describe. It feels like fire and ice and a massive pressure, as if a weight is pushing them from all sides. It hurts to move, and it hurts to stay still."

Probably the most common myth about rheumatoid arthritis is that it's a disease of old people. "Most people are surprised when I tell them I have arthritis because I'm relatively young," says Bachali, who is also on the board of Arthritis Australia. "In fact, two-thirds of people with arthritis are between 15 and 60 years old."

Prospects for sufferers have improved significantly in recent years thanks to combination anti-inflammatory therapies. Still, Bachali lives in hope of "an amazing new development that will put me in complete remission".

"We now recognise that the benefits of staying on medication – so inflammation doesn't occur – far outweigh any drawbacks," says Professor Susanna Proudman, director of the rheumatology unit at the Royal Adelaide Hospital. "In severe disease, the inflammatory cells produce proteins that digest the underlying cartilage and bone, creating holes or 'erosions' in the bone around the joint, causing damage and reducing function. These erosions can be prevented thanks to disease-modifying anti-rheumatic drugs (DMARDs), which preserve joint function."

Of course, anyone suffering an inflammatory disease such as RA is more vulnerable to infections, including COVID, especially if they're on immunosuppressants. "I've had to find a balance where I have some pain on a lower dose of medication in order to minimise the side effects," notes Bachali. Acknowledges Proudman: "Those taking DMARDs, which can suppress the immune function response to infection, have an increased risk of more severe COVID."

Still, once a person has an autoimmune disease like RA, they have an increased risk of other autoimmune diseases such as thyroid disease. "Rheumatoid arthritis is a systemic disease, meaning there is potential for other organs to become inflamed," explains Proudman. "This occurs far less commonly these days, but it can include lung inflammation and inflammation around the heart."

The good news is that in the fight against inflammatory disease, we now live in a world of opportunity. Multiple research studies are underway at the Hudson Institute and the Centenary UTS Centre for Inflammation. Thanks to the focus on inflammation research over the past decade or so, we have a much richer understanding of how it behaves in our bodies, explains the Hudson Institute's Professor Elizabeth Hartland. "We have a better knowledge of the viral and bacterial triggers of inflammation, how cytokines act on different tissues, and the genetic basis of inflammation disorders. All this has led to new treatments."

Until last year, there weren't many reports of long-COVID patients making a full recovery, but that appears to be changing now that more time has elapsed. Widespread vaccination also appears to have successfully blunted long COVID: studies from the UK and the US indicate that getting a jab at least halves the risk for those infected with the earlier Alpha and Delta variants. The jury is still out on whether long COVID is less common or milder with the wildly infectious Omicron strain, but again, vaccination appears to radically reduce the risk of prolonged illness.

Sarah Coombes is hopeful that, after the setback late last year, she's now on the road to recovery. "It won't be a smooth ride, but I'm hopeful I will get back to where I was before. They used to call me Superwoman – able to work long hours and exercise hard, every day. I miss that."

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