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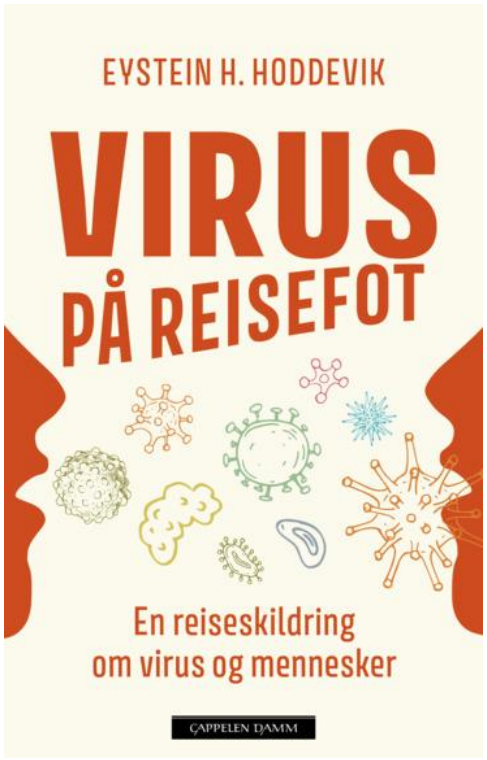


## Viruses on the Loose

What is a virus? Even experienced microbiologists need to stop and think before answering this simple question. Viruses are vanishingly tiny. The SARS-CoV-2 coronavirus is no larger than a ten-thousandth of the size of a pinhead. But an invisible enemy like this can bring a whole world to its knees.

Through carefully selected stories, the author shows you what a virus is, what it consists of, how it is transmitted and how it produces disease.

Viruses and humans have coexisted forever, so this journey covers biological evolution, our own bodies, historical events, diagnostics, global politics, genetic material, ethics and biological warfare. The book is also about vaccines, one of our most important weapons in the war against viruses. Producing vaccines is a science in itself and is based on knowledge of how viruses are constructed and produce disease.

In this book, you'll get to know different kinds of viruses: some of the most common, some that are extremely cunning and some that are so dangerous their fatality rate is close to 100%. Viruses cause contagion by travelling, just as we do, but their journey doesn't stop there. The way they produce disease inside us can be viewed as a microscopic travelogue. We shall therefore follow some viruses as they travel through our bodies to reach the cells they both hijack and harm.

If you are prepared to face up to your fear of viruses, you'll discover that knowledge of viruses is extremely helpful. In certain situations, it may help you avoid sicknesses like cancer, immunodeficiency, warts, cold sores, shingles and blindness.

foreignrights@cappelendamm.no
www.cappelendammagaency.no

## Eystein Hellstrøm Hoddevik
*b.1980*

Eystein Hellstrøm Hoddevik (b. 1980) is a doctor of internal medicine and pathology, and has a doctorate in molecular biology and neuroscience. He has lived in France, Scotland, Germany and Sweden and has worked as a doctor in the navy, on ships, in the emergency room and at internal medicine departments. He is employed at the Department of Pathology, Oslo University Hospital, and teaches at the Faculty of Medicine, University of Oslo.

# Viruses on the Loose

**by**

**Eystein Hellstrøm Hoddevik**

Sample translation by Lucy Moffatt

## Introduction

Are you scared of viruses?

If so, maybe you'd better stop reading right now. Because this book has been written with one clear aim in mind: to increase the reader's insight into what viruses are. Many people will find this sort of knowledge reassuring, but others may think quite the opposite: that ignorance is most decidedly bliss. And a lot of what I'm planning to tell you is liable to give you the very worst kinds of nightmares. You have been warned!

So, what is a virus?

Short and precise as it is, this question gives even experienced microbiologists pause for thought. First off, viruses are vanishingly small. The SARS-CoV-2 coronavirus is barely ten-thousandths the size of a pinhead, which makes the proverb 'little strokes fell big oaks' particularly appropriate in this context. The Covid-19 pandemic – caused by this very SARS-CoV-2 in 2020 – is the most topical example imaginable of how an invisible foe can force a whole world to its knees. Yet it is difficult to give a concise answer to the question of what a virus is. So, step by step, side by side, let us go through some selected themes and stories to try and home in on an understanding of this phenomenon, finding out how viruses are transmitted, how they make us sick and what they consist of.

The fact is that viruses and humans have coexisted forever; they have travelled on the same journey via biological evolution, our own bodies, human history, diagnostics, global politics, genetic material, ethics and biological warfare. If you are prepared to face up to your fear of viruses, you will, I hope, discover that knowledge of viruses is extremely useful. Practically speaking, there are certain situations in which such knowledge may help you survive, and avoid cancer, immunodeficiency, warts, cold sores, shingles and blindness.

Every chapter in this book details concrete and historical events that are easily understandable and require no knowledge whatsoever of biology. Viruses are specially equipped to spread and don't think twice about setting off on long journeys between continents, like travel-loving stowaways. Did you know, for example, that HIV already existed in Norway in 1962, long before the world had any idea of its existence? The first chapter starts with the almost incredible

detective story about the Norwegian scientists who didn't just solve the mystery of how HIV came to Norway but simultaneously proved that the virus originated in Africa.

There are far too many disease-causing viruses in the world to describe all of them in one short book. So the ones I've selected for closer scrutiny are not random choices. Of course some of the most common ones must be included; but I've also covered what you might call viral versions of the World's Most Wanted – some extremely 'cunning' viruses and others so deadly that you can die just days after contracting them.

Descriptions of viruses in action read almost like microscopic travelogues. So the title of my book is no accident: viruses are always on the loose, either on the move, or in the process of packing their bags. Put simply, we could say that they travel around – and through us – to spread contagion, then travel into us to reproduce and sometimes cause disease. Incredibly enough, all disease-causing viruses have specific – we might even say pre-ordained – destinations in our bodies. In this book, we will follow in the footsteps of HIV and rabies, as well as the zika, polio, herpes, Ebola and influenza viruses, tracking their journey into our bodies, all the way into the cells where they make mischief and cause disease.

Viruses are extremely small, although not too small for us to take pictures of them. With the aid of specially constructed microscopes, we can study them, and I've decided that this is what we'll do together here: make these hidden foes into something concrete; see how they are put together. Because just as a house is built according to an architect's design, every component of a virus is encoded in its genetic material, and the microscope can reveal whether a virus is alive or not. So let's dive in, down into the world of molecular biology, deep into our cells! Then, once we've started to understand our enemy, we'll move onto the really difficult work: how to combat viruses. And the story of our struggle against them may as well start with a tale of travel:

In the run-up to Easter in March 2020, when Norwegians were barred from taking their traditional trip to their holiday cabins, travel fever among city-dwellers rose to such feverish heights that the authorities virtually had to put up roadblocks to stop them. Our strategy for treating or preventing viruses shares many features with this measure. Roadblocks also have to be set up inside our bodies to slow the virus or stop it in its tracks. Since they are among our most important weapons in the war against viruses, it is impossible to write a book on this topic without mentioning vaccines. And if reading about scary viruses is liable to give you nightmares, take heart: as a whole, this introduction to vaccination will probably have an uplifting effect.

When SARS-CoV-2 paralysed the planet in 2020, it wasn't long before vaccination was proposed as the solution to everybody's problems. The one pesky detail was that obtaining the vaccine would involve research, testing and production. How that gets done is a science in itself, based on knowledge of – that's right – how viruses are put together and how they cause disease.

But true protection against viruses is something we have all carried within us since the day of our conception. All vaccines do is stimulate our own immune system to produce a specially adapted, targeted defence. Fascinatingly enough, our immune system must have come about as a result of attacks from viruses and other micro-organisms. So it is an over-simplification to

see viruses exclusively as enemies. They are so much more than that. In a way, they have also shaped our development and have become part of us.

In my experience – as both student and teacher – we remember what we understand. That's why I have done my best to use plain language in this book. I have simplified where simplification is possible. If you happen to find any mistakes, omissions or over-simplifications, that is my responsibility – but I must emphasise that this is in no way intended to be a virology textbook. What I do hope, however, is that it will serve as a good introduction to knowledge of viruses, written in such a way that most people will be able to grasp what they are reading. Unfortunately, medical language and literature has a tendency to carpet-bomb us with foreign words and abbreviations – to the extent that even doctors can lose their way. In this book, I've opted for the opposite strategy: I have consciously taken the time to explain exactly why certain things are called what they are.

Take the very first vaccine in the history of the world, produced by the British physician Edward Jenner in 1796. He managed to prevent smallpox in humans by exposing them to pus from cows that were infected with cowpox. And since the Latin name for cow is vacca, that is where this practice got its name. Today's vaccines have little or no connection to cattle, but the name remains the same.

I honestly believe that we humans remember things better and for longer if we have a few pegs to hang our memories on. For that reason, I've tried to make this an entertaining book, and have sometimes introduced digressions that may take us a long way away from viruses and disease but will, I hope, make this book more readable.

Happy travels on your journey through the incredible world of viruses!

**POLIO**

**A paralysing tale of rocking beds, iron lungs and Franklin D. Roosevelt**

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This chapter is about polio and takes us on a journey via the 1954 Nobel Prize, through the gut, out of the bottoms of children and onward into the spinal cords of our benevolent grandparents, Superman and Franklin D. Roosevelt. The disease has caused considerable suffering and death but, for that very same reason, it has succeeded in spurring medical science on to almost fantastical advances. The iron lung and the rocking bed were invented in response to polio. Both were functional but primitive breathing machines that paved the way for the modern respirator. The lives saved by the rocking bed include that of a polio-stricken Norwegian patient whom it rocked through a 26-year hospital stay, earning him the highly apposite nickname of

‘rocking Ola’, and a Danish polio outbreak is considered to have sown the seeds of modern-day intensive care medicine. The outbreak also resulted in an unparalleled collective effort from hospital staff, which involved so much overtime that it gave Danish physicians and medical students a veritable baptism of fire in trade union work. So hold on tight: the story of polio is anything but sleep-inducing.

Nobody who lived through the mid- and post-war polio epidemics could ever forget the terror they inspired. Polio was a much-feared disease – indeed it still is, although not in Europe. Contagion with the polio virus can lead to permanent paralysis. Many a victim has been forced to spend their life in a wheelchair – or worse still, bedbound, with paralysis of both arms and legs.

At the same time, combating poliovirus has been one of the greatest feats of modern medicine. In 2002, the WHO declared that Europe was at last polio-free. This has been such a tremendously positive achievement that many young people today have barely heard of polio and even fewer have a clue that it is a viral disease. To the extent that polio is mentioned at all, it usually happens when new parents receive information about the national child vaccination programme, or when people need to have the vaccine because they are travelling ‘somewhere exotic’ on holiday. Almost never other than that.

Viruses come by their names in lots of different ways, but poliovirus type 1 is in a class of its own. It is called *Brunhilde*, after the chimpanzee from which the virus was first isolated. The chimpanzee was, in turn, called after the legendary shield maiden Brunhilde – a Valkyrie in Norse mythology, and a character in Wagner’s opera cycle, *Ring of the Nibelung*. The name was fairly common among people back in those days but is unique in the context of virus names. Poliovirus Type 2 is called *Lansing*, by the way, after the town in Michigan where it was first isolated, while Type 3 – *Leon* – is named after the first known patient, who was from California.

Which of these three types would you rather have, given the choice? Intuitively, contracting a virus named after an armour-clad, opera-singing Valkyrie doesn’t sound good – and indeed the Brunhilde variant is the one that has most frequently led to severe disease involving paralysis.

In the first half of the 1900s, countries in Northern Europe and North America were struck by polio epidemics every single year. Poor access to vaccines, treatment or good, preventative measures made polio a disease that was feared by rich and poor alike. All strata of society were affected. It was often impossible to work out how the virus had spread, which only increased the fear of infection. It is only too easy to be frightened of an enemy one can neither understand nor see – and given the potential consequences of polio, the fear was unquestionably justified.

The full name of the disease, *poliomyelitis*, indicates an inflammation in the grey matter of the spinal cord. *Polios* means ‘grey’ in Greek, while *myelo* means ‘marrow’ and *itis* denotes inflammation. In cross-section, the spinal cord is reminiscent of a slightly ramified letter H and the two protrusions that point forward are called the ventral horns. Here, in the grey matter of the spinal cord, are the groups of motor neurons that can be destroyed during the infection. These are the same neurons we touched on in the chapter about rabies.

It seemed almost random whether those infected contracted the most severe form of the disease involving paralysis or simply experienced a few symptoms of the virus. And in a 1951 study of twins, where at least one of them had suffered paralysis, a surprising fact emerged: the risk that both twins would be stricken with polio was far greater among *identical* twins. Why? Because, unlike non-identical twins, they are genetically the same. The genetic material of one is identical to that of the other. No research was done (or could be done, at that time) into which genes and gene variants increased the risk of paralysis, but at any rate scientists could conclude for the very first time that genetics influence the outcome of infectious diseases. Science has since identified several examples of this, as we will see elsewhere in this book.

Sometimes different mutations in our genes can be an advantage when dealing with a virus – but other times, they’ll be a disadvantage. In other words, the severity of the course of the disease is not determined solely by the nature of the virus itself; to a great extent, it will also depend on how the body of the infected person responds to the intruder. In conjunction, all these considerations are known as *host factors* – and genes, in particular, are among them. But when people fall ill, it rarely occurs to them that their genes might be a factor. In this chapter we will take a look at several people whose destiny was rewritten after they were stricken with the poliovirus infection – including a strong-willed American woman, an equally valiant Norwegian, and the illustrious US president Franklin D. Roosevelt. In all three cases, the virus pursued roughly the same internal path in their bodies. One that we will shortly tread with the viral intruder.

Perhaps the word that best sums up the story of Ola Olsen is *incredible*. He was born in 1930 and worked at a mechanics workshop in Oslo. When the first polio vaccine became available in the 1950s, he turned up to get vaccinated. But a lot of other people had had the same idea. There was a long, long queue. Olsen was a diligent man and when, after a while, he felt he had been away from work for too long, he chose to leave the queue. He didn’t end up having the vaccine in the years that followed either, a fact that would have serious consequences.

In 1961, Ola Olsen became infected with poliovirus and developed severe poliomyelitis. His brainstem and spinal cord were both affected, he became paralysed and lost the ability to breathe and move his arms and legs. The only thing he could move was his left thumb. He needed help with absolutely everything and couldn’t even breathe on his own. As a result, Olsen spent the whole of the next 26 years at Ullevål Hospital. That must be a record-breaking hospital stay – at least on a ward for infectious diseases.

Ola Olsen’s story demonstrates the merciless ravages of poliovirus. At the same time, it illustrates something beautiful about a unique person and his many human qualities. In 1990, Norway’s national broadcaster, NRK, shared the story of Olsen’s fate with the general public some 29 years after he first became sick. The striking thing about this report was its subject’s

impressive capacity to keep his spirits up, to maintain his good humour. And when Olsen was later asked if he minded people referring to him as 'handicapped' in their talks, he replied at once with a broad grin: 'Handicapped? I'm healthy, I am!'

This attitude is probably all it takes to explain why Ola Olsen managed to stay alive for 52 whole years after becoming paralysed.

The story of 11-year-old Martha Mason from Lattimore in North Carolina is no less moving. She started to display symptoms on the very same day her parents buried her 13-year-old brother, who had died of polio. Martha had also been infected – and after a year's treatment at the hospital, she was sent home in an 'iron lung'. The only part of the patient that emerges from this machine is their head; the rest of their body is encased in a metal cylinder, where pumps increase and decrease the pressure. This is essential if the patient is to breathe.

Martha's doctors delivered a stark message to her parents: She may survive for another year. It is an understatement to say Martha Mason defied that prognosis: She didn't die until the age of 71, meaning that she spent 60 years – virtually the whole of her life – lying horizontal in this tank. That must have been a world record, not least considering the logistical challenges: the system weighed 362 kilos and was far from easy to move. When Martha became a college student, she had to be transported in a delivery truck.

Martha Mason probably wasn't *entirely* incapable of surviving outside the iron lung. At any rate, there is a breathing method that Ola Olsen and other polio patients with reduced respiratory function have practiced: 'frog breathing'. Using the tongue as a piston against the palate of the mouth, they build up pressure so that some air is forced down into the lungs when they swallow. Video recordings of Ola Olsen and others who used the technique make it clear why the method is called 'frog breathing'. And the end justifies the means. We all need to breathe and this method enables patients to get by without assistance for many minutes, perhaps even several hours. Consequently, a short power outage wouldn't have been fatal for either Olsen or Mason.

The combination of good logistics and a strong will made it possible for Mason and Olsen to do the impossible. Despite extreme challenges, both of them managed to achieve a tremendous amount. That is what makes their stories so unique. Against all the odds, Martha – lying horizontal in her iron lung – managed not only to graduate from school with exceptional results but even to pursue a university education, obtaining a Bachelor of Arts in English in 1960. This then led to a journalism job with her local paper. Imagine the situation: you have a journalistic assignment and know what you're supposed to write but aren't equipped to write it yourself. Martha Mason's solution was to dictate to her mother as she herself lay in her iron lung. This worked perfectly well until Martha's parents became ill but around that time, computers became sophisticated enough to be able to recognise speech. Martha then resumed her writing and one result of this was her book *Breath: Life in the Rhythm of an Iron Lung*, which was published in 2003.

Iron lungs were enormous, heavy, impractical beasts. Another equally odd device was the first ‘rapid-rocking’ bed, which medical journals hailed as an innovation on its arrival. The invention’s name is self-explanatory: the patient literally lay in the bed being rocked back and forth.

Because human intestines float relatively freely in the abdominal cavity, they – along with the other contents of the abdomen – move back and forth when a person is rocked like this. That also causes the diaphragm to move up and down. In this way, the rocking motion ensures that there is enough underpressure in the lungs to fill them with air. That is what enables the rocking bed to work as a breathing machine. And that is why Ola’s nickname in Norwegian, ‘Vipp Ola’ – which means ‘rocking Ola’ – had nothing to do with his VIP status. Ola Olsen didn’t see himself as a Very Important Person, but viewed this name as a literal description: he wasn’t just rocked to sleep, he was rocked all the time.

Because Olsen’s rocking bed was on the ground floor of a hospital building that looked out onto the street, it was no secret that he was lying there. It must have been quite a sight for passing pedestrians to see this man lying motionless in a bed that rocked him back and forth at a rate of 20-22 times a minute. Although the TV report about Ola Olsen lasts just a few minutes, it is so compelling that it leaves a much longer-lasting impression. Until you see just how quickly this bed rocked Olsen up and down, it’s impossible to grasp what this life entailed. Didn’t he ever get dizzy? What did he do to pass the time during the day? Olsen slept, ate and lived in his rocking bed for 26 consecutive years. That’s a total of close to 10,000 days. Even if we assume that the bed was switched off for a bit now and then, and lower the average frequency to 20 times per minute, Olsen will still have been rocked a total of 273,321,000 times. I still find it impossible to grasp just how high that number is – and it feels even more dizzying if you try to express it in words: seventy-three million three-hundred-and-twenty-one thousand. The only comparison that comes close to giving me a workable image is the idea of ‘moving into’ a gigantic roller-coaster and riding it continuously for 26 years. Ask yourself how you would cope with eating, sleeping, going to the toilet and all other aspects of your life without paying attention to the fact that you’re constantly rocking up and down. So that next insurmountable challenge you encounter? Greet it with a smile, just like Olsen.

We often say people talk *without taking a breath* when they speak a lot – and quickly! But if you’re a patient in a rocking bed or an iron lung or on a respirator, that is necessarily impossible. For Ola Olsen, the rhythm of his breathing machine determined when the air would pass through his vocal cords and when he could speak; that happened when he was literally in the trough of the rocking movement. The rocking bed dictated the entire rhythm of his life.

Whereas other people can use pauses in the flow of their speech to create an effect – dramatic pauses – the pauses in Olsen’s everyday life merely underscored the severity of his challenges. For 52 years he was obliged to live with this off-and-on rhythm. Many people would probably have viewed this rocking as a kind of torture, but humans can adapt to most things. Even after Olsen moved back home with a home-based respirator, he still slept in his rocking bed. Fascinatingly enough, he is said to have enjoyed extremely good health – and on the rare occasions when he had to undergo surgery for other conditions, he recovered with unusual speed.

It isn't easy to write a fitting end to Olsen's story. The fact that this man managed to survive 52 years in a rocking bed with a smile on his face is a feat that will go down in history. If any of us managed to show even a fraction of that determination and persistence, few goals would be beyond our reach. That is why I think, quite seriously, that when humanity sends an expedition to Mars, the stories of Olsen and Mason should be an obligatory part of the astronauts' curriculum. Forget interviews with world-class athletes. You won't find any finer examples of what humans can achieve and how much they can endure – if and when necessary – than these two polio survivors.

Unfortunately our understanding of how poliovirus causes disease is limited by a couple of factors. The first, ironically enough, is that we have been so good at combatting these viruses. Since the 1950s, polio vaccination programmes have been so comprehensive and targeted that scientists have had trouble finding cases to study – making it hard to acquire new knowledge. Secondly, tissue and blood samples are needed in order to truly study a disease but it is virtually impossible to take biopsies of the brain and the spinal cord without causing permanent damage. This is also the reason why diseases of the nervous system and the brain are studied so little relative to other types of disease.

So what alternatives remain when it is impossible to obtain such samples from humans? Modern medicine often turns to animal research. But since viruses don't necessarily infect all types of animals, this can often be a challenge. Poliovirus only infects primates – so the solution is either to alter the virus or genetically manipulate an animal species so that it can become infected. Scientists refer to this as an 'animal model'. More recently, they have managed to develop several such models, thereby obtaining new opportunities to study how certain diseases behave. But in the case of polio, some unanswered questions remain. Including the most obvious one: Why does the virus attack some particular neurons – motor neurons – in preference to others?

Polioviruses are *enteroviruses*. This name refers to the fact that they are mostly to be found in our gut system – *entero* means 'gut'. In fact, they rarely spread to areas outside the gut. The virus only finds its way into the blood vessels in as few as one in a hundred cases of infection, up to a maximum of five in a hundred. And on the rare occasions when this happens, it is probably accidental: this spread does not form part of the virus's lifecycle and brings it no benefits whatsoever. Poliovirus thrives best in the gut. It has no business in the blood or the spinal cord, so spreading to those places is nothing but a blind alley, of no use to the virus or the host. In a worst-case scenario, hosts can die from the paralysis, taking the virus with them to the grave, possibly before it's even had a chance to spread further.

This wasn't the first time an enterovirus went astray in human brains. Between 1917 and 1926, a virus spread through the world leaving some of those affected with Parkinsonism – a syndrome with symptoms akin to those found in Parkinson's disease. We don't tend to associate such symptoms with contagious diseases, but you read correctly: this was caused by a virus. The worst-affected sufferers became totally immobile, their muscles contracted and rigid, incapable of movement. The condition was dubbed *encephalitis lethargica,* a name alluding to the exhaustion that sufferers experienced. Even today, nobody can say precisely

which virus caused this disease and fortunately the world has never seen a similar epidemic since. But in 2012, a group of researchers gathered the few existing brain samples from people who had been stricken by the sickness and examined them afresh. It can pay to conserve biological material: in this case, experiments involving new and more refined methods yielded results. And what the researchers found in these brains was, most probably, an *enterovirus* – just like polio.

It's impossible to write about *encephalitis lethargica* without mentioning the fact that this tale made its way onto the silver screen. Everybody who suffers symptoms of Parkinson's disease has lost the brain cells that produce a hormone called dopamine. But towards the end of the 1960s, it became possible to produce dopamine synthetically, which offered hitherto unimaginable opportunities. A young neurologist, Oliver Sacks, gave the new medicine, called L-Dopa, to *encephalitis lethargica* patients in the hope that it might do them some good. The result was far more dramatic than expected – nothing short of an awakening. The patients literally came back to life again. They started to move, speak and interact socially just like everyone else. Dr Sacks went on to write the book about these events, *Awakenings*, and a Hollywood film adaptation followed in 1990, with Robert de Niro and Robin Williams in the starring roles.

Several of the viruses I discuss in this book attack the brain and nervous system. This applies to both the rabies virus and HIV – and polio illustrates only too well what can happen when neurons are lost. What's more, some of the most feared vaccine side effects are diseases that affect the brain, the spinal cord or the nerves. This happens when our immune system unexpectedly attacks our own body; consequently, these types of illnesses are called *autoimmune* diseases – *auto* means 'self' in Greek.

I therefore think it may be useful to understand some features of the cells that form our nervous system – and why infections in the brain or nerve tissue are best avoided, regardless of which virus, which bacteria or which micro-organism is involved. One of the reasons is that neurons do not divide, so any that you lose are lost forever. With some few exceptions, you never acquire any more neurons than the ones you were born with. That is why people should also give it some very careful thought – *while they still can* – before embarking on sports that involve repeated blows or trauma to the head. If, for example, you need objective proof of the adverse effects boxing can have on the brain, I strongly recommend studying interviews with ageing heavyweight boxers. Research has shown that areas of their brains are measurably smaller than for non-boxers of the same age. The saying 'less is more' definitely applies here because these findings tell us that – in all probability – neurons have been lost.

It isn't all that easy to count the number of neurons in a human brain, but the counting goes faster in some brains than others. The average number stands at around 90 billion cells. While this may sound like an awful lot, neither you nor I have any neurons to spare because these cells have to last us our entire life. The brain and nervous system form an ingenious three-dimensional jigsaw puzzle that consists of several billion pieces with even more connections between them. Although the number of cells is far from insignificant, the connections between them are the main reason why the brain and nervous system work as well as they do. And therein lies the explanation for why neurons do not generally divide. Try to imagine the practicalities of trying to solve this kind of three-dimensional jigsaw puzzle if the

pieces were constantly dividing and multiplying. It would be exceedingly difficult. The way our brain and the nervous system are organised is therefore not especially compatible with cell division, even though, of course, it would be an advantage to be able to replace destroyed cells. However, the brain's need for organisation trumps the importance of cell renewal. Evolution has compensated for this by giving us robust mechanisms for protecting our neurons, which helps ensure that these cells can survive for a long time.

One example of this is the long transport pathway between the nerve cells' offshoots and the cell body, for the recycling of vital components. Scientists have demonstrated that this is how polioviruses gain access to our central nervous system – a 'back door' the rabies virus also makes use of. The polio virus gets 'drawn' into the neurons' long offshoots to the muscles, which then transport the virus to the neural cell body in the spinal cord. Once the virus is inside the neuron, it also has the capacity to hitch itself to – and hitch a lift with – the neurons' own transport mechanisms back to the cell body in the spinal cord. This transport travels in the opposite direction to the signal the neurons send to the muscles and the offshoot is called an *axon*. For that reason, this is known as *retrograde axonal transport*.

Among the one to five percent of polio-infected patients mentioned earlier, the virus will also find its way into the blood vessels, thereby entering the bloodstream in the spinal cord and the brain. This probably explains how the meninges – the sheath that covers the brain – becomes infected and inflamed, whereas it is less likely to serve as a gateway into the neurons in the spinal cord. That is because the brain and the nervous system have well-developed defences against uninvited guests that attempt to gain access via the blood vessels – a phenomenon described by the German Nobel prize-winner Paul Ehrlich and his student Max Lewandowsky as early as 1900. When they injected dye into the blood vessels of lab animals, Ehrlich and Lewandowsky discovered that all the organs except the brain were stained. In that region, the dyeing substances remained in the blood vessels and did not cross over into the brain tissue. Ehrlich and his student were actually aiming to study the 'oxidisation status' of different organs – and since the brain proved impossible to study, this ruined part of their experiment. However, they made a vital discovery: the blood-brain barrier: *Bluthirnschranke*. I have pointed this out before and I'll say it again now: unexpected research discoveries often turn out to be ones of most consequence. The moment a scientist exclaims 'Hm, that's odd!' often marks the start of something new. Conversely, an 'Aha!' may convey the discovery of something one had foreseen – bringing an otherwise exciting scientific journey to its end.

Our brains and nerves consist of nerve tissue, and hardly any cell division takes place here. This is to ensure that they will maintain the unique configuration they depend upon to function. And for *precisely* this reason, the immune system in the brain cannot work in the same way it does in other parts of the body. When a cut gets infected, it becomes red, hot, swollen and painful, and the skin loses its capacity to function normally. An equivalent reaction in the brain would undoubtedly act effectively against the infection itself but as a 'bonus' it would rapidly take a toll on both neurons and brain function; consequently, our body always does its utmost to keep viruses, bacteria and parasites out of the brain. Ideally, the battleground should not be on the inside but on the outside of the blood-brain barrier – in the blood vessels or other tissue that can take the strain.

The brain's self-protective strategy can often work extremely well. It takes rather a large dose of bad luck to be paralysed by a poliovirus infection: most people who are infected (around 70 to 90 per cent) will barely notice a thing while the infection runs its course. And these people are actually the biggest problem. Even if they don't have any symptoms they are still infectious, and can, unbeknownst to them, spread the virus for weeks through faecal-oral and droplet transmission. Even though direct contact transmission from person to person is the typical polio transmission route, it can also happen via coughing: small drops of secretions from the throat of the infected person are hurled out into the air and can find their way into the mouths of passers-by. Around one in four will experience non-specific influenza-like symptoms such as fever, sore throat, fatigue, nausea, head and stomach ache, but only for a short period. One to two per cent may suffer meningitis or brain tissue inflammation, while just one in a hundred – perhaps as few as one in a thousand – develop the most severe form of polio involving paralysis. This type is known as 'paralytic' polio.

In certain respects, the challenges people faced during the polio outbreaks all those years ago share some features with the Covid-19 pandemic that hit the world in 2020. With coronavirus SARS-CoV-2, too, fewer than one in a hundred die of the infection, while the vast majority of those who contract it experience mild – possibly no – symptoms. Unfortunately, the large number of symptom-free people creates ideal conditions for transmission of the virus, since they all move around as if they were not infection-bearers. Calculating percentages is simple mathematics: once enough people are infected, even the smallest percentage can add up to a highly significant number of patients. One per cent of a hundred is only one, whereas one per cent of a million is 10,000. And this last number is not entirely random. All countries that experienced polio epidemics during the 20th century will have a significant number of polio survivors. And of these, a significant number are still living with the delayed effects of contracting polio during the great epidemics of the 1940s and 1950s.

Even though the vaccines against the three different polioviruses have, fortunately, been successful, the aftereffects of the disease itself are still very much a problem, in Europe as well as in the rest of the world. Even if no new cases of polio occur in Europe, many of those who have had polio will experience a worsening in their symptoms 30 or 40 years after the first paralysis occurred. Here too, the explanation lies in the spinal cord. Although the virus is long gone, along with the dead neurons, our body is equipped with an enormous capacity for compensation.

In order for a patient to suffer acute polio, the bulk of the neuronal cell bodies in the ventral horn of the spinal cord must be affected. But because the remaining neurons manage to compensate by forming connections with far more muscle cells, some patients can avoid paralysis even if the virus has found its way into their spinal cord. Although this form of compensation for the loss of neurons prevents paralysis, the flipside is that the neurons also become much more vulnerable. And as the years pass, the strain can become unpleasantly severe for the remaining neurons, which must now transmit information to far more muscle cells than previously. It's like having to drive a car in first gear all the time, regardless of what speed you're going at.

This is how 'post-polio syndrome' emerges, three or four decades after the onset of the disease. Some patients may suffer paralysis for the first time even though the virus has long since left their body. Others with existing paralysis find that it worsens. Further symptoms can

also appear, such as fatigue and chronic pain. So, even though Europe has long been free of polioviruses, we still have to live with the after-effects of the epidemics.

The term ‘polio-free’ has undoubtedly taken on a political dimension. The authorities in some countries have clearly felt the need to emphasise the successful eradication of these viruses. But polio is not only caused by the three types of poliovirus people are vaccinated against. A further five such viruses can create a similar clinical picture involving acute paralysis – and do so pretty regularly. Several tens of thousands of cases are documented worldwide every year. And since it appears to be so unpopular to say out loud that polio still exists, the diagnosis assigned to patients with such symptoms is likely to be given a different name. That prevents an otherwise excellent statistic from being ruined.

As fate would have it, one of the world’s worst polio epidemics struck Copenhagen just before the vaccines became available. From August to December 1952, no fewer than 2,241 patients with acute polio were hospitalised at the city’s Blegedam Hospital, of whom 345 had difficulty breathing and/or swallowing. Breathing problems occur in polio when the nerves that enable movement of the diaphragm are affected. The diaphragm is a fairly thin, dome-shaped, utterly vital sheet of muscle between the thorax and the abdominal cavity. When it contracts, it pulls our lungs downwards, creating the underpressure that sucks air into us. The nerve that controls this muscle emerges from the very upper part of the spinal cord, right beneath the cranium. This point up here is where you really don’t want to break your neck: if that happens, it can result in paralysis from the neck downwards.

One of the most famous people to have suffered this fate was Christopher Reeve, the American actor who immortalised the role of Superman in the 1978 film of the same name. Reeve did not have poliomyelitis but when he fell off his horse in 1995, he broke his neck so high up that he was left unable to either breathe or move his arms and legs. ‘Superman’ died nine years later at the age of just 52 but will always be remembered for his commitment to getting spinal cord injuries on the public agenda. Reeve spread the message through his many compelling speeches, including one at the opening ceremony of the Atlanta Paralympics in 1996. The many – and regular – pauses he had to take as his respirator breathed for him only emphasised the gravity of his words. As with Ola Olsen and all the other people who have ever needed to use a respirator, the machine literally determined the rhythm of the rest of Reeve’s life.

Polio paralysis may be temporary for some people but permanent for others. And when breathing difficulties arise – regardless of how short-term they are – they must be treated at once. In 1952, enormous numbers of patients in Copenhagen suffered this kind of breathing difficulty to a greater or lesser degree. That set Danish doctor Bjørn Ibsen pondering how to help them. Ibsen was an anaesthesiologist, so he was experienced in administering anaesthesia to patients about to undergo surgery, but on 26$^{th}$ August 1952, he became the first person in the history of the world to take this knowledge out of the operating theatre – and simultaneously founded modern intensive care medicine. Ibsen’s ground-breaking realisation was that polio patients needed help with breathing in just the same way as patients under anaesthetic did. He was right about that. Many polio patients turned out to have unusually high levels of $CO_2$ in their blood because they were unable to make full use of their breathing muscles. Although they had not stopped breathing entirely they were not breathing enough

either, so many of them died of slow suffocation. Ibsen administered muscle relaxants and breathing assistance to the patients who might need it. At peak levels, no fewer than 70 patients are said to have been treated in this way simultaneously, with what was known as 'ventilation'. The term comes from the Latin *ventus*, which means 'wind', and is therefore an apt description of how breathing assistance works: air is blown into the patient.

In 1952, the modern respirator was not yet invented and the primitive breathing machines that did exist were few in number. That meant human hands were needed to squeeze air into the patient manually. The word 'manual' comes from *manus* – 'hand' – and literally means that a job is not done by a machine. Today, the system that is used is called a 'bag valve mask'; it is a kind of elastic balloon, which self-inflates after the air has been squeezed out of it. This method of breathing assistance involves compressing the bag as many times a minute as we humans breathe. Bearing in mind that as many as 70 patients were simultaneously being given this treatment, the collective effort required must have been enormous. In all, 1,500 students are said to have contributed a combined 165,000 working hours over the course of the outbreak. The hierarchy in the hospital was abruptly reversed: now the surgeons, who were used to being the kings of the hill, were being taught to ventilate Ibsen's patients. Another unforeseen consequence of this collective effort came from the medical students, who organised to protect their rights. None of the doctors I know who have studied in Denmark are in any doubt about it: Danish medical students are better than anyone else at negotiating overtime payment and building a strong trade union. They learnt how to do this when they literally suffered cramp after giving thousands of hours of breathing assistance to polio patients in 1952.

We humans grow through the challenges we encounter on our path through life. It may seem ironic, but a fatal virus like polio has ultimately compelled us to innovate, and the modern breathing machine – the respirator – is a good example of this. All the anaesthesiologists I have spoken to are clear about the fact that the respirator was developed in order to deal with an acute clinical need: never before had so many patients required breathing assistance over a prolonged period of time. And it was a device just like this that Ola Olsen had to thank when, after 26 years at Ullevål Hospital in Oslo, he was at last able to return home after being allocated a home respirator in 1987.

The polio epidemics of the first half of the 20th century also contributed to the development of crucial methods for studying viruses. Towards the end of the 1940s, scientists managed to cultivate viruses in cell cultures – specifically poliovirus – which was the key to producing polio vaccines. Such ground-breaking experiments often garner prestigious prizes and in 1954, Dr. John Enders was informed by the Nobel Committee that he had been awarded the prize for his research in the field. But Enders turned it down! The American virologist wrote back saying that if a prize was to be awarded, it must be shared with his two colleagues, Frederick Robbins and Thomas Weller – 'those who did the work'. The Nobel Committee heeded his request, and the prize was shared equally among the three of them. Articles written about Enders confirm this impression of him as an unselfish, modest and decent man.

The same year that Enders, Robin and Weller were honoured by the Nobel Committee, the American virologist Jonas Salk managed to produce an inactivated polio vaccine (ie one that used 'dead' virus) – and three years after that, Albert Sabin produced a live weakened – also known as a 'live attenuated' – vaccine. The fact that several decades would still pass

before entire continents could declare themselves polio-free is largely down to a lack of will and logistical challenges.

Experience acquired during the polio epidemics indicates that the risk of developing paralysis is higher in pregnant women, people who have had a tonsillectomy and those who have been extremely physically active. It isn't easy to find a good explanation for these phenomena but there are no grounds for doubting their veracity. Prior to the pandemic year of 2020, I never took time off work for 'a cold' and I dare say I'm not the only person in the world who assumes that hard work and exercise are good for us even when we are sick. But polio is definitely the exception that proves the rule: there are numerous well-documented cases of paralysis that resulted from gruelling physical activity. Indeed, Ola Olsen's story fits into this framework: the day before he became paralysed, he took a long walk that left him physically exhausted. And in the same breath, we might mention Franklin D. Roosevelt, US president from 1933 to 1945: he developed paralysis after an arduous sailing trip on the 9th and 10th August 1921, during which he fell into the cold water and rounded off his punishing efforts with both a swim and a run. As the day was drawing to a close, the 39-year-old got the shivers – and lay freezing for the rest of the night. The next day, he woke up with a bad leg, which became completely paralysed over the course of the day. And his symptoms became steadily worse. After three days, he was paralysed from the thorax down.

But does this prove that Roosevelt contracted polio? With hindsight, people have speculated that he may in fact have suffered a rare neurological disorder called Guillan-Barré Syndrome. The clinical picture and age may reduce the probability that Roosevelt had polio, which was particularly likely to affect children. However, we shall never find out the answer to this, so Roosevelt will probably remain a poster-boy for polio, demonstrating how a virus can literally force a person to their knees. Roosevelt spent the remainder of his life in a wheelchair.

There is much speculation about why gruelling exercise – and possible muscle damage – increases the likelihood of being stricken by poliomyelitis. But there is no reason to cast doubt on the existing documentation: all evidence suggests that in the event of contagion it is wise to avoid over-exertion. The mechanism may be that intensive and prolonged muscular effort increases axonal transport, causing even more virus to be transported into the neurons' cell body. And it seems likely that an increase in the viral load could be associated with more severe progression in the disease. So there are good reasons to avoid acting in a way that enables more of the virus to find its way into the spinal cord. You're better off lying down and relaxing instead.

As in other European countries, the polio vaccination programme in Norway started in the late 1950s. Only inactivated vaccines were available. The most vulnerable people were vaccinated first: children in the three lowest classes of primary school. Gradually, more and more people were vaccinated and, in the years that followed, everybody under the age of 40 was offered the vaccine. Incidence of poliomyelitis fell significantly but it did not disappear entirely – so in 1965 the health authorities decided to switch to the second vaccine type, which was now available: the live attenuated polio vaccine developed by Sabin. And pretty soon, polio was eradicated in Norway.

Why was this the case? Why is there a difference between a live attenuated vaccine and an inactivated vaccine of the kind Norway originally used? Experience suggests that immunity developed through the use of a live attenuated vaccine lasts longer and is more extensive than the immunity provided by an inactivated vaccine. So does that mean all vaccines should be live attenuated variants? Not necessarily – as illustrated by the polio vaccine itself.

A sad little detour: Anybody who has ever changed a baby's nappy knows it can sometimes be a challenge – if not impossible – to avoid a mess. And in 1965, neither disposable nappies nor wet wipes were widely used. People's general hygiene was probably also poorer than it is today. So a few years passed and several fully grown adults started to develop polio symptoms. What was the cause? Among others, contagion from nappy-wearing children who had been orally administered the live weakened polio vaccine.

When Louis Pasteur carried out experiments to infect rabbits with rabies, science discovered for the first time how to weaken viruses' capacity to cause disease, what we call their *virulence*. And if a mutated virus is described as 'less virulent', that means it has lost much of its capacity to cause disease. Even though rabbits are mammals and can be infected with the rabies virus, they are less natural hosts for these viruses than dogs are. And if you infect rabbit after rabbit (a process known as 'passages'), some of the viruses will mutate in such a way that they no longer cause such severe disease and can, instead, be used to produce a live attenuated vaccine.

One of the challenges of the oral vaccine is that disease-causing viral particles may be found in the faeces of certain individuals. Consequently, in rare cases, the vaccinated person may develop polio or, worse still, be capable of infecting others. There are two different explanations for this, both of which centre on the fact that the human gut is the poliovirus's home ground – the place where it can most easily be transmitted and reproduce. Alternative one is that some of the mutated viruses in the vaccine will continue to mutate, thereby regaining their former properties. Alternative two is that the oral vaccine may contain a small proportion of non-mutated poliovirus, so-called 'wild type' poliovirus.

A football team that is playing at its home ground generally enjoys an advantage. The same is true of viruses. And even though any potential proportion of wild-type virus in the vaccines will be vanishingly small, that may still be enough to cause disease. Suddenly, the vaccine is no longer attenuated – just live. Fortunately this kind of transmission was not widespread enough to become a major problem: in the period 1965-69, a total of 20 patients were registered with paralytic polio in Norway. It is likely that only six of these were caused by the vaccine.

There have been no cases of poliomyelitis in Norway since 1970. Eventually, it became so difficult to justify continuing to use the live attenuated oral polio vaccine that the inactivated vaccine started to be used again in 1979 – and is the type we use today.

One reason why the oral live attenuated vaccine was so much more effective was that it built up our immune system precisely where it mattered most – in the mucous membranes of the gut where the polioviruses attack us. This is an issue we will discuss further for other viruses, since their point of entry always involves some mucous membrane or another (puncture wounds and needle use account for very few infections) and that is where we most need the antibodies and immune cells that can stop them.

The vast majority of people think of a vaccine as ‘a jab in the arm’. But that isn’t always the case. A vaccine need not hurt to work. It is just as effective if it’s taken in the form of drops administered orally – or via other mucous membranes. It all boils down to one thing: does the vaccine have the desired effect?

Sabin’s polio vaccine was the world’s first mucous membrane vaccine. Since then others have been produced – and today, we also have live attenuated mucous membrane vaccines for typhoid fever, cholera and rotavirus infection. These have the clear advantage that they can be administered as drops rather than injections. In principle, the individual *vaccinee* – the person being vaccinated – could have the vaccine mailed to them and drip it into their own mouth. Done! The logistics of distributing these sorts of vaccines is easy, enabling vaccination to be carried out in areas where it would otherwise be difficult.

The inactivated polio vaccine now used in Norway is administered via an intramuscular injection – an entirely different tissue from the one where the viruses cause the disease. This may also be one reason why the inactivated vaccine does not offer such good protection against the disease as the oral variant, which, after all, gives us antibodies in the mucous membrane of the gut. Once you’ve had a vaccine, its effect does not last forever. Some vaccines only work after we have had several doses, and their protective effects can also lessen over time. An extra dose intended to build new immunity is often called a ‘booster’.

One crucial factor in the success of vaccines is high uptake – for a large enough proportion of the population to opt to be vaccinated against the disease in question. This creates *herd immunity*, which can be a lifesaver for some people. Vaccines are, of course, intended to have a protective effect for the vaccinee, but their most important impact may be the contribution they make to preventing the virus from spreading to others.

When we speak about vaccines, we tend to use words that suggest they combat the disease itself rather than the virus. We talk about the polio vaccine, not the poliovirus vaccine. However, the best vaccines fulfil both functions, ensuring that an infected person does not develop the disease – and that the vaccinee will not become infectious, and will therefore not spread the virus to others.

The few individuals in our communities who are especially vulnerable to infectious diseases but cannot have (live) vaccines – or must perhaps avoid them owing to allergies – gain the effective protection they need from all the people around them who *are* vaccinated. We are literally their human shields. But if we are to protect them properly, they need to be surrounded by enough vaccinated people, Every non-vaccinated individual will represent a risk to these people. Since 1976, all vaccination in Norway has been voluntary, whereas other countries may have much stricter practices. In Singapore, for example, your child must be vaccinated in order to get a nursery place. This may sound drastic – after all, nursery provision is a legal entitlement and is supposed to be available to all. But it is an understandable measure. As parents of school- or nursery-age children, we are, of course, required to observe anti-infection measures that benefit the community. If your child has a tummy bug, the regulations clearly state that he or she must be kept home for at least 48 hours after the last

time they had diarrhoea or vomited (and, incidentally, that isn't always long enough!). The underlying arguments here can also be applied to preventative measures. The reality is plain and simple: non-vaccinated children can pose a risk to other children if any of them pick up a virus others aren't vaccinated against. And when it comes to public health, Singapore isn't just any old country, by the way: it tops the global statistics for the longest average life expectancy!

While we're on the subject of fear of vaccines, the story of the MMR vaccine (against measles, mumps and rubella) is worth mentioning. A 1998 UK study based on just 12 patients sowed the myth that this vaccine triggered the onset of autism. The study was later shown to be entirely lacking in any scientific basis: few of the patients named had autism and the causal connection was far from unequivocal. The doctor who wrote the paper was later struck off the medical register but, unfortunately, the damage was already done. The myth and scepticism about the MMR vaccine live on to this day.

Scepticism about vaccines has also been documented – and had consequences – in many other countries. In the early 2000s, for example, there was a poliomyelitis outbreak in Nigeria, a country where polio had previously been declared eradicated. The vaccine available to the country was produced in the West and the outbreak was caused by resistance to vaccination in some segments of the population: they had a fixed, collective belief that the West had produced the vaccine to achieve sinister aims – such as reducing Nigerians' fertility or harming them in other ways. It is in situations like this that diplomacy both comes into its own and is put to the test. Long discussions apparently took place between the WHO and the country's leaders and fortunately, they bore fruit: the situation was resolved at last by giving Nigeria access to a vaccine produced in Indonesia – another Muslim country. That said, by the time the vaccination programme got under way, the outbreak had managed to spread to neighbouring countries, as well as Yemen and indeed Indonesia itself.

This is a prime and crystal-clear example of how insane conspiracy theories can cause disease – and claim lives. But with this exception, the polio vaccination must be deemed a highly positive chapter in modern history. One last anecdote to demonstrate this: the vaccine has contributed to a number of ceasefires. Polio largely affects small children and, even in the bitterest conflicts, both sides will be keen to prevent disease in such a blameless segment of the population. The WHO's website contains a long list of all the cases where vaccination has been carried out during wartime, including in the conflict between the Tamil Tigers and government forces in Sri Lanka. In 1995, 1996 and 1997, both sides observed a week's ceasefire. Why? To give children polio vaccinations.

As you have now learned, there is a lot one can and must say about polio – the disease that many have forgotten but which remains among us. A brief summing-up could include the following points.

1. Anybody who calls themselves a 'principled anti-vaxxer' should sit down for a cup of coffee with somebody who has suffered polio-induced paralysis. Or perhaps two or three cups to make sure that the message really hits home.
2. Nappy-changing has always been a somewhat risky business. But in the days when the live attenuated polio was in use, in rare instances it could even be life-threatening.

3. Polioviruses have considerable room for improvement, they just don't know it themselves. The paralysis they can cause serves absolutely no purpose.
4. 2020 did not bring us much good news on the virus front but one honourable exception is worth mentioning: the African continent was declared polio-free!
5. The West has not produced vaccines in order to reduce African women's fertility.
6. Gruelling physical activity is best avoided by people infected with poliovirus. However, no European has any justification for using this as an excuse to skip P.E.: there is no polio in Europe.
7. Norway's answer to Christopher Reeve? Ola Olsen. An all-round superman.