Virusphere

Also by Frank Ryan

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Virusphere

From Common Colds to Ebola Epidemics

Frank Ryan

WILLIAM
COLLINS

William Collins
An imprint of HarperCollins*Publishers*
1 London Bridge Street
London SE1 9GF

WilliamCollinsBooks.com

First published in Great Britain by William Collins in 2019

2022 2021 2020 2019
10 9 8 7 6 5 4 3 2 1

A catalogue record for this book is available from the British Library

ISBN 978-0-00-829667-4 (hardback)
ISBN 978-0-00-829668-1 (trade paperback)

Typeset in Plantin by Palimpsest Book Production Ltd, Falkirk, Stirlingshire

Printed and bound in Great Britain by CPI Group (UK) Ltd, Croydon

This book is produced from independently certified FSC™ paper to ensure responsible forest management.

For more information visit: www.harpercollins.co.uk/green

I would like to thank my editors,
Myles Archibald and Hazel Eriksson,
and my agent, Jonathan Pegg,
for their support of my writing this book

We all play hideous games with each other.
We step inside each other's chalk circles.

Anthony Hopkins

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Introduction

What springs to your mind when you sit back and consider viruses? I am altogether aware that even if you come, as will many of my readers, from a non-scientific background, you will likely be uncertain as to the strange and ill-definable nature of viruses. Even among scientists, viruses are among the most enigmatic of the biological entities that are to be found on our precious blue-girdled planet. Certainly, there is a good deal of misinformation about them. You might, for example, be apt to confuse them with bacteria, a confusion that is not helped by the fact that we doctors caused this confusion in the first case by lumping two radically different entities together as the 'microbes' that are the root cause of infectious diseases.

Viruses frighten us. They elicit a primal fear of the unknown. They are capable of crashing through our natural barriers and defences, turning healthy cells into microscopic factories to produce exponential numbers of daughter viruses. These swarm through the bloodstream, drawing the attention of the immune system. This provokes our own white blood cells and other immune defences to become an aggressive reactionary force, fixated on annihilating the invaders, regardless of the devastation in their

wake – indeed our very own immune system contributes to many of the familiar symptoms of the resultant illness, from runny noses to violent, bloody haemorrhages. In effect, every infection becomes a pitched battle that will determine the outcome for us, the host. As we come to know viruses better, we discover that they have also come to know us intimately, taking advantage of our very behaviour to facilitate their infectiousness and spread among us. All in all, that is rather scary. Especially so when we consider that some of those viruses include some of the most dangerous entities on the planet, entities eminently capable of making us very sick indeed – even killing us.

It is hardly surprising that we should fear them and consider them an epitome of menace, perhaps even evil. But contrary to what we might think about viruses, they are not driven by malice. Their ultimate goal, just like that of all living organisms, is simply to survive and multiply, thereby ensuring the success of their kind. That's all very nice to know but this lack of malice is hardly a comfort to us when we are infected by a virus. It is only natural in such circumstances that we might resent viruses and what they might do to us. It is equally natural that we should also feel the need to protect those we love from viruses while knowing that, if and when one of them comes along, it will arrive among us, unseen and unknowable, causing damage and pain among us, even to the most innocent, without feeling or rational explanation.

We are comforted by the knowledge that there are vaccinations available to protect us and our families from these viruses. But that same misinformation about various different vaccination campaigns has sown confusion among us. Meanwhile, there appears to be little to nothing that we can do about certain epidemic varieties, such as the norovirus or the common cold, which sweep through our populations as common experiences,

albeit experiences we would rather avoid, provoking altogether negative associations in relation to viruses. Is it any surprise that we are inclined to wonder what other capacity for mischief viruses are capable of? You might well take the question further and wonder aloud: what is the purpose of these minuscule entities? Wouldn't our world be a good deal better off if these dratted parasites were simply eliminated from the scene, never to bother us any more?

The curious thing is that, while as a doctor I sympathise with such sentiments, I cannot entirely agree with them. Counter-intuitive as it might seem, I know that a world without viruses would not be one in which I would care to live. Why do I suggest such a thing? It introduces what might appear to be a contradictory question. Does the existence of viruses really matter to you and to me? I can assure my readers that, contrary to what our primal instincts might suggest, the answer is, strangely, but indubitably, yes!

In his elegant essay 'The Lives of a Cell', the late Lewis Thomas drew attention to the fact that we humans are not above the rest of life. In his words, 'Man is embedded in nature.' While accepting the fundamental truth in this, I would further extrapolate from it the fact that nature is embedded in humankind. And the nature I am referring to includes viruses. I don't, however, expect you, my readers, to simply take my word on this. But even the possibility that we humans owe our existence to, and remain dependent on, the very existence of viruses is more than enough to suggest we take the trouble to understand them.

That is what I hope to achieve in writing this book. It is my intention to enable you, my readers, to understand viruses.

In fact, even at a self-interest level, it is only natural that we should feel the need to understand entities that are capable of seriously hurting us. We surely need to know how they might

threaten us and our loved ones and what we can possibly do to mitigate this threat. I freely confess that this was my perspective when, as a youthful medical student, I performed my first experiments on viruses long ago. Years later it remained my perspective when, as a busy hospital physician dealing with serious medical emergencies, it was my duty to diagnose and treat many patients suffering from viral infections. But then, during a period of international travel aimed at examining what was actually happening when new 'emerging viruses' were threatening entire populations, I discovered that my former perspective was somewhat blinkered in relation to viruses. Here I invite my readers to remove those same blinkers and look beyond the undoubted mischief of viruses to find answers to their behaviour and presence among us.

Key to such understanding is to get to know their strange and extraordinary world. Thanks to the most modern advances in the science of virology, we are now in a better position than ever before to understand that world. We are about to explore what, in scientific circles, is now called 'the virosphere', a play on which forms the title of this book.

How could such an exploration be anything other than an odyssey? Viruses circumambulate our world with the speed of a passenger jet, paying no heed to national boundaries, or circumscribing notions of nationality, ethnicity, race or religion. They pay no heed to sex or age, or social class, or indeed any human hubris of fame, celebrity, wealth or power. They are devoid of any sense of justice or morality, so that our social or religiously derived morals prompting concepts of goodness, badness, justice, sin, simply do not apply. Now add to this situation the fact that these threatening entities are, for the most part, utterly invisible, even under the most powerful magnification of the light microscope, making them all the more enigmatic – and perhaps also the more

scary. These invisible entities invade not just our tissues and organs, but, to borrow the metaphor from Anthony Hopkins, they step inside the chalk circles of our most intimate and innermost being: the nucleus of our living cells, the repository of our coding DNA.

It is not a bad thing that we should be wary of viruses, but in this exploration we need to rise above mere scare stories. The fact is that the vast majority of viruses in this world – and there really are very many of them – have no mischievous interest in humans. This rather begs a new question: if such viruses are not interested in you and me, what are they interested in?

My purpose in writing this book is to explain what viruses really are, to accurately define them, and from such an understanding to explore their role in our human history and the wider history of our world. I hope to do so in a way that readers, whether they come from a scientific background or have no prior knowledge of viruses, will understand the true importance of viruses to life and to the biosphere. Given such potential importance, how can we possibly get to grips with such minuscule entities? How can we even hope to visualise their quintessentially viral way of life in their complex ultramicroscopic world? As with historic explorations of alien worlds, it might help our exploration if we could avail ourselves of some guide.

I would suggest that there is an obvious guide, one that is entirely apposite, whose perspective has only recently been opened up to us in wonderful detail through the deepest penetration of the living world by the enlightenment of modern scientific techniques. In this new age of ultramicroscopic exploration, we shall be getting up close and personal to the viruses themselves. As we shall discover, viruses really are far more embedded in us, and in the biological and ecological world that we inhabit, than most ordinary folk might possibly imagine.

I

What Are Viruses?

Only in the last decade have we come to realise that, from its very beginnings, all of cellular life has inhabited not only the visible biosphere – of solid earth, air and oceans – but also a less familiar and invisible virosphere. The viruses that constitute this virosphere are not merely surrounding us, they are within us, both as evolving extrinsic organisms in themselves and as interactive symbiotic entities that are an intrinsic part of our being. We might not be aware of the presence of these minuscule passengers within us from moment to moment, but the passengers are, in their quintessentially viral way, aware of us.

This might seem somewhat daunting, even frightening, to some of us, but there is no need for alarm. They have always been there. It is likely that they preceded any origins of human life on planet Earth, or indeed, going further back, the origins of the mammals, or any animals or plants, or fungi, or, if I am right, even the single-celled amoebae. All that has changed is that the world of virology is coming to understand the role of viruses in the origins and diversity of life, and what might appear incongruous to any notion of viruses being exclusively agents of disease, the health of the biosphere.

For viruses to achieve all this they must surely possess some remarkable properties. For example, they have no means of locomotion yet they move among us: in pandemic forms they effortlessly circulate around the globe. Although they have no sense of vision, hearing, touch, smell or taste, they detect with uncanny precision the cell, or organ or tissue that is their target destination. This they achieve despite the relentless opposition of powerful immune defences designed to prevent this happening; and once arrived, they penetrate the defences of the target cell, break entry through its protective surface membrane, and once inside take over its physiological, biochemical and genetic programming to compel the cell to become a factory for the production of a new generation of themselves.

Welcome to the world of viruses!

It is, admittedly, a very strange world replete with mysteries. It becomes all the more quixotic when we attempt to examine it at the most basic level.

What then are viruses? How do we even begin to define them? What, for instance, is the difference between, say, a bacterium and a virus? While viruses and bacteria are often confused in the minds of ordinary folk, because they cause many of the common infectious diseases, bacteria and viruses are very different entities. Viruses are more difficult to define than bacteria because they are said to occupy a position somewhere between the biological notions of life and non-living chemicals. This has tempted a distinguished colleague to dismiss them as 'a piece of mischief wrapped up in a protein'. While the hubris contains a grain of truth, there is rather more to viruses than being merely a source of mischief. So let us delve a little deeper! Do viruses rely on genes, and genomes, like all of the more familiar forms of life, from whales to humans and buttercups to the so-called 'humble' bacterium? The answer

to that question is, 'Yes!' Viruses do indeed have genomes, which contain protein-coding genes. We shall discover more about those viral genomes in subsequent chapters when we shall also observe some important differences between the genomes of viruses and all other organisms.

Do viruses follow the same patterns of evolution as, say, plants and animals? The answer again is, 'Yes!' But the patterns of evolution – the specific mechanisms involved – are heavily influenced by a facet of their organismal existence that is confined to viruses. Viruses can only replicate by making use of the host cell's genetic apparatus, and because of this, viruses were formerly defined as 'obligate genetic parasites'. But with our increasing understanding of viruses, and of their complex roles in relation to the evolution of their hosts, this definition is no longer sufficient to characterise them. A more adequate definition must take on board the fact that viruses are symbionts. Indeed, we now know that viruses are the ultimate symbionts, exhibiting many examples of all three patterns of symbiotic behaviour, namely parasitism, commensalism and mutualism. Moreover, since viruses will sometimes employ aggression as an evolutionary pattern of behaviour in relation to their hosts, they are also potentially 'aggressive symbionts'.

The more we examine viruses, in their evolutionary trajectories and in the influence of that trajectory on the evolution of their hosts, the stranger and more fascinating their story becomes. Is it reasonable to propose that viruses were born at the stage of chemical self-replicators before the actual advent of cellular life on Earth? If so, how then, from those primal beginnings, did viruses evolve, to interact with, and thus contribute to, the evolution of all of life on this planet?

The aim of this book will be to enlighten readers through a step-wise progression, starting with a familiar territory: we shall

confront the wide range of illnesses that are caused by viruses. For example, we shall examine what is really going on in the common cold, the childhood illnesses such as measles, chickenpox, herpes and mumps, rubella, as well as less familiar examples such as rabies, 'breakbone fever', haemorrhagic fevers such as Ebola, and virus-induced cancers such as Burkitt's lymphoma. In such an examination we shall discover what makes viruses tick, exploring what's actually going on inside us when we encounter the virus, how this gives rise to the symptoms we get from the infection, and, key to deeper understanding, probing what the virus itself gets from the 'interaction' with its human host. We shall employ the same virus-orientated perspective to explore important epidemic forms such as influenza, smallpox, AIDS and polio, which will illustrate how viral infections have impacted on human social history, from the wall paintings of the Ancient Egyptians to the colonisations of the Americas, Australasia and Africa. We shall also take a close look at vaccines as a measure to prevent epidemic infections, from the first introduction of vaccination against smallpox centuries ago to the recent controversy concerning the triple vaccine and the papilloma virus vaccine.

The science of virology grew out of the study of viruses in the causation of disease. Through understanding the viruses already familiar to us, we shall widen our enlightenment by examining the role of viruses in the evolution of life, and in particular we shall explore the role of viruses in our human evolutionary history. We shall see how, throughout our prior evolution, we have shared our existence with these powerful invisible entities, and how they really have changed us at the most intimate level, to help make us human.

I hope that, like me, you will come to appreciate the enormous importance of viruses to life, in its origins and complexity, while

also marvelling at the existential nature of what is one of the great wonders of life on our beautiful blue-oceanic planet. Viruses, by and large, have had a bad press. This is understandable, given the experiences of earlier generations of virologists, whose only contact with viruses was in dealing with the infections caused by them. But today a major wind of change is blowing through the world of virology – so much so that recently a distinguished evolutionary virologist declared that we were witnessing what he called 'The Great Virus Comeback'. What does he mean by this? Why have some of the modern pioneers of virology introduced the term 'virosphere' as the key to a new exploration of the importance of viruses to the entire biosphere? Could it be true that, as some would have us believe, viruses should now be seen as the 'Fourth Domain of Life'?

2

Coughs and Sneezes Spread Diseases

Historically, viruses were included with the so-called 'microbes' – tiny organisms that were originally discovered as the cause of infectious diseases in humans, animals and plants. Interestingly, there is a part of us that has long been intimately acquainted with microbes in general, and with viruses in particular. This is our inbuilt system of defences against infection: what doctors refer to as our immune system. It is perhaps as well that we possess this inbuilt immunological protection, because we inhabit a world that teems with microbes.

A veritable zoo of such microbes covers our skin and other surface membranes. Biologists call this the 'human microbiome'. Although it might cause some of us to squirm a little just to acknowledge its existence, this secret world is no real threat to us. It is an intrinsic part of our being, comprising a variety of bacteria, as well as other microbial forms, that inhabit our surface skin, mouth and throat, nostrils and nasal cavities, and in the case of women, the genital passages. Our bodies are said to contain roughly 30 to 40 trillion cells – if you are mathematically inclined,

this is 3 to 4 times 10^{13} – which comprises the sum total of living cells that make up our living tissues and organs. Meanwhile our 'microbiome', which amounts to all of the microbes that inhabit our skin, gut, oral and nasal passages and throat, and genital tract in women, accounts for some ten times as many microbial cells, comprising such organisms as bacteria, Archaea and protists. It is natural enough, given our awareness of past epidemics and day-to-day troublesome infections, to assume that such microbes are invariably harmful; but these microbes that make up our personal microbiomes are not hostile. Some simply live off us in commensal fashion without causing us any harm; while many others help to maintain our normal health. For example, the zoo of microbes that inhabit our large bowels, or colons, play an important beneficial role in our human nutrition – such as in helping us to absorb vitamin B12 – as well as helping to protect us from invasion of our digestive tract by pathological visitors. The bodies of this 'colonic flora' account for no less than 30 per cent of the bulk of our faecal waste.

There is also growing evidence that we benefit in a number of other ways from this microbial flora of our skin, and other abdominal cavities. This holistic realisation begs a relevant question: could viruses be a part of this human biome, capable of contributing to our human health? For any group of microbes to contribute to the nutrition or general well-being of a host, this would imply a lengthy period of symbiotic evolution with the same host. Immediately we even come to consider such a curious virus–host interaction, we are obliged to consider something profoundly different about viruses when compared to cellular symbionts, such as the bacterial flora of the human intestine or skin. Viruses inhabit the landscape of the host genome.

This means that viruses are certainly not going to contribute,

for example, to human vitamin digestion. What it really implies is that, if viruses are to contribute in some way to host health – or indeed host evolution – that contribution is likely to be much more subtle, involving, perhaps in the human host, an interaction with our immunological defences, or more profoundly still, an interaction with our human genetic machinery – or most profound of all, changing our very human genome, the repository of our human heredity, buried deep in the nucleus of every human cell. If this were to happen, viruses would have contributed to what makes us human.

These are weighty questions. Perhaps many of my readers might be inclined to make the point that, so far as they are aware, only the less helpful kinds of viruses appear to have come their way.

In this book we shall explore the truly strange, and intriguing, world of viruses. We might make a start by dispelling a common misconception; many people tend to confuse viruses with bacteria. This is perfectly understandable since viruses, like bacteria, cause many of the common ailments that afflict us in our ordinary lives, and particularly so the fevers that beset the lives of our children. Family doctors deal with these common ailments on a day-to-day basis, and they tend to treat them in similar ways, with antibiotics for bacterial illnesses and vaccination programmes or antiviral drugs aimed at protecting kids from the common viral infections. It is little wonder that people are apt to confuse viruses with bacteria. What then is the difference between the two?

In fact there are major differences between bacteria and viruses. The most obvious difference is one of scale: most viruses are much smaller than bacteria. We readily grasp this if we take a closer look at what is going on during those coughs and sneezes that we recognise as the harbingers of that bothersome cold. While a few other viruses can cause an illness resembling a cold, the

majority of colds are caused by a particular virus, which goes by the name of 'rhinovirus'. If one harks back to the sneezing, snuffling and nose-blowing that are the familiar symptoms of that developing cold, the name rhinovirus is apt, since 'rhino' derives from the Greek word, *rhinos*, for nose. Rhinoviruses are the commonest virus infections to afflict humans worldwide, with a seasonal peak in the autumn and early winter. The more we learn about the rhinovirus, the more we witness how well-suited it is to its natural environment, and to its life cycle of infectious behaviour and spread.

The rhinovirus is exceedingly tiny, at about 18 to 30 nanometres in diameter. A nanometre, or nm, is one-thousand-millionth of a metre. This clearly tells us that a single rhinovirus organism – it is referred to as a 'virion' – is absolutely minuscule. In the evolutionary system of classification known as 'taxonomy', rhinoviruses are classed as a genus within the family of the 'picornaviruses', a word derived from *pico* for small, and *rna*, because the rhinovirus genome is made up of the nucleic acid RNA rather than the more familiar DNA. Let us put aside any discussion of these genetic molecules for the moment, but we shall return to consider some remarkable implications of RNA-based viral genomes in subsequent chapters.

Returning to the differences in scale between viruses and bacteria, rhinoviruses are far too small to be seen under the ordinary laboratory light microscope. The virions can only be visualised under the phenomenal magnification of the electron microscope, when they appear to be roughly spherical in shape, resembling tiny balls of wool. In fact, if we examine the individual virions more closely under the electron microscope, we see that they are not really spheres but have multifaceted surfaces, rather like cut diamonds. In the technical jargon, the multifaceted surface

of the rhinovirus is the viral 'capsid', which is the viral equivalent of a human cell's enclosing membrane. This capsid has a striking mathematical symmetry comprising 20 equilateral triangles. All viruses have genomes, made up of either DNA or its sister molecule, RNA. The protein capsid acts as a protective shell that encloses the viral genome. It is the capsid that gives rhinoviruses their quasi-crystalline appearance, known as 'icosahedral' symmetry – the term is simply the Greek for 'twenty-sided'. The multifaceted symmetry is not comprised of diamantine crystal, however, but constructed by a biochemical protein assembly.

Microbiologists had long recognised the presence of viruses before the electron microscope was invented. They found ways of detecting the presence of viruses from their effects on host cells, and they could even count their precise numbers from their cytopathic effects in cultures. It will come as no surprise to discover that the best cultures for growing rhinoviruses are cells derived from the human nasal lining, or the lining of the windpipe, or trachea. We are equally unsurprised to learn that the best temperature at which to culture cold viruses is between 33°C and 35°C, which is the temperature found within our human nostrils on a cold autumnal or winter's day.

Rhinoviruses are highly adapted for survival in their host environment. They are also highly adapted to infect a specific host. This became apparent when scientists attempted to infect laboratory animals, including chimpanzees and gibbons, with a variety of different subtypes of rhinovirus that readily infected humans. They could not replicate the symptoms of a typical cold in any of the animals. From this we glean an important lesson about viruses: the rhinovirus is most particular when it comes to its choice of host, which is exclusively *Homo sapiens*. This has a pertinent significance; it means that human infection is vitally

important to virus survival. Only through human to human contagion can the virus be passed on and breed new generations of rhinovirus. We are the natural reservoir of the cold virus.

But a moment or two of reflection on such exclusivity provokes a tangential thought – and a pertinent question. These minuscule polyhedral balls have no obvious means of locomotion. How can they possibly move about through our human population to effortlessly spread their infection across national and even international boundaries?

In fact, we already have the answer: it is implied in the very title of this chapter. Why do we cough and sneeze? We do so because this is what happens when our noses, throats and windpipe passages feel irritated. It is part of the natural defences against foreign material entering passages where it could block our airways and, implicitly, obstruct them and threaten our breathing. What rhinoviruses do is to provoke the same physiological responses by irritating the linings of our nasal passages. The viruses spread from person to person because they are explosively ejected into the ambient air with every cough and sneeze, to be inhaled and subsequently infect new hosts. And here, once again, we learn something vitally important about viruses. The viruses do not need any mechanism of locomotion because they hitch a ride on our own locomotion, and everywhere we go, we further oblige them by spreading their contagion by coughing and sneezing.

How clever, we are inclined to think, are viruses!

But viruses could not possibly be clever. They are far too simple to be capable of thinking for themselves. We are instead confronted by another of the numerous enigmas in relation to viruses. How, for example, could an organism some paltry 30 nanometres in diameter acquire such devious but also such highly effective patterns of behaviour as we discover in the common cold? The

answer is that viruses do this through their evolution. Indeed, viruses have an extraordinary capacity to evolve. They evolve much faster than humans, even much faster than bacteria. Over subsequent chapters we shall see how that viral employment of host locomotion is one of many such evolutionary adaptations.

What then do rhinoviruses do when they get inside us?

We have seen that the rhinovirus has a specific target cell, the cilia-flapping cells lining the nasal passages. Once inhaled, the virus targets these lining cells, discovering a specific 'receptor' in the cell's surface membrane, after which the virus uses the receptor to break through the membranous barrier and gain entry into the cell's interior, or cytoplasm. Here the virus hijacks the cell's metabolic pathways to convert it into a factory for the replication of daughter viruses. The daughter viruses are extruded into the nasal and air passages, there to search out new cells to infect and continue the invasive process. It seems to require only a tiny dose of virus to be inhaled from the expelled cough or sneeze of an infected person to initiate infection in a new individual. After arrival, the incubation period from virus entry to infected nasal cells exuding new daughter viruses can be as little as a day. We don't have much of a chance of escaping infection once the virus has been inhaled. Virus replication peaks by day four.

Fortunately, it isn't all one way. Even as the virus is launching its attack, the human immune system has registered the threat, and it has recognised the viral antigenic signature – what we call the serotype. The problem is that the arrival of a *new* serotype requires time for the immune system to recognise the threat and to build up a formidable arsenal of responses. By day six the nasal passages are the focus of a virus versus immunological war zone, with no quarter asked or given on either side. This intense immune response causes the nasal passages to shed most of their lining

cells, exposing highly inflamed raw surfaces, with narrowed breathing passages exuding copious mucus, which contains rising levels of antibodies to the virus. The rhinovirus is eventually killed off by the neutralising antibodies and the 'war detritus' is cleared away by the gobbling action of phagocytic white cells. During this immunological conflagration the new host follows the same unfortunate cycle of being infectious to others, through coughing and sneezing, for a period of anything from one to three weeks.

There is an adage that colds will not kill you. This is largely true, but colds can make children more liable to sinusitis and otitis media, a nasty bacterial infection of the middle ear. Colds can also precipitate asthma in people constitutionally prone to it, and they can provoke secondary bacterial chest infections in people suffering from cystic fibrosis or chronic bronchitis. Nevertheless, the salutary consolation is that, in the great majority of human infections, the rhinovirus eventually passes on by and we make a complete recovery.

Is there anything we can do to minimise the risk of contracting that cold – or is there any effective treatment when we are afflicted?

In Roman times, Pliny the Younger recommended kissing the hairy muzzle of a mouse as a remedy for colds. Benjamin Franklin was more sensible, suggesting that exposure to cold and damp in the atmosphere was responsible for the development of a cold. He also recommended fresh air and avoiding the exhaled air of other people. More modern times have seen a veritable cornucopia of quack remedies for prevention or treatment of colds. One of the most popular was vitamin C, championed by the distinguished American chemist, Linus Pauling. But alas, when subjected to scientific scrutiny it proved no more effective than the mouse's whiskers. Perhaps we should focus more on common sense? Colds are contracted from the coughs and sneezes of infected people.

People in congested offices, or even relatives who find themselves ill at home, should follow the old adage: trap your germs in a handkerchief. If an individual is deemed to be at a particularly high risk from a cold, wearing a virus-level face mask would certainly reduce the likelihood of infection when exposed to an infectious source.

A pertinent question remains: why, then, if our immune system has come to recognise and react to the rhinovirus, are we still susceptible to further colds during our lifetime? In fact, there are roughly 100 different 'serotypes' of the rhinovirus, so immunisation to any one type would not provide adequate protection from the others. Added to this is the fact that serotypes are capable of evolving so that their antigenic properties are apt to change.

3

A Plague Upon a Plague

In 1994 the East African nation of Rwanda erupted onto the world's news and television screens when a simmering civil war between the major population of Hutus and minority population of Tutsis erupted into a genocidal slaughter of the minority population. But despite the deaths of half a million Tutsis, the Hutu perpetrators lost the war, causing more than two million of them to flee the country. Roughly half of these fled northwest, across the border of what was then Zaire, these days the Democratic Republic of the Congo, where they ended up around the town of Goma. Up to this point Goma had been a quiet town of some 80,000 people, nestling by Lake Kivu in the lee of a volcano. Goma now found itself overwhelmed by a desperate torrent of refugees, carrying everything from blankets to their meagre rations of yams and beans. Two hundred thousand arrived in a single day, confused, thirsty, hungry and homeless. They camped on doorsteps, in schoolyards and cemeteries, in fields so crowded that people slept standing up. Agencies from the world's media flocked to the vicinity, reporting the chaos and the urgent need for shelter, food and water.

A reporter for *Time* magazine estimated that the volume of

refugees needed an extra million gallons of purified water each day to prevent deaths from simple thirst, meanwhile the rescue services were managing no more than 50,000. Desperate people foraged for fresh water, scrabbling hopelessly in a hard volcanic soil that needed heavy mechanical diggers to sink a well or a latrine. Human waste from the relief camps fouled the waters of the neighbouring Lake Kivu, creating the perfect circumstances for the age-old plague of cholera to emerge. Within 24 hours of confirmation of the disease some 800 people were dead. Then it became impossible to keep count.

Viruses are not the only cause of plagues, which include a number of lethal bacteria, such as the beta-haemolytic streptococcus, tuberculosis and typhus, as well as some protists, which cause endemic illnesses such as malaria, schistosomiasis and toxoplasmosis. Cholera is a bacterial disease, caused by the comma-shaped *Vibrio cholerae*. The disease is thought to have originated in the Bengal Basin, with historical references to its lethal outbreaks in India from as early as 400 CE. Transmission of the germ is complex, involving two very different stages. In the aquatic reservoir the bug appears to reproduce in plankton, eggs, amoebae and debris, contaminating the surrounding water. From here it is spread to humans who drink the contaminated water, where it provokes intense gastroenteritis, which proves rapidly fatal from massive dehydration as a result of the fulminant 'rice-water' diarrhoea. This human phase offers a second reservoir for infection to the bug. If not prevented by strict hygiene measures, the extremely contagious and virulent gut infection causes massive effluent of rice-water stools that are uncontrollable in the individual sufferer, so that they contaminate their surroundings, and especially any local sources of drinking water, leading to a vicious spiral of very rapid spread and multiplication of the germ.

During the nineteenth century, cholera spread from its natural heartland, provoking epidemics in many countries of Asia, Europe, Africa and America. The massive diarrhoeal effluent of cholera is unlike any normal food poisoning. An affected adult can lose 30 litres of fluid and electrolytes in a single day. Within the space of hours, the victims go into a lethargic shock and die from heart failure.

The English anaesthetist, John Snow, was the first to link cholera with contaminated water, expounding his theory in an essay published in 1849. He put this theory to the test during a London-based outbreak around Broad Street, in 1854, when he predicted that the disease was disseminated by the emptying of sewers into the drinking water of the community. Snow's thoughtful research led to the civic authorities throughout the world realising the importance of clean drinking water. Today the life of an infected person can be saved by very rapid intravenous replacement of fluid and electrolytes, but the size of the outbreak around Lake Kivu, and the relative paucity of local medical amenities, limited the clinical response. The situation was made even worse by the recognition that the cholera in the Rwandan refugee camps was now confirmed as the 01-El Tor pandemic strain of *Vibrio*, known to be resistant to many of the standard antibiotics. This presented immense problems for the medical staff from local health ministries and those arriving from the World Health Organization. Even though the response was one of the largest relief efforts in history – involving the Zairian armed forces, every major global relief agency and French and American army units – the spread of cholera was too rapid for their combined forces to take effect.

Three weeks after the outbreak began, cholera had infected a million people. Even with the modern knowledge and the desperate efforts of civic and medical assistance, the disease is believed to

have killed some 50,000. It is hard to believe that so resistant a plague bacterium as the *Vibrio cholerae* might itself be prey to another microbe. But exactly such an attack, of a mystery microbe upon the cholera vibrio, had been recorded in a historic observation by another English doctor close to the very endemic heartland of the disease, a century before the outbreak at Lake Kivu.

In 1896 Ernest Hanbury Hankin was studying cholera in India when he observed something unusual in the contaminated waters of the Ganges and Yamuna Rivers. Hankin had already discovered that he could protect the local population from the lethal ravages of the disease by the simple expedient of boiling their drinking water before consumption. When, in a new experiment, he added unboiled water from the rivers to cultures of the cholera germs and observed what happened, he was astonished to discover that some agent in the unboiled waters proved lethal to the germs. It was the first inkling that some unknown entity in the river waters appeared to be preying upon the cholera bacteria.

Hankin probed the riddle further. He found that if he boiled the water before adding it to the cholera germ cultures this removed the bug-killing effect. This suggested that the agent that was killing the cholera germs was likely to be of a biological nature. He needed to know if it was another germ – sometimes germs antagonised one another – or if it was something completely different, a truly mysterious agent, that was killing the germs. Hankin decided that he would set up a new experiment using a device known as a Chamberland-Pasteur 'germ-proof' filter, which had been developed 12 years earlier by the French microbiologists Charles Chamberland and Louis Pasteur. The Chamberland-Pasteur filter was a flask-like apparatus made out of porcelain that allowed microbiologists to pass fluid extracts through a grid of pores varying from 0.1 to 1.0 microns in diameter – from 100-billionths

to 1,000-billionths of a metre – that were designed to trap bacteria but allow anything smaller to pass through. Two years after the filter's invention, a German microbiologist, Adolf Mayer, showed that a common disease of tobacco plants, known as tobacco mosaic disease, could be transmitted by a filtrate that had passed through the finest Chamberland-Pasteur filter. Unfortunately, he persuaded himself that the cause of the disease must somehow be a very tiny bacterium. In 1892 a Russian microbiologist, Dmitri Ivanovsky, repeated the experiment to get the same results. He refuted a bacterial cause, but still arrived at the mistaken conclusion that there must be a non-biological chemical toxin in the liquid extract. Finally, in 1896, the same year that Hankin was looking for his mystery agent in the Indian river waters, a Dutch microbiologist, Martinus Beijerinck, repeated the filter experiment with tobacco mosaic disease; but Beijerinck concluded that the causative agent was neither a bacterium nor a chemical toxin but rather 'a contagious living fluid'. Although Beijerinck was closest of all to the truth, he was once again wrong. Today we know that the cause of tobacco mosaic disease is a virus – the tobacco mosaic virus. But thanks to Beijerinck's mistaken finding of a 'contagious fluid', the current Oxford English Dictionary definition of a 'virus' has it as: 'a poison, a slimy fluid, an offensive odour, or taste'.

Viruses are not poisons, or slimy fluids, or offensive odours or tastes, but rather organisms – truly remarkable organisms – that are different from bacteria, indeed utterly different from any other organisms on Earth. The great majority of viruses are very small, tiny enough to pass through Chamberland-Pasteur filters.

Of course, Hankin knew nothing of the existence of viruses when he passed the river water through the refined sieve of a Chamberland-Pasteur filter. Although he was in no position to offer a likely explanation or name for the mystery agent, he had

discovered one of the most important and ubiquitous of viruses on Earth: a member of the group known today as 'bacteriophage' viruses, so-named from the Greek *phagein*, which means to devour. That is exactly what was happening to the cholera germs in Hankin's experiments: they were being 'devoured' by bacteriophage viruses.

The true nature of Hankin's discovery remained a mystery until 1915, when English bacteriologist Frederick Twort discovered a similarly minuscule agent that could pass through the Chamberland-Pasteur filters and yet remained capable of killing bacteria. By now viruses were known to exist even though biologists knew very little about them. Twort surmised that he was observing either a natural phase of the life cycle of the bacteria, the result of a fatal enzyme produced by the bacteria themselves, or a virus that grew on and destroyed the bacteria. Some two years later, a pioneering, self-taught, French-Canadian microbiologist, Félix d'Herelle, finally solved the mystery.

D'Herelle was born in the Canadian city of Montreal but considered himself a citizen of the world. Before becoming involved with viruses, he had already travelled widely, working in numerous American, Asian and African countries, to finally settle at the Pasteur Institute in Paris. At this time the discipline of microbiology was a fashionable scientific research endeavour and it was rapidly expanding its knowledge base. During his researches in Tunisia, d'Herelle had come across what was probably a virus infecting a bacterium that itself caused a lethal plague in locusts. Now working at the famous Institute, even as the First World War raged nearby, he took a particular interest in the grimy disease known as bacterial dysentery, which was killing soldiers in their muddy trenches.

Bacterial – as opposed to amoebic – dysentery is caused by a genus called *Shigella*, which is passed on from the infected

individuals through faecal hand-to-mouth contagion. The resultant illness ranges from a mild gut upset to a severe form, with agonising griping spasms of the bowel accompanied by high fever, bloody diarrhoea and what doctors call 'prostration'. In July and August 1915 there was an outbreak of haemorrhagic bacterial dysentery among a cavalry squadron of the French army, which was stalemated on the Franco-German front little more than 50 miles from Paris. The urgent microbiological investigation of the outbreak was assigned to d'Herelle. In the course of intensive investigation of the bugs responsible, he discovered 'an invisible, antagonistic microbe of the dysentery bacillus' that caused clear holes of dissolution in the otherwise opaquely uniform growth of dysentery bacteria on agar culture plates. Unlike his earlier colleagues, he had no hesitation in recognising the nature of what he had found. 'In a flash I understood: what caused my clear spots was . . . a virus parasitic on the bacteria.'

D'Herelle's hunch proved to be correct. Indeed, it would be d'Herelle who would give the virus the name we know it by today: he called it a 'bacteriophage'. Then the French-Canadian microbiologist had an additional stroke of luck. When studying an unfortunate cavalryman suffering from severe dysentery, he performed repeated cultivations of a few drops of the patient's bloody stools. As usual, he grew the dysentery bug on culture plates and passed a fluid extract through a Chamberland-Pasteur filter, thus obtaining a filtrate that could be tested for the presence of virus. Day after day, he tested the filtrate by adding it to fresh broth cultures of the dysentery bug in glass bottle containers. For three days the broth quickly turned turbid, confirming teeming growth of the dysentery bug. On the fourth day new broth cultures initially became turbid as usual, but when he incubated the same cultures for a second night he witnessed a dramatic change. In

his words, 'All the bacteria had vanished: they had dissolved away like sugar in water.'

D'Herelle deduced that what he was witnessing was the effects of a bacteriophage virus, which must also be present in the cavalryman's gut – a bacteriophage virus that was capable of devouring the *Shigella* germ. But then he had an additional stroke of genius. What if the same thing was happening inside the infected patient? He dashed to the hospital to discover that during the night the cavalryman's condition had greatly improved and he went on to make a full recovery. At this time bacterial infections, such as dysentery, typhoid fever, tuberculosis and the streptococcus, were a major cause of disease and death throughout the world. With no known antibiotics to treat infections, there was a desperate need for any form of therapy. His observations with the dysentery bug bacteriophage gave d'Herelle the idea that, perhaps, phage viruses might be cultivated with the express purpose of treating dangerous bacterial infections.

During the 1920s and 1930s, d'Herelle conducted extensive research into the medical applications of bacteriophages, introducing the concept of phage therapy for bacterial infections. This therapy saw widespread use in the former Soviet Republic of Georgia, and also the United States, continuing in use until the discovery of antibacterial drugs in the 1930s and 1940s. The use of drugs was much simpler to apply and proved dramatically effective, thus supplanting bacteriophage therapy. But this did not stop d'Herelle from continuing to study this marvellous if deadly entity that was so very tiny that it was completely invisible even to the most powerful light microscope, and yet appeared to be so powerful when it came into contact with its prey bacteria.

In 1926, d'Herelle published a now-historic book, *The Bacteriophage*, in which he described his work, and thoughtful

extrapolations, concerning bacteriophage viruses. As we shall duly discover, the importance of the bacteriophage, as we recognise it today, has eclipsed all that even its pioneering researcher, Félix d'Herelle, could possibly have imagined in those early years.

In retrospect, it is remarkable that, even so many decades ago, d'Herelle clearly grasped that he was dealing with a wonder of the natural world, declaring in his book that these agents that were so dreadfully lethal to bacteria were also capable of exerting an extraordinary balancing effect in the interactions between the bacteriophage virus and its host bacterium. In his words: 'A mixed culture results from the establishment of a state of equilibrium between the virulence of the bacteriophage corpuscles and the resistance of the bacterium. In such cultures a *symbiosis* obtains, in the true sense of the word: parasitism is balanced by the resistance to infection.' This is the first use of the term 'symbiosis' in reference to viruses in microbiological history. In a footnote, d'Herelle took the implications further by drawing a parallel between what he was observing in the interaction of the bacteriophage virus and bacterium and the symbiosis that had recently been discovered in all land plants, where fungi in soil invade the plant roots to form a 'mycorrhiza', whereby the fungus feeds the plant with water and minerals and the plant feeds the fungus with the energy-giving metabolites that derive from the photosynthetic capture of sunlight. In d'Herelle's words: 'The respective behaviour between the bacterium and the bacteriophage is exactly that of the seed of the orchid and the fungus.'

D'Herelle is now recognised by many scientists as the father of both virology and molecular biology. But it would take many years before the world of virology, and microbiology in general, would come to rediscover d'Herelle's original vision of the symbiotic nature of the bacteriophage.