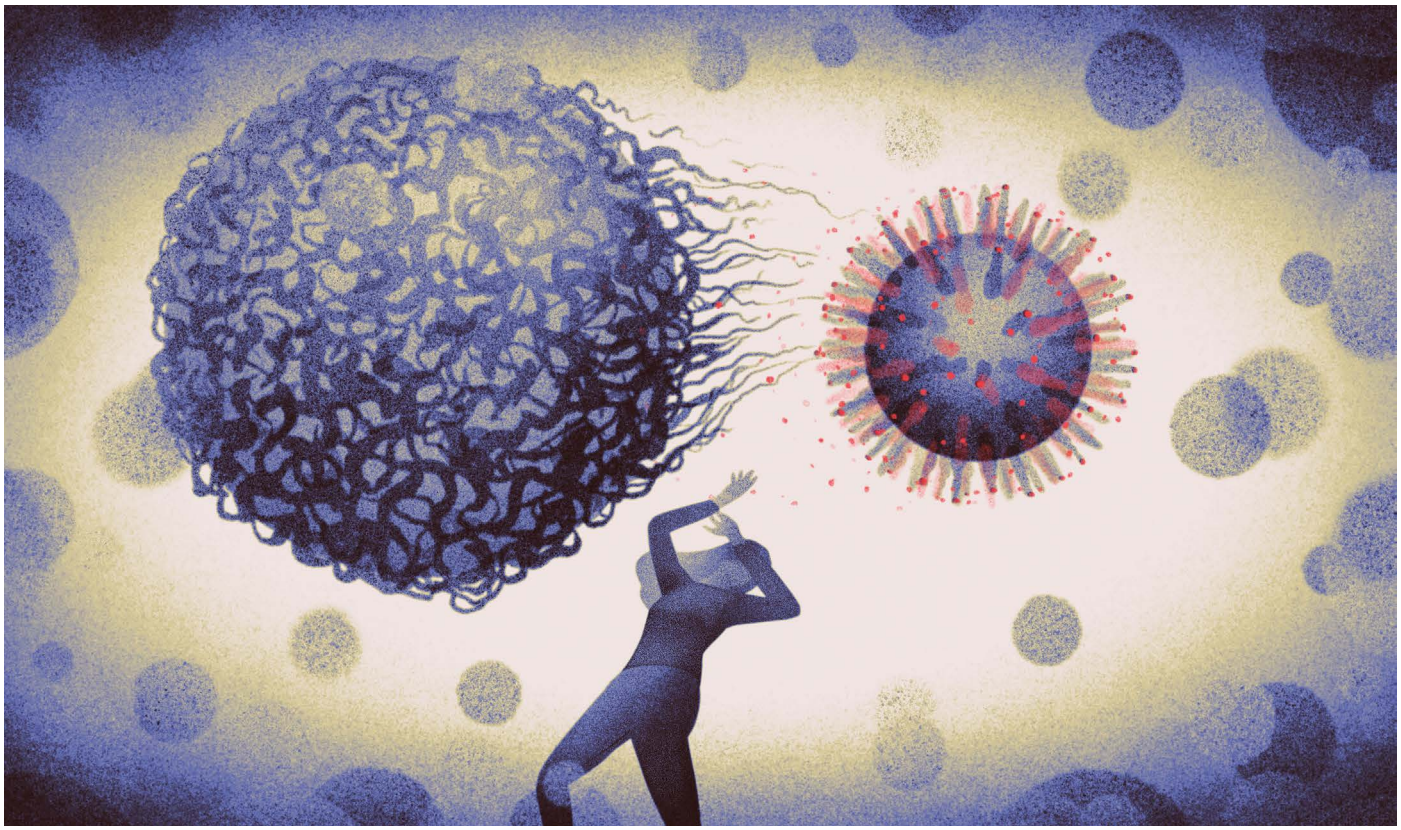

ILLUSTRATION BY DANIEL STOLLE

Infectious triggers

The body's response to viruses has long been proposed to spark autoimmune disease. Pandemics could clarify the connection. **By Anthony King**

When neurologist Russell Dale met a 15-year-old with an acute condition resembling Parkinson's disease in 2000 while working in London, it was like seeing someone with an illness from a century ago.

The teenager had initially had an infection, possibly viral. In a week, he could barely move. "He walked like an 80-year-old with Parkinson's, with poor arm swing and expressionless face," recalls Dale, who is now at the University of Sydney, Australia. Over the next 4 years, Dale would describe 19 more people with similar Parkinson's-like symptoms, as well as sleep disorders, lethargy and psychiatric problems[1].

To Dale, these symptoms seemed similar to the brain condition encephalitis lethargica. An epidemic of the disease spread around the world between around 1916 and 1926. About the same time, people also faced an influenza pandemic. The H1N1 virus behind the 1918 pandemic is thought to have infected around 500 million people, and claimed the lives of at least 50 million. Although H1N1 has never been confirmed as the cause of the rise in cases of encephalitis lethargica, the largely concurrent timing has led to much speculation.

Dale's hunch was that the people he saw had had an acute infection that caused their immune systems to attack their tissues. He found that they produced autoantibodies that seemed to target neurons deep in the brain. After a month of steroid treatment, most people had made a full recovery. The idea that viral infections can trigger a sustained immune attack against the body's tissues has simmered among immunologists for decades. In some rare instances, the link between an infection and autoimmunity is clear. But for common autoimmune diseases, such as multiple sclerosis, type 1 diabetes, lupus and rheumatoid arthritis, concrete evidence has proved harder to come by.

Viruses cannot typically be recovered from diseased tissue, and gathering epidemiological evidence is hampered by the often lengthy time between infection and the noticeable onset of an autoimmune condition. Such difficulties mean that a link is not generally accepted. "There's intense interest from people like me," says Danny Altmann, an immunologist at Imperial College London, "but it is not a chapter in medical or immunology textbooks."

Improved understanding of the mechanisms by which viruses trigger autoimmunity is shedding light on the role that viruses have in common autoimmune diseases. In addition, investigations into the long-term impact of viral pandemics, in which many millions of people experience an acute infection at a similar time, are allowing researchers to draw firmer links between specific viruses and autoimmunity. Just as some researchers suggested a connection between the 1918 pandemic and encephalitis lethargica, associations have also been suggested between autoimmune disease and the 2009 swine flu and the ongoing coronavirus pandemics. As knowledge of viral involvement builds, new targets for treating or preventing autoimmune disease could follow.

Infection response

When a virus enters the body, the immune system jumps into action. In hours, immune cells including neutrophils and natural killer cells

begin attacking anything that does not clearly belong to the body. Inflammation sets in, followed by the activation of immune cells called T cells and B cells. Unlike the early immune response, these cells target markers, known as antigens, that are specific to a particular invader. Effector T cells use these antigens to target infected cells, and helper T cells have a coordinating role. B cells, meanwhile, respond by producing antibodies that bind to invaders' antigens and tag them for destruction.

Sometimes, however, B cells erroneously generate antibodies against the body's own proteins. When people are exposed to Epstein–Barr virus (EBV) for the first time, for instance, "a number of autoantibodies arise", says Gregg Silverman, an immunologist at NYU Grossman School of Medicine in New York City.

One reason for this misbehaviour by B cells is that in the heat of the battle, the correct targets can become unclear — and more intense fights generate greater confusion. "The more cells killed by an infection, the more autoantigens are released," says Silverman. In the case of infection with the virus SARS-CoV-2, there can be so much tissue injury that "the immune system cannot figure out initially whether it should be recognizing the virus or self-antigens that are being released from our own cells", he explains. This phenomenon, known as epitope spreading, leads to both friend and foe being hit.

The body can also fall victim to mistaken identity when a protein associated with an invader closely resembles one of the body's proteins. The standard example of this molecular mimicry is acute rheumatic fever, a rare complication of a throat infection caused by the bacterium *Streptococcus pyogenes*. One of the bacterium's proteins is structurally similar to a cardiac muscle protein, leading the immune system to target both, and causing inflammation in the heart.

Other factors also contribute to errant targeting. For example, tissue damage can reveal self-antigens that are not normally seen by the immune system, which can result in them becoming unfortunate targets. In addition, because viruses use the body's cells to replicate, they contain pieces of human phospholipids, which can make it difficult for immune cells to tell friend from foe. For most people, however, these autoantibodies don't pose a major problem. "You might have autoreactive cells, but you don't have disease," Ballesteros-Tato says.

As the immune system starts to win, it pulls several levers to quell friendly fire. Regulatory T cells, for example, secrete chemicals that dampen inflammation, soak up pro-inflammatory cytokines and suppress other immune cells (see page S60). "These cells are putting brakes on the process by limiting the help B cells get," Ballesteros-Tato explains.

But if the brakes fail to engage, disease can take hold. This effect can be seen in the cancer drugs known as checkpoint inhibitors. These drugs block proteins on T cells that act as off switches, to negate the ability of cancer cells to manipulate the switches to shield themselves from attack. However, doing so can lead to potentially severe autoimmune side effects, such as encephalitis — even in people with no history of autoimmune disease.

"The immune system cannot figure out initially whether it should be recognizing the virus or self-antigens."

In people infected with viruses, Ballesteros-Tato thinks that higher levels of inflammation make it more likely that autoimmunity will be allowed to run amok. "In order to have autoimmunity you have to have a breakdown of tolerance," he says. "In a high inflammatory environment, this is easier." Some people might also be predisposed to brake failure. In unpublished work, his lab took mice prone to developing lupus in old age and infected them with a flu virus. The virus accelerated disease development. "That can happen", he says, "when a viral infection gets out of control."

Trigger hunt

Some viral infections have well-documented autoimmune effects. For example, among people who have brain inflammation owing to a herpes infection, around one-quarter will relapse a few weeks into recovery — usually owing to autoantibodies against a type of receptor found on the surface of neurons, called an NMDA receptor. "We've clearly shown that this is indeed an autoimmune process," says Dale. Similarly, the mosquito-borne chikungunya virus typically causes fever and severe joint pain lasting around a week, but it can lead to chronic arthritis. The infection seems to cause T cells to home in on joints, says Altmann.

Links between the most common autoimmune diseases and viruses, however, are generally less clear. For example, in 1979, researchers at the US National Institutes of Health recovered traces of coxsackievirus B4 — a common virus implicated in several diseases, including hepatitis and myocarditis — from the pancreas of a child with type 1 diabetes[2]. Mice infected with the virus were subsequently found to develop defects in the pancreas and to release abnormal insulin levels after six months[3]. "Everyone thought we had found the cause of type 1 diabetes," recalls Matthias von Herrath, an immunologist at La Jolla Institute for Immunology in California. "But then it got really complicated." In the decades since, numerous other viral suspects have turned up in studies of diabetes, including rotaviruses, enteroviruses, human herpesvirus 6 and cytomegalovirus.

Researchers are continuing to explore the potential for a viral trigger for type 1 diabetes. In February, a team of researchers reported that it had found a heightened antiviral response and signs of stress in pancreatic cells called β cells in people with type 1 diabetes[4]. The immune system might be failing to clear an infection, leading to ongoing inflammation that makes β cells more vulnerable to immune attack. "A picture is emerging of something being wrong with virus defences," says von Herrath.

One of the strongest associations between an autoimmune disease and a specific virus is that between multiple sclerosis and EBV. The virus is one of the most common to affect people, and most children develop antibodies to it by the age of two. People first infected with it as teenagers, however, can develop glandular fever. "Best to get EBV early in life," says Gunnar Houen, an immunologist at the State Serum Institute in Copenhagen.

The virus has been linked to multiple sclerosis for decades, with numerous studies finding associations between the disease and markers of infection, such as the protein EBNA1. Multiple sclerosis does not typically develop in children who have not been exposed to EBV, and EBV antibody levels are higher in those with the autoimmune disease[5]. "It is enormously significant as a driver of multiple sclerosis," says immunologist Lawrence Steinman at Stanford University in California.

Several mechanisms by which EBV might cause or exacerbate multiple sclerosis have been proposed. One involves the resemblance of a fragment of EBV to anoctamin-2, an ion channel in the central nervous system that can be targeted by autoantibodies. "I favour this molecular mimicry hypothesis," says Tomas Olsson, a neurologist at the Karolinska Institute in Stockholm. Other possibilities include the destruction of nerve tissue as part of efforts to fight off the virus, and the direct interaction of the virus with B cells — it uses the cells as hiding places and might disrupt their immune function in the process. After having glandular fever, a person's immune system is "completely topsy-turvy", says Altmann. "You chucked a hand grenade in and it has done wacky things."

Despite many lines of evidence suggesting that EBV has a role in multiple sclerosis, the connection is still difficult to prove — mainly because the virus is so common, infecting

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Local residents queue up for COVID-19 tests in Ditan Park, Beijing.

around 95% of adults. "Essentially all humans become infected," Houen says. The difference seems to be "whether you are able to control the infection during your lifetime".

Pandemic insight

The COVID-19 pandemic has pushed the link between viruses and autoimmunity into the spotlight. Over the past year, research suggesting that people with COVID-19 carry numerous autoantibodies in their blood has been widely reported – although the mechanism at play is as yet unclear. Akiko Iwasaki, an immunologist at Yale School of Medicine in New Haven, Connecticut, who was responsible for some of this work[6], thinks that this autoantibody effect might partly explain the phenomenon of long COVID, in which people experience symptoms weeks or months after their initial infection. Some people's symptoms might be due to persistent infection with the virus, but others could be experiencing immune dysregulation that leads to the continued targeting of their own cells.

Viral pandemics can do more than simply draw attention to the problem, however – they could also help to solve it. When a person with symptoms of an autoimmune disease first visits a physician, the acute infection that could have resulted in the disease might be a distant memory. Pandemics, however, are population-wide events that can generate a much clearer signal. "The sample size is very large in a pandemic, and the medical community is vigilant for rare effects," says Steinman.

In 1999, Emmanuel Mignot, director of the Stanford Center for Sleep Science and Medicine, found that hypocretin, a neuropeptide that influences wakefulness and appetite, is involved in the sleep disorder narcolepsy in dogs[7]. In people, there tend to be more cases of the disorder after winter, and Mignot suspected that *Streptococcus* might play a part, as it does in rheumatic fever. Then, in 2009, the swine flu pandemic hit, and cases of narcolepsy rose several-fold on the Chinese mainland and in Taiwan.

Mignot turned his attention to flu, and found that one piece of the H1N1 surface protein haemagglutinin closely matches part of hypocretin. Mignot's team also uncovered evidence of T cells in people with narcolepsy that target the same piece of the hypocretin molecule[8]. Evidence linking narcolepsy with flu has continued to build – Steinman's team has found that a flu nucleoprotein also has similarities to hypocretin[9]. And a variant of a gene involved in presenting antigens to T cells is thought to be present in nearly everyone with narcolepsy, suggesting that the immune system has a role in the condition.

Treat and prevent

Compiling the evidence for the role of viruses in autoimmune conditions could lead to new approaches to treat or prevent immune dysfunction. If a specific virus is known to trigger or exacerbate an autoimmune disorder, for instance, then a vaccine against that virus could be a powerful tool. Indeed, vaccine developers are already interested in many microorganisms with suspected links to autoimmune diseases.

In 2020, biotech firm Moderna in Cambridge, Massachusetts, announced it was developing a messenger RNA vaccine candidate against EBV. Its aim is to reduce the more than one million cases of glandular fever in the United States each year. Potentially, however, a vaccine against the virus could do much more than that. "EBV does lots of bad things in humans, whether it's multiple sclerosis or Burkitt lymphoma or nasopharyngeal cancer," Altmann says. An EBV vaccine could also finally prove causation in multiple sclerosis, Olsson adds.

Moderna's first mRNA vaccine candidate for an infectious disease targeted cytomegalovirus, a herpesvirus. Merck in Kenilworth, New Jersey, and Astellas Pharma in Tokyo are also developing cytomegalovirus vaccines. Both the Moderna and the Merck candidates are in phase II trials, and Astellas's has advanced to phase III. The vaccines are being developed mainly because the virus can cause long-term health problems in infants when a person is newly infected while pregnant. But cytomegalovirus has also been associated with lupus, rheumatoid arthritis and type 1 diabetes.

As well as the possibility of developing vaccines to treat autoimmune disease, Ballesteros-Tato thinks that it might be possible to use a dose of the original virus to redirect immune targeting back to the original infectious agent. And in Norway, Knut Dahl-Jørgensen and a colleague at Oslo University Hospital are testing two antiviral drugs to see whether they can stop or delay the destruction of β cells in children and adolescents who show signs of early onset type 1 diabetes. The researchers had previously detected[10] mild viral infection in the pancreases of adults who were newly diagnosed with type 1 diabetes, as well as traces of enteroviral infection in the pancreases of people who had died as a result of diabetes. "If we can kill the viruses, maybe the [autoimmune] mechanisms will calm down," says Dahl-Jørgensen.

For a long time, the link between viruses and autoimmunity has been pushed to the sidelines. "I've always felt that infectious diseases in general were totally underestimated as a general cause of autoimmunity," says Mignot. But the fresh attention on the effects of viruses that has come with the COVID-19 pandemic could leave a lasting impact on the field. "This is an opportunity for us to clear this up once and for all," Iwasaki says.

Anthony King is a science writer in Dublin.

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