

Virolution

*To the memory of Terry Yates, for the courtesy
and generosity of his help and the inspiration
that gave rise to this life-changing journey.*

FRANK RYAN

Virovolution

**The most important
evolutionary book since
Dawkins' Selfish Gene**



Collins

Collins
An imprint of
HarperCollins Publishers Ltd
77–85 Fulham Palace Road
London W6 8JB

www.harpercollins.co.uk

First published in 2009 by Collins

Text & diagrams © FPR-Books Ltd 2009

The author asserts his moral right to be identified
as the author of this work.

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

13 12 11 10 09
10 9 8 7 6 5 4 3 2 1

ISBN 978 0 00 731512 3

Proofread by Janet McCann
Designed and typeset by seagulls.net
Printed and bound in Great Britain by Clays Ltd, St Ives plc

All rights reserved. No parts of this publication may be reproduced,
stored in a retrieval system or transmitted, in any form or by any
means, electronic, mechanical, photocopying, recording or
otherwise, without the prior permission of the publishers.



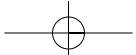
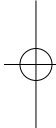
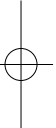
FSC is a non-profit international organisation established to promote the responsible management of the world's forests. Products carrying the FSC label are independently certified to assure consumers that they come from forests that are managed to meet the social, economic and ecological needs of present and future generations.

Find out more about HarperCollins and the environment at
www.harpercollins.co.uk/green

Love this book? Visit www.BookArmy.com

contents

Acknowledgements	vii
Introduction: A Wind of Change	1
1: An Enigma from the World of Plagues	9
2: A Crisis in Darwinism	28
3: The Genetic Web of Life	50
4: The AIDS Dimension	72
5: The Paradox of the Human Genome	100
6: How Viruses Helped Make Us Human	130
7: The Implications for Medicine	155
8: The Autoimmune Diseases	178
9: Cancer	201
10: The Wider Dimension	223
11: Sex in the Evolutionary Tree	242
12: Are We Polyploid?	268
13: The Genie that Controls the Genes	292
14: The Coming Epiphany	319
15: At Journey's End	345
Glossary of Terms	357
References	362
Index	377



acknowledgements

Without the support of Myles Archibald, my editor at Collins, and my agent, Jonny Pegg, this book would not have been published – my everlasting thanks. Julia Koppitz was a godsend in taking care of editing and production. I am also indebted to the many scientists, who, in large or small, gave generously of their time and support on this personal odyssey, in particular Luis P Villarreal and Lynn Margulis, who were as close to mentors as I have experienced in this phase of my life. Others include, of course, Terry Yates, Marilyn Roossinck, Loren Rieseberg, Jan Sapp, Massimo Palmarini, Max Essex, Eric Larsson, Joshua Lederberg, Mauricio Linares, Oliver Quarrell, Douglas Zook, Rachael Tarlinton, Eva Jablonka, Marion J Lamb, Robin Holliday, James W Truman, Lynn M Riddiford, Eckard Wimmer, Corrado Spadafora, Barbara K Mable, Gerry Wilson, Andy Bannister, Roger Butlin, Klaus Roemer, Klemens Ruprecht, Colin McInnes, Claudiu Bandea, Patrick Forterre, John Godwin, Mark Jobling, James B Whitfield, Michael Syvanen, Hugh Dickinson, Robert Grant-Downton, Donald Williamson, Beatrice Lanzrein, Alan

Virolution

J Chalk, Andy Bannister, Sidney Pierce and Mary E Rumpho. These colleagues have variously enlightened me, debated with me, argued and even disagreed with me, and thus educated me. I cannot pretend to do justice to everyone who assisted me over the many years, so labyrinthine and various have been the routes I have followed, but would like to express my debt and gratitude to them all. On reflection, what a privilege and honour it is to have been a small part of the curious – and, however humble and arduous at times, yes “questing” – world that is the very human nature of science. This list would be utterly inadequate without also thanking those rarely acknowledged but highly influential colleagues – the editors of scientific journals, who have variously helped publish my evolutionary ideas for professional consideration and debate, including Douglas Zook, Robin Fox, David Cutler, John Allen, David Richardson, John Streeter and Kamran Abbasi.

Science knows no country because it is the light that illuminates the world.

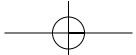
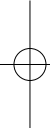
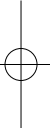
LOUIS PASTEUR

Like science, emerging viruses know no country. There are no barriers to prevent their migration across international boundaries or around the 24 time zones.

RICHARD M KRAUSE

A relatively small number of investigators have been pre-occupied with the biology of viruses ... and how they tick; these scientists are more sensitive to the ... evolution of their symbiotic relations with their hosts.

JOSHUA LEDERBERG¹



introduction

A Wind of Change

I am quite sure that our views on evolution would be very different had biologists studied genetics and natural selection before and not after most of them were convinced evolution had occurred.

JBS HALDANE¹

In the opening line of his celebrated book, *The Ascent of Man*, Jacob Bronowski declared that ‘man is a singular creature. He has a set of gifts which make him unique among the animals.’ Putting aside the now outmoded sexual conventions implicit in his terminology, our natural instinct is to believe he was right. Surely we humans are unique. We are unique in recognising, at sentient level, our own existence. We have risen above the other animals in the landscape so that, for good or for bad, we now shape and control that landscape. But does this intellectual uniqueness mean that we are so radically different that we should be set apart from all other life in our evolutionary origins, which have governed the very nature of our beings?

Virolution

When, on 12 February 2001, two rival organisations announced simultaneously that they had completed the first comprehensive analysis of the human genome, surely this would have confirmed any such purported uniqueness of our human nature. Here, laid bare, for the first time in our history, was the complete library of our genes, the make-up of the 46 chromosomes that make us human. Alas, of any purported uniqueness it registered little. Nevertheless, it was remarkable for what it did reveal.

The first surprise was the modest size of the human genome, at about 20,000 genes. We had anticipated that our human complexity would have demanded 100,000, or more. To put it into perspective, we have only ten times as many genes as a bacterium, a third more than a fruit fly and not many more than a nematode worm. It seems that, at least in quantity of genomic memory, we are not vastly more complex than these humble life forms, though our genome is far more complex in the way we convert genes to proteins, so we can code for a great many more proteins with the same number of genes. Most revealing of all was the confirmation of our common inheritance with other forms of life on Earth. For example, we share 2,758 of our genes with the fruit fly, 2,031 with the nematode worm – indeed, all three of us, human, fly, and worm, have 1,523 genes in common.

While some of my readers might feel humbled by this news, I suspect that Darwin would have been exhilarated because he would have realised that this shared inheritance could not have arisen by chance. We are familiar with the extreme accuracy of genetics in forensic science where a small piece of genetic coding can prove that a certain individual,

Introduction

and nobody else, committed a crime. To have 1,523 whole genes in common is rather more conclusive evidence – I could not even begin to calculate the order of the odds of this happening by chance, whether billions or trillions to one. And this touches upon the reasons why evolutionary biology is among the most fascinating and important of the sciences, and indeed generally of human endeavours: it alone seeks, through the application of logic and experiment, to understand the origins of life, from its beginnings in such humble and terrible surroundings as existed on our newborn planet, to the beautiful and beguiling diversity we see on our fecund blue world today.

There are other great mysteries in the universe, for example in the forces of astronomy and in the minuscule yet equally wonderful world of particle physics, yet no other scientific study sets out to explain how, for example, we shapers-of-the-landscape came to be. The religiously devout may disagree, in attributing life to the creation of an omnipotent creator, but this viewpoint does not derive from science but from the application of faith. In my view, religion and science are based on different belief systems, and they ask quite different questions of those belief systems, so that little is to be gained in such comparative argument. But in one respect I will highlight an aspect I believe to be important. Creationists, including those proposing the anti-evolutionary philosophy of intelligent design, will proclaim that evolution is based upon a theory – Darwin's concept of natural selection – so that, ultimately, the reality of evolution cannot be taken as proven. From this perspective, natural selection will never be capable of absolute proof, since a theory is a

Virolution

construct in logic, not fact. This view prevails among creationists in spite of the fact that scientists have subjected natural selection to remorseless experiment for some 150 years, and it has emerged ever victorious. Yet even here, at the very heart of such passion and division, I believe that a broader perspective is emerging, which is part and parcel of the wind of change blowing through evolutionary biology, and this is capable of offering the hard and irrefutable evidence needed.

Evolutionary theory has profound implications for society, as can be seen in the broad and diverse literature relating it to the humanities. Take the statement of the distinguished French biologist, Jacques Monod, who shared the Nobel Prize with fellow Frenchman, François Jacob, for work on the way living organisms control the production of proteins from their coding genes. In his book, *Chance and Necessity*, he made the telling statement... 'Even today a good many distinguished minds seem unable to accept or even to understand that from a source of noise natural selection could quite unaided have drawn all the music of the biospheres.' Monod's book was published in 1970, ironically coinciding with first publication of the pioneering views of Lynn Margulis on the critical importance of symbiosis in the origin of nucleated cells, and of Susumu Ohno on the inevitability of gene and genomic duplication in the origin of animals and plants.

I'm an admirer of Monod and his contribution to biology. But in evolutionary terms his viewpoint was exclusively reductionist and selectionist. Like most of his contemporaries, he believed that evolution took place through the

Introduction

action of natural selection on a single source of genetic change, mutation. Since the contribution of mutation was essentially random, its role was non-creative – he even uses the term “informationless”. This is what he refers to as “noise”, a metaphor for random genetic change comparable to the static one hears on a radio. Only when the meaningless static – the random mutations – are moulded by natural selection, does meaningful sound emerge. I very much doubt that anybody has ever captured the zeitgeist of Modern Darwinism better. It is a seductive argument, beautifully amenable to the mathematical extrapolations of calculus in analysing selective fitness and population dynamics. How could it be wrong?

In fact it was not wrong – it was simply a part, and not the remarkable whole, of the story. The humanities have been heavily swayed by such reductionist thinking, which is often, if understandably, misquoted as “nihilistic” in the rebuffs of angry creationists. In this book I shall paint a very different perspective of evolution than selection working on informationless noise. The core message of this book is that mutation – what Monod has so brilliantly conceptualised – is not the exclusive source of genetic, or, for that matter, genomic variation. It is my intention to prove, from an entirely scientific standpoint, that natural selection alone could not have given rise to the evolution of life, and its subsequent diversity, for it depends on a number of driving forces, each of which is an important source of heritable genetic change, and without which selection would achieve nothing. Great evolutionary forces, such as symbiosis and hybridisation, are of vital importance to the variation that Darwin so desperately

Virovolution

needed, and they invoke a creativity that is very different from, and far more powerful than, meaningless static. Indeed, they bring to their respective genomic unions novel combinations of meaningful pre-formed genes, to create virgin genomes with enhanced potential for survival. Our understanding of these other forces of evolution has been growing over the last decade or two, until, today, we can see that they too have played, and are still playing, important roles that taken together are equal with, and essentially complementary to, natural selection. This important and rapidly growing field of knowledge has never been drawn to public attention. In this book I shall show how these various driving forces are not theory but fact, which can be confirmed and thus proven with the tools of modern science – indeed, they can be confirmed, repeatedly and predictably, with far greater certainty than that of the forensic scientist with his or her DNA confirmation of guilt or innocence.

Through this new window of exploration, I shall set out to prove beyond all reasonable doubt that evolution is real and ongoing.

The most astonishing implication of this new perspective is the light it throws on our own human evolution, which is proving to be stranger, a mystery more fantastic than anybody could have predicted even a generation ago. Moreover, the new evolution is eminently practical, not only for the light it sheds on our human origins but also for the real understanding it offers in terms of our embryological development, our physiology, genetics and internal chemistry. This is of great personal interest to me, both as a physician and as an evolutionary biologist, since it brings into focus key lines

Introduction

of research and thinking I have been developing over the course of many years. In the world of modern medicine, with its growing understanding at the molecular level and its increasing potential for genetic therapy, we need to know how our normal genes work as part of the machinery of the nucleus and its component chromosomes, which, all added together, make up the complex whole of our human genome. To know this is to deconstruct the mechanisms that made it. How else can we achieve this other than through understanding the mystery of our human evolution?

In *Virovolution* I invite you to accompany me on rather an unusual journey – a new and, I believe, highly original exploration of the genetic and genomic forces that constructed our human genome. For me, as a doctor as well as an evolutionary biologist, it has been gratifying to discover major new implications for medicine along this journey, insights that offer important understanding of the genetic underpinning of a great many important and common diseases, including cancer, the autoimmune diseases, multiple sclerosis, and mental illnesses, such as schizophrenia. Indeed, for me the journey also has an additional personal interest, one that began with a more conventional, if harrowing, interest in the nature of plagues, but which, thanks to the inspiration and assistance of informed colleagues, led me to follow new lines of scientific investigation and then to propose some relevant ideas of my own. I hope you will enjoy the vignettes about how this happened and that you will find the new ideas stimulating in themselves as well as helpful to understanding. Welcome then to an exciting odyssey, one you may find exotic, even a little scary at times, but at journey's end I believe that

Virovolution

you will be thrilled, and perhaps even a little awed, by the powerful forces that made us, and that are still actively working within us, as we continue to evolve as a species.

one

An Enigma from the World of Plagues

A man can learn wisdom even from a foe.

ARISTOPHANES¹

Elysia chlorotica is a beautiful leaf-shaped sea slug that inhabits the salt marshes of the eastern seaboard of the United States, from Nova Scotia in the far north to the warmer waters of coastal Florida in the far south. As the name implies, it is a semi-transparent emerald-green colour and it swims with elegant undulations of its gold-hemmed skirts, which, in biological fact, are the frilly extensions of its slug-style foot. The colour also signals a mystery, for *Elysia* is one of the “plant-animals”, aptly named by the English botanist, Frederick Keeble, at the turn of the nineteenth century – creatures that really do embody the living features of plants and animals.² Yet *Elysia*’s mystery lies deeper still, for in this exotic and beautiful creature we encounter a more profound enigma, one that is both terrible and enlightening. To appreciate the

Virolution

mystery, we need to visit *Elysia* in its coastal habitat and examine its very curious life cycle.

Life for the hermaphroditic slug begins as the first warmth of spring rouses it from the torpor of winter. Only now will it lay its egg masses into the brackish water, where, a week or so later, they hatch out as larvae. The larvae spend the next few weeks swimming here and there in the planktonic layers of the coastal marshes, all the while searching for the green filaments of a single species of seaweed, the alga *Vaucheria litorea*, to which they home and firmly attach. Having found the right alga, they complete their metamorphosis to tiny slugs, when they immediately begin to feed, rasping through the algal walls and sucking out the contents of its cells. *Vaucheria* is a green alga, which, like the green leaves of trees, is packed with tiny bun-shaped organelles, known as chloroplasts, which capture the bountiful energy of sunlight. This process, known as photosynthesis, is fundamental to the cycles of life, enabling plants to convert sunlight into chemical energy that can be stored, and further shared, by the animals that feed on plants. In essence, all of the familiar life forms we see around us depend on photosynthesis, without which our world would be a very different place. There would be no oxygen in the atmosphere, no trees or flowering plants, no fish to swim in the oceans, and no birds, mammals or people.

Photosynthesis began perhaps as long ago as 3 billion years, when some early bacteria, known as cyanobacteria from their blue-green colour, evolved on our exceedingly young, and volatile, planet. A good deal later, through the evolutionary process known as symbiosis, these pioneering photosynthetic

An Enigma from the World of Plagues

microbes were incorporated into early nucleated life forms, formerly known as protozoa but today called protists, which became the forerunners of the green algae and plants. But the cyanobacterial forerunners never went away. They still thrive in the planktonic regions of the oceans, and their ancestral forms also survive, though somewhat whittled down in their genomes, within the tissues of algae and plants as the tiny cellular inclusions known as chloroplasts. All of *Elysia*'s rasping and sucking are directed at these chloroplasts, which it somehow separates out from the other contents of the algal cells, before secreting them away into special cells lining its gut. Soon the gut expands, branching out into various tiny channels all over the body of the growing slug, so that the precious chloroplasts end up in a confluent layer immediately beneath its skin. Thus replete, the slug abandons its mouth to become exclusively solar-powered for the remainder of its life, deriving all of the energy it needs from the algal chloroplasts, which, like a myriad fairy lights within its leaf-shaped body, have switched on the illumination and turned it green.

However, we are far from done with the Elysian mystery. The ingested chloroplasts must now continue to gather the energy of sunlight throughout the slug's life, and this in turn would normally rely on a continuous supply of proteins, which would be coded by the algal nucleus. How then, since the chloroplasts are no longer connected to the algal nucleus, do they continue to survive and function throughout the nine months of the slug's day-to-day life cycle?

In fact, we now know that, at some time during the previous evolution of *Elysia chlorotica*, key genes have been transferred from the nucleus of the alga to the nucleus of the slug.³

Virolution

Much remains to be discovered about this natural genetic engineering, but there is gathering evidence that it is made possible by viruses that inhabit the slug's nucleus and tissues. One very interesting discovery about these viruses is that they possess a special chemical, the enzyme known as reverse transcriptase, which usually tells us that we are dealing with a retrovirus. I shall explain a good deal more about these curious organisms, the retroviruses, in subsequent chapters, but let it suffice for the present to know that this enzyme, reverse transcriptase, enables a retrovirus to invade the nucleus. Exactly how such viruses might have made possible the union of such disparate kingdoms as the plants and animals within the sea slug is not presently known. Indeed, precious little is really known about these viruses, which appear rather ancient in the lineages of retroviruses, though they are seen to assemble, on occasion, in the nuclei of the slug's cells, and from there to make their way as seemingly harmless visitors in the various spaces and compartments of the internal organs and tissues, including, it would appear, the captured chloroplasts. However, there is a final twist to the tale.

At the end of the slug's life cycle, when spring is stirring the torpid animals back into life, and soon after the eggs for the future generation have been laid, the adult slugs begin to sicken and die. All of a sudden the viruses that previously appeared innocuous now teem and swarm throughout its tissues and organs. This is no chance observation since viruses are found to be multiplying in every dying slug, and virulent pathological changes throughout the tissues would point to an aggressive viral attack.⁴ These viruses are not invaders coming in out of the oceans since exactly the same

An Enigma from the World of Plagues

pattern is seen in slugs that have been maintained in aquaria, in artificial sea water. It is hard to draw any conclusion other than that this attack is brought about by the very retroviruses that appear to inhabit the slug's own genetic make-up, those same enigmatic viruses that enabled the genetic transfer of the chloroplast genes from the alga, and made possible the solar-powered life cycle. If so, we appear to be witnessing a programmed annihilation of the entire adult population, as if the viruses that had previously enabled the slug's somewhat idyllic life cycle had now switched behaviour and were acting out some more brutal pattern of programming, culling the now-redundant adults after they had laid the eggs for the start of a new generation.

If the circumstantial evidence is indeed correct, we are looking at an illuminating example of a powerful evolutionary mechanism known as "aggressive symbiosis". A chance discovery amid perilous circumstances led to my proposing this concept many years ago – though I little realised back then that it would play such a major role in the future direction of my professional life.

★

On Monday 25 July 1994, I happened to be interviewing Terry Yates, then Professor of Mammals at the University of New Mexico. He was explaining to me how he came to be linked with a newly emergent plague that had broken out in New Mexico in May of the previous year. This all-American plague was still killing one in two of the people it infected in the surrounding towns and countryside as Yates showed me round the cavernous atrium of the New Mexico Museum of

Virovolution

Southwestern Biology, its walls decorated with the splendidly horned heads of Alaskan rams and African antelopes, and its floor space crammed with specimen cupboards that, when drawn, displayed rows of tiny carcasses – bats with their wings extended to full stretch, and rodents, tens of thousands of tiny bodies, all neatly arranged, from whiskers to tautly stretched tails. The collection was not merely exhaustive in numbers, it was also comprehensive in time, dating back to the 1880s when naturalists had accompanied the new railroads out west. Hidden away in those myriad rows of cupboards, with their meticulously tagged corpses, lay the answer to the emergence of the plague outbreak.

Those extreme circumstances began on 14 May 1993 with an ambulance screaming westwards through the dry desert roads of New Mexico, heading for the Indian Health Service Hospital in Gallup. The ambulance crew had radioed ahead so that, as the ambulance reversed back into the admissions bay, the emergency medical staff, under the direction of Dr Bruce Tempest, were already waiting by the entrance to lift the occupant, a young Navajo male, onto a gurney and rush him to the emergency area, where he was subjected to an emergency chest x-ray even as cardiopulmonary resuscitation began. The chest x-ray showed a bizarre picture – instead of the normal, slightly feathery transparency of healthy lungs, the young man's chest showed a solid opaque white. The air sacs had been flooded with some pathological process, whether fluid or pneumonic exudates, leaving no room at all for air to get through. In effect, he was drowning in his own body's secretions. Resuscitation was unsuccessful and the young man was pronounced dead right there in the emergency room.

An Enigma from the World of Plagues

In such tragic circumstance arrived a new or “emerging” plague into the Four Corners States of New Mexico, Arizona, Utah and Colorado. Although it began in the territory of the Navajo Nation, it soon manifested in the non-Navajo areas of the other states, and spread far and wide throughout the rest of America. But the epicentre was always focused on the desert areas of New Mexico and Arizona, where it terrified the local community, often infecting previously fit young people who could be reduced from rude good health to death, with whited-out lungs, in 24 hours. When I first arrived in New Mexico, the plague was still rampant, with the entire intensive care unit at the University Hospital in Albuquerque devoted to looking after newly diagnosed cases. Through intensive modern investigation and devoted medical management by the medical staff in various cities and hospitals, the death rate had been clawed back from an initial 70% to something closer to 50%. My purpose in coming to New Mexico was to examine new, or “emerging plagues”, and particularly those caused by viruses, such as Ebola and HIV-1, as part of the researches for my book, *Virus X*,⁵ and so the emergence of this all-American plague afforded me a rare opportunity to examine the most intensive modern medical and scientific response, in day-to-day detail. I found that the investigation of the plague, and the medical management of its victims, was still at its height, and I was duly grateful to my hard-pressed and dedicated colleagues, who allowed me to sit in with them in their clinical meetings and scientific experiments.

I knew that scientists working in the Special Pathogens’ Branch of the Centers for Disease Control in Atlanta – the

Virovolution

world-famous plague hunters – had discovered that the Four-Corners’ epidemic was caused by a hitherto unknown virus. Here then was the opportunity to see for myself where such emerging viruses came from in nature, and why they behaved as aggressively as they so often did when they encountered a new host, such as our human species. In Albuquerque I would spend some time observing the doctors in the University Hospital, fighting to save the lives of infected patients. Here they did me the great courtesy of allowing me to interview victims and their relatives, with the normal medical confidentiality, and to witness for myself the harrowing experience of contracting an emerging plague virus. I travelled to Atlanta to observe the work of the virologists and geneticists at the Centers for Disease Control, where they had first realised that they were dealing with a newly emerging virus, which was a member of the genus of viruses known as the “hantaviruses”, using molecular techniques only 13 days after the onset of the epidemic. It took them six more months to see the actual virus, which would subsequently be called the *Sin Nombre* hantavirus – the hantavirus with no name. I sat in on the online discussions between the virologists and the epidemiologists at CDC and the internists and medical investigators in Albuquerque. I found myself gazing with curiosity at images of the new virus taken with the electron microscope, which looked as innocuous as minuscule balls of cotton wool. I moved on to California, where I interviewed virologists who had investigated the first African outbreak of Ebola and who had been intimately involved with the investigation of the emerging virus we now know as HIV-1, the cause of the AIDS pandemic. It was towards the end of my

An Enigma from the World of Plagues

exploration of the *Sin Nombre* outbreak, and after I had collected a great many interviews with the scientists investigating it, that I returned to Albuquerque to talk to Terry Yates, one more interview as I supposed among many, when I wanted to look at what the biologists had discovered about the animal source of the virus.

I knew by then that the virus that was so lethal in people had come from the commonest rodent in America, the humble deer mouse, the equivalent of the common field mouse back in the UK. And in that conversation, I sensed the ground shift beneath my feet, as I listened with a growing astonishment to the slightly built and dark-haired Yates as he explained, with a fast and engaging Kentuckian accent, his own take on plague viruses, and hantaviruses in particular.

★

In addition to his chair in zoology, Yates was also the director of an important biological field reserve in New Mexico, known as the “Sevilleta”, where biologists are conducting one of the most comprehensive ecological surveillance programmes in history. This, in major part, is where the gigantic collection of mammals in the museum has come from. Yates was a world-famous expert in mammalian evolution. He did not focus, as most biologists do, on a single species or even a genus. His interest lay in evolutionary systematics: in the patterns and processes that lead to the diversity of animal species and how this gives rise to the branching tree of their evolution. The outbreak of the *Sin Nombre* hantavirus epidemic in his own back yard added a new, and unforeseen, practical significance to the theoretical work he and his team had been engaged in

Virovolution

for decades. Not only could Yates and his fellow scientists look for the hantavirus in living deer mice, but they could also extract viral sequences from the vast trawl of carcasses stored in the museum and from there they could trace important facts about the virus' own evolution. What then, I ventured to ask him, was the ultimate purpose of this exercise?

'We're interested,' he told me, 'in the co-evolutionary potential of the hantavirus as it evolves in direct parallel with the host.'

His reply surprised me. Like most doctors, I thought of viruses as nothing more than parasites. I was taught modern Darwinian evolution as part of the core biology that underpins our understanding of medicine. Lay people often confuse viruses with bacteria but they are radically different organisms. Most viruses are a lot smaller than bacteria, so small in fact that most are completely invisible even under the highest magnifications of the light microscope. Only through more subtle detective work, using immunological probes, or molecular chemistry, or, ultimately, the vast magnification of the electron microscope, can we bring them into focus. In their genetic arrangements viruses also differ markedly from bacteria. Their DNA is usually packaged in the linear clusters we call genes, rather like our own, while the DNA of bacteria is packaged in a single ring. Viruses are also the ultimate masters of evolution through mutation. They mutate with astonishing speed, something like a thousand times faster than bacteria, which in turn mutate approximately a thousand times faster than we do. Mutation of this order is an important consideration for medicine since it is one of the ways in which bacteria and

An Enigma from the World of Plagues

viruses become resistant to antibacterial and antiviral drugs. For example, it is the key to understanding resistance to therapy in conditions such as AIDS and tuberculosis, where the phenomenal mutational capacity of the HIV-1 virus and the tuberculosis bacterium means that we are obliged to prescribe a cocktail of different drugs to control them.

In this conversation with Terry Yates, I discovered that many different species of rodents around the world appeared to have hantaviruses that infected them. The first hantavirus ever discovered came from a rodent in Korea – it emerged close to the Hantaan River, which gave its name to the genus of viruses as well as to the human illness the virus caused, which is known as Hantaan fever. So when Yates told me he was looking into the evolutionary aspects of the hantaviruses, I presumed that he was talking about mutation. I knew nothing about the co-evolution of a virus in parallel with its host. Indeed, I was still thinking along the conventional medical and evolutionary lines when I asked him another question.

‘What do you perceive as a virus?’

‘That’s a good question. Some people will argue that viruses are not life. I disagree with that, certainly. Perhaps a more pertinent question to me is not “what is a virus?” but “what is a species as far as a virus goes?” Are there species of viruses analogous to mammalian species? Basically I am only recently into viruses. I became interested, almost accidentally, because of the work we do with mammals. It just happens that mammals are the main reservoirs of these viruses. So for me the question “what is a species when it comes to viruses?” is best understood in the context, are they evolving, and are they co-evolving with their reservoir

Virolution

organism? I think that viruses are lineages that have their own evolutionary trajectory and their own historical fate. By analysing the history of that evolution and studying the branching patterns of those viral lineages, we can define viruses based on the branches of the tree. And when we look across the board at these hantaviruses, our evolutionary analysis thus far has shown a very tight correlation between the evolutionary tree that illustrates the history of the mammalian host and the evolutionary tree that illustrates the history of the viruses.'

This still made little sense to me in the way I had been educated to think about viruses, not from the medical perspective and not, as I was already beginning to suspect, from the evolutionary perspective.

'When you say you are studying the virus, do you imply studying its genome?'

Here I should explain, for my non-scientific readers, that a genome is the sum total of all the genes of a life form. While all other forms of life, including humans, have genes coded by DNA, viruses can be coded by DNA or, as in the case of the hantaviruses, by its sister molecule, RNA.

'Studying its genome,' he confirmed, 'or any other characters that would be applicable. They are such simple organisms that – for example, in the case of hantavirus – to get enough characters to be able to understand the evolution of the virus, the best thing to use is the RNA sequences. So we're having better luck with this because each of the bases in the RNA sequences is applicable.'

'How do you manage to do that? Have you been studying the viral genome as and from when you first noticed it, or

An Enigma from the World of Plagues

have you some way of going back in time to see what the virus was like some time ago?’

‘That’s a complicated subject and one that has been debated at the Natural History Museum at the exhibit on the evolution of man. We use a methodology called Cladistics. It’s basically a phylogenetic analysis [tree of life analysis] of the different lineages of viruses.’

‘This is where you observe them in different species?’

‘Not exactly, no. We’re talking about [analysing sequences over] enormous periods of time here. We have been successful in extracting viruses from our frozen tissue collection and we are having success with extracting DNA from fossil organisms. People have successfully amplified and sequenced DNA from plants that were embedded in Miocene rocks – these are 30-million-year-old plants. So what you can do with this phylogenetic analysis is take a viral sequence from a hantavirus of the Four-Corners deer mouse and compare that to other species of viruses that occur on other branches [of the parallel virus-rodent trees]. From this you can extrapolate what the historical condition was. So we can trace the evolutionary sequence back in time and make comparisons to other lineages that diverged from the lineage you are interested in, much earlier in time.’

The implications were slowly dawning on me. ‘So you see a link between the virus and the mammal that is very close?’

‘That’s right. For example, if we were looking at eutherian mammals [the placental mammals including humans], we might compare the sequences of eutherian viruses to those of the marsupials and egg-laying mammals, which are more ancient.’

Virovolution

‘Because they are similar, but not the same viruses, you raise the question that sometime in the past, just as the animals had a common ancestry, perhaps their viruses might also have had their own common ancestry?’

‘That’s right.’

A surprising idea had entered my mind. From my background knowledge of evolutionary biology, and in particular of evolutionary virology, I could assume that virologists, sharing the same conventional viewpoint as I had up to now, would assume that the viruses, given that they mutate at a vastly faster rate than the mammals, would fast-track their own evolutionary trajectories, to stay close to the evolutionary pathways of their mammalian hosts. But now, thanks to the surprising idea that Terry Yates had planted in my mind, I asked myself the question:

What if both the virus and its mammalian host are influencing one another’s evolution, one evolutionary tree interacting with the other, over the vast time periods of their co-evolution?

I spent a good deal longer than I had initially envisaged with Professor Yates, visiting the Sevilleta and enjoying the courtesy of a stay with him and his family, when I had ample opportunity to examine his work, and to think about his ideas in more detail. When I put my question to Yates himself, he could provide no definite answers other than the observation that viruses and hosts appeared to be following very close co-evolutionary trajectories. Nevertheless, over the months that followed, his explanation of virus-mammalian co-evolution intrigued me deeply and it caused me to look much harder at the relationships between viruses generally and their hosts. In particular I spoke to other biologists, and especially

An Enigma from the World of Plagues

virologists, and I explored the literature far and wide. As far as I could determine, nobody was even thinking along the lines of viruses and hosts influencing each other's evolution. And thus it would appear that, entirely by chance, I had stumbled across an idea that, if true, would have major implications. It was one of those exciting moments a scientist hopes will come along at some stage of his or her career, a new idea that makes you think long and hard, and even to question some of those ordinary assumptions you have carried with you since your undergraduate years.

★

What, then, is a virus?

Biologists will differ very widely in their answers to this question. Some will quote the distinguished immunologist and writer, Sir Peter Medawar, Nobel Laureate for his work on tissue transplantation, who caricatured the virus as a piece of bad news wrapped in a protein. But this definition, however whimsical, adds little to any real understanding. Others, usually molecular biologists or geneticists, will adopt a chemical perspective, while Darwinian evolutionists – and until recently symbiologists too – are inclined to see viruses as mere agents of “horizontal gene transfer” between different species. We saw a very interesting example of this with *Elysia chlorotica*, when the strange retroviruses in the slug's genome appeared to enable the transfer of key genes “horizontally” across the kingdoms of plants and animals, as represented by the alga and the slug. Another interesting perspective is that of Eckard Wimmer, a professor in the Department of Molecular Genetics and Microbiology at

Virovolution

Stony Brook, New York, who became famous in 2002 for reconstructing the polio virus from mail-order components back in his lab.⁶ This experiment provoked a good deal of interest and notoriety. But what Wimmer and his co-workers wanted to do, amongst other things, was to make a conceptual, and perhaps philosophical, point. If you know the genetic formula of a virus, you can reconstruct it. They even quoted an empirical formula for the polio virus, as follows:

C332,652H492,388N98,245O131,196P7,501S2,340

It is strange to think of an organism, even if exceedingly small, being reduced to a list of atoms. One is reminded of the bitter opposition of the gentle French naturalist, Jean-Henri Fabre, the so-called poet of entomology, who, although he greatly respected Darwin as a man and fellow scientist, opposed Darwin's line of thinking. In Chapter VIII of his book, *More Hunting Wasps*, Fabre described a 'nasty and seemingly futile' experiment he had conducted, rearing caterpillar-eating wasps on a 'skewerful of spiders'. We need not consider the experiment in detail here, only Fabre's conclusion, which led him to dismiss the concept of evolution through natural selection. In Fabre's own words, 'It is assuredly a majestic enterprise, commensurate with man's immense ambitions, to seek to pour the universe into the mould of a formula ... But ... in short, I prefer to believe that the theory of evolution is powerless to explain [the wasp's] diet.'

It is perfectly true that, in certain circumstances, viruses do behave like inert chemicals. Indeed, I once performed a series of experiments that proved this. When I was a medical

An Enigma from the World of Plagues

student at Sheffield University, I was interested in how our mammalian immune system would respond to viral invasion. The penetration of such alien organisms into our bloodstream – literally the very heart of our being – would be a major, and extremely threatening, event. With the help of my mentor, Mike McEntegart, Professor of Microbiology, I set up an experiment in which I injected viruses into the bloodstream of rabbits. Some readers might react with concern about hurting experimental animals, but the virus I used was a bacteriophage, known as Φ X174 – a virus that only attacks bacteria – so the rabbits suffered no illness. Yet their adaptive immune system responded in exactly the way it should to any alien invader, with a build-up of antibodies in two waves, rising to a peak by 21 days, where a single drop of their serum would be seen to inactivate a billion viruses in mere moments.

The point I am making is that this experiment, by its very design, did not really reproduce the living behaviour of viruses. Injecting a virus into such a host was the virological equivalent of landing people, unprotected, on the surface of Mars. The circumstances were unnatural to the virus and it could neither survive nor respond, in the behavioural sense, and so it died. Had I injected smallpox, or influenza, or HIV-1, into people, the result would have been altogether different. The virus would have come alive in its natural host and a fearsome interaction, virus-with-human, would have followed. As this suggests, it is a waste of time, from the definitional perspective, to consider viruses outside of their natural ecology. Outside the host, it could be argued that a virus really does behave much as Professor Wimmer's formula – as an inert assemblage of genes and proteins. Only in the real

Virovolution

circumstances of its life cycle, when it interacts with its natural host, do we witness the real nature of viruses.

This is why, like Terry Yates, I take the view that viruses, in their natural life cycles, should be regarded as life forms. In this sense the extreme reductionism of depicting a virus as a list of chemicals is implicitly absurd. We might similarly contrive a chemical formula for a human being, when we would end up listing a similar collection of atoms, albeit their numbers would be far more gargantuan. People who view viruses only as chemical assemblages miss the vitally important point that viruses have arrived on the scene through a vast, and exceedingly complex, trajectory of evolution, much as we have ourselves. And though Professor Wimmer might seem to be promoting the viewpoint of a virus as inert, this is not his thinking at all. His view of viruses is much the same as my own, and that of the majority of biologists. A virus may appear inert outside its host, but when it enters the host cell, he too regards it as coming alive. And what an extraordinary life form it turns out to be – for here, in the landscape of the host cell, it has the unique ability of taking over and driving the host genome to make it manufacture new viruses.

Here, in the cells of their natural hosts, viruses are born, like all other life forms. Moreover, they can die. When we treat viral illness with viricidal drugs, our purpose is to kill viruses, much as we use bactericidal drugs to kill bacteria. And, perhaps most important of all, the powerful forces of evolution apply to viruses, just as they do to all other life forms. That is why it is so difficult to cure people infected with viruses. If a virus was nothing more than an inert collection of chemicals, there would never have been an AIDS pandemic. The human

An Enigma from the World of Plagues

immune system would have mopped them up from the circulation without any difficulty.

It is clearly important that we take the trouble to understand viruses. We all know that this is important to medicine in combating viral illness in people. It is important also to veterinary medicine in combating diseases in animals, as it is to agriculture in combating diseases in plants. But there is another, even more profound, reason why we should take the trouble to understand viruses. My subsequent researches, and those of virologists such as Luis Villarreal and Marilyn Roossinck, have made it increasingly evident that viruses have played a key role in the evolution of life, from its very beginnings on Earth to the magnificent diversity we see today. Nowhere has the contribution of viruses been more significant than in the evolution of the human species. Perhaps most amazingly of all, this creative role in human evolution and disease has been played by viruses with a very close resemblance to HIV-1.

I realise that these will appear to be startling claims. When I first proposed such novel concepts, they provoked a heady mixture of bafflement and denial. The reaction was hardly surprising since, if I was right, it appeared to threaten the hegemony of the so-called “synthesis theory”, the trilogy of principles that has stood fast for more than seventy years as the theoretical foundation of modern Darwinism.