VIRUS X

Understanding the Real Threat of New Viral Plagues

Frank Ryan

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BY THE SAME AUTHOR

Tuberculosis: The Greatest Story Never Told (in the US, The Forgotten Plague)

Virus X

Metamorphosis: Unmasking the Mystery of How Life Transforms (in the US, The Mystery of Metamorphosis: A Scientific Detective Puzzle)

Virolution

The Mysterious World of the Human Genome

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We would like to express our thanks for permission to show the cover picture, which is one of the earliest photomicrographs of the ebola virus, taken by Fred Murphy at the Centers for Disease Control in Atlanta.

In Memory of my mother and father

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PREFACE

The Question Why

Plagues frighten people. This is a very natural human reaction. Throughout history they have caused more death and terror than war or any other calamity. Plagues caused by new or 'emerging' viruses are particularly frightening since there is often no cure or preventive vaccine.

Threat of one kind or another is nothing new to life on earth. For half a century we have lived in the shadow of nuclear Armageddon. Today, with the thawing of the Cold War, this fear, though omnipresent, seems to be subsiding, just as new worries are surfacing. Epidemic infections, once thought to be defeated, have surprised us all by making a worrying comeback. This had been paralleled by another very real worry, and one that may in some respects be linked with the threat of new epidemics: I am referring, of course, to the growing ecological disturbance of the world about us.

The most beautiful pictures I have seen are the views taken by the Apollo 8 astronauts as they performed the first lunar orbit. For the first time in our history, we saw the wonder of earth as it rose over the arid grey sand and stone of the moon. Life even from such a great distance was beautiful, in the ultramarine of our oceans, the mellow golds and violets of our land and vegetation, the white swirl of wind-borne clouds. Yet today,

with the possibility of global warming, the mass destruction of the rainforests and the pollution and plundering of the oceans, that beautiful biosphere is under unrelenting threat.

Is there, as many people now wonder, a provable connection between the emergence of new plagues and the effects of human behaviour, the vulnerable 'monoculture' of twentieth-century population expansion, together with the associated effects of human exploitation and need on the delicate ecology of our world? This is as important a question as it is difficult to answer. Part of the problem lies in our emotional responses to such calamities. It has become fashionable to shout ecological rape. Yet without hard evidence of this link, the very people who might be in a position to change things simply will not listen.

A number of recent books have explored related territory, beginning some fifteen years or so ago with William H. McNeill's *Plagues and Peoples* and Richard M. Krause's *The Restless Tide*, complemented more recently by Laurie Garrett's encyclopaedic *The Coming Plague,* Robin Marantz Henig's finely tuned *The Dancing Matrix,* and the wonderful *Emerging Viruses,* edited by Stephen S. Morse. Each has made an important contribution – so why produce another? There can be only one satisfactory answer: I believe that I have something new to say.

My purpose, though it necessitates some degree of overlap with each of these, is to explore the scientific facts at a fundamental level and, through understanding, to arrive at the kind of synthesis that can only come from asking not only the question how but also the question why. The eminent science writer, Stephen Jay Gould, believes that difficulties in understanding result more from conceptual blocks than factual ignorance. To break through such difficulties, I have introduced some new and beguiling concepts.

These conclusions may prove a little controversial at first but I hope the initial surprise will soon give way to new lines of biological research. To arrive at those conclusions I have travelled extensively and discussed these questions with many distinguished experts around the world.

Most of the experts I have spoken to believe that we are skating on ice. How thin that ice may be differs from one expert to another. New plagues, caused by 'emerging' microbes, and new viruses in particular, increasingly threaten humanity: meanwhile there is a continuing, evolving, menace from those that are already all too familiar.

But why do such plagues exist at all? At a time when we live under the threat of the lethal new epidemic of AIDS, where do new viruses, such as HIV, come from? Why do such viruses emerge? Is AIDS the worst that could happen or is our modern and highly technical world at risk of even more dangerous epidemics? The most important, and also the most frightening question of all: could a BSL-4 virus, such as Ebola, ever threaten us by aerosol spread, rather as a cold or influenza virus spreads from one person to another? This threat goes a long way beyond the responsibility of doctors. Indeed, this is a question for governments and even international health-care organizations. For such a pandemic could be as catastrophic as a nuclear war. The question must be factually and responsibly aired. We need to know how real – or unreal – the possibility is. And if it is real, what precautions need be taken to help protect us from it.

Scientists first have the responsibilities of ordinary citizens, but then they have a responsibility because of their understanding of science, and of those problems of society in which science is involved closely, to help their fellow citizens to understand, by explaining to them their own understanding of these problems.

Linus Pauling

PART ONE

The Emerging Menace

ONE

The Age of Delusion

> Since the days of the cave man, the earth has never been a Garden of Eden, but a Valley of Decision where resilience is essential to survival ... To grow in the midst of dangers is the fate of the human race.
>
> René Dubos: *The Mirage of Health*

1

It is 30 July 1994, and outside a relief tent on the crown of a hill, a child's eyes glaze over and in a terrible moment, all the more disturbing for its seeming banality, he dies. Another child wanders amongst corpses wailing. His father, who is somewhere nearby, explains in a quiet voice to a reporter with outheld microphone that the child's mother died the day before. The father has another dead baby strapped to his back. The news photographer's camera pans a scene of pitiable desolation, a field of bodies, men and women, old and young, a scatter of colourful African waxes, exposed heads, naked limbs still clutching their pathetic bundle of transportable possessions, all recently dead, the crop of another morning at one refugee camp called Munigi.

On the evening news, day after day, the affluent world watched as exhausted men threw bodies off the backs of trucks into mass graves. It

was a scene, ominous in its portent, that could have been taken from the descriptions of the Black Death in the Middle Ages.

To most people these harrowing events must have evoked a sense of shock, of disbelief. Surely such ancient horrors, the great plagues of history – cholera, tuberculosis, typhoid, bubonic plague – were no more than nightmarish anachronisms. Those old-fashioned 'Men of Death' might have been a romantic invention, etched in a gothic woodcut by Albrecht Dürer: if remotely recalled, it was with a breath of relief that assumed their place on the dusty shelves of history. Suddenly, in these vivid scenes, carried into people's living rooms by the inquisitive eye of television reporting, such perceptions were disturbingly shaken. Yet it was not so very long ago that the common perception was very different.

A few years ago, I visited the parsonage in the village of Haworth, in North Yorkshire, the home of Charlotte and Emily Brontë. I came away with two powerful impressions. The first was the small size of their gloves, which were so tiny they would barely fit the hands of a child today. The second impression was of a fearful mortality. Indeed, the first writer in the family was neither of the women but the unfairly maligned father, Patrick. When Charlotte and Emily were young children, their father was fighting a personal crusade against a mortality that carried away most of his parishioners before they were thirty. Open sewers coursed down the village streets. Half the children died in infancy.

By the turn of the nineteenth century, the mean life expectancy in Britain, as in the USA, Japan, Germany and all developed countries, was still only forty-five years. Most of the human race still died from infections.

Sometimes this happened dramatically, as in the bubonic plague, which, in its most formidable manifestation, known as the Black Death, fell upon Europe from its origins in Southeast Asia, killing a third, and sometimes even half, the population of entire countries. Plagues seemed to attack out of the blue, or retreat in a similar aura of mystery, creating reigns of terror. Why did plagues happen? Where did they come from?

Throughout most of our history, people did not know. But there were clues that might be recognized from the behaviour of the plagues. Even during the Middle Ages, people looked hard at their deadly patterns, searching desperately for signs, extrapolating reasons. At the height of the Black Death, people recognized the infectious nature of the buboes that disfigured the bodies of its victims. They also recognized that the hacking, blood-stained cough could transmit the deadly contagion to others. The clothes and the bedcovers were burnt and the bodies of the dead were buried away from society in grotesque charnel pits, strewn with quicklime.

Even the twentieth century has not been immune to Bunyan's so-called Men of Death. Fulminating epidemics of influenza and typhus scourged the weary population of Europe in the wake of the First World War, inflicting more casualties than all of the carnage. Though there are hieroglyphs from ancient Egypt depicting the typical wasting of limbs that results from poliomyelitis, the epidemic form of this paralysing illness only emerged in the first half of this century. Even today, in the tragic dystopias of the developing world, the terror so vividly described by Daniel Defoe in his *Journal of the Plague Year* is apt to return, little altered from when he wrote it, almost three centuries ago.

Dramatically, between the 1940s and the 1960s, the medical and biological sciences discovered many new and effective answers. Thanks to the genius of Paul Ehrlich the drug treatments of infection had started with salvarsan, used from the early 1900s to treat syphilis. Penicillin, discovered by Alexander Fleming in the late 1920s, was first manufactured for general use in the 1940s. Prontosil rubrum, the sulphonamide prototype discovered in Germany by Domagk, Klarer and Mietzsch, had by then been generally available since 1935. Stimulated ironically by the military objectives of the Second World War, science had entered a new era of enlightenment which has been termed 'continuous revolution'. In 1943 the two anti-tuberculosis drugs, streptomycin and PAS, were simultaneously discovered by Waksman and Schatz in America and by Lehmann and Rosdahl in Sweden respectively.[1] These were quickly followed by a

proliferation of further antibacterial discoveries, including Hubert Lechevalier's neomycin, the first antifungals, the cephalosporins and macrolides. Every known bacterial infection became treatable.

On all fronts, the biological and medical sciences, and the applications that derived from them, had entered a stage of acceleration more dramatic than had ever been seen before. And even those most refractory infections of all, those caused by viruses – formerly dismissed as untreatable because viruses disappeared into the inner labyrinths of the living cells, merging into the very genomes – were becoming amenable to early treatments: idoxyuridine, designed as an anti-DNA metabolite, proved useful for herpes simplex infections, virugon for influenza, methisazone, derived from Domagk's thiosemicarbazones, was showing potential in the treatment of early smallpox. A new frontline of antiviral drugs seemed to harbour exceptional promise – the interferons, based on the body's own antiviral mechanisms.

The global spirit of optimism that followed was aptly summed up in a speech made by President Nixon before Congress in 1971. 'I would ask for an appropriation of $100 million to launch an intensive campaign to find the cure for cancer... The time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned towards conquering this dread disease.'

Gone was the fear of infection. In declaring war on cancer, President Nixon was no more than reiterating the *Zeitgeist* of popular medical and lay opinion. On 4 December, 1967, Dr William H. Stewart, the US Surgeon General, informed a meeting of state and territorial health officials that infectious diseases were now conquered. Under the umbrella of 'A Mandate for State Action', he extolled the findings of the Centers for Disease Control a year earlier. Epidemic diseases such as smallpox, bubonic plague and malaria were things of the past. Typhoid, polio and diphtheria were heading in the same direction. While syphilis, gonorrhoea and tuberculosis were not quite so readily defeated, it was only a matter of

time before every plague that had ever struck fear into the heart of decent Americans would be a distant memory. Cervical cancer was listed as one of the diseases that could be brought under effective control. Even cancer, it seemed, would be quickly solved. All that was needed was the money to lubricate the intellects of scientists.

In such a climate of optimism, Stewart urged the experts to focus the lion's share of health resources onto the 'new dimensions' of ill-health, the problems that would face the space age: chronic diseases.[2] Confidence was brimming over. It was as if in a single intoxicated summer, humanity had convinced itself that winter would never come.

Since 1960, when global war was declared against the disease, tuberculosis, which had killed roughly three quarters of a billion people in the century and a half up to 1960, was being beaten back on all fronts. Year by year, as a result of a massive and coordinated campaign, in America, in Britain, Europe in general, in Japan and even Russia, its prevalence was declining. But it was never an easy victory. It still harnessed great expenditures of ingenuity, money and manpower. Nevertheless, it seemed just a matter of time before those same methods that had worked for affluent countries would be put into effect to bring down the horrific death rate from tuberculosis throughout the developing world, where a staggering three million people were still dying from the disease each year.

Malaria, second in line for the greatest killer amongst the infections, was responding dramatically to antimalarial drugs, drug prophylaxis and efforts at mosquito control. Plans were formulated, the banners aloft, for two of the greatest plagues that had afflicted humanity to be wiped off the face of the earth. Similar hopes existed for poliomyelitis, the plague that paralysed children. Thanks to Sabin's brave initiative with live virus in sugar lumps, paralytic poliomyelitis was largely eradicated in the developed world. Triple vaccine was reducing the incidence of tetanus, whooping cough and diphtheria to such low levels that young doctors might not see a case throughout the years of their training. Measles vaccine would soon be added.

These planners did not perceive themselves as overly optimistic. On the contrary, they were imbued with certainty, based on a sound understanding of the microbes they were battling and on the most up-to-date results of vaccine development, epidemiology and antibacterial drugs. So, on a broad front in what amounted to a clandestine Third World War, the Men of Death of medieval imagination were being faced on the battlefield, beaten back, and in some instances should soon be dead and buried.

When it came to plague viruses, none had ever caused such a fearful global mortality as smallpox. Believed to have originated in India in ancient times before first ravaging the Roman world as early as AD 165, since then it had scourged humanity in what amounted to a permanent pandemic, causing incalculable loss of life and misery through morbidity and disfigurement.[3] In its more virulent form caused by the virus *Variola major,* it still caused up to 50% mortality in its victims. In 1958, when Russian doctors pressed for a concerted world campaign against it through the World Health Organization, two million people still died from its effects each year. The resultant global campaign against smallpox began in 1967, involved the vaccination of as many as 250 million people yearly, and was led by the tenacious American physician Donald A. Henderson. After ten years of backbreaking struggle, pressing to isolate cases and vaccinate populations through famine and war zones, success was finally pronounced in 1977. It was a remarkable achievement to match that of the war against tuberculosis: the realization of a hitherto impossible human dream. But it also tended to confirm the growing hubris. If we could eradicate smallpox, we could eradicate all of the viral plagues as well.

A certain vainglorious spirit of celebration was surely understandable. There was universal hope for the advance of human civilization. Other more subtle wars had been fought in real, philosophical and sociological fronts against a historical legacy of tyranny and those wars had, in part or in whole, been won. Outmoded despotic arrogance had been supplanted by a

democratic spirit of emancipation which, though led by Western enlightenment, was rapidly disseminating throughout the world. Civil rights and sexual liberation went hand in hand with the new expectation of health. In developed countries nuclear families condensed to the 2.2 average number of children: liberated from the fear of epidemics, women could make full use of the newly available systems of birth control to facilitate their own emancipation. The same generation that had created hydrogen bombs, jet air transport, rockets to take men to the moon, had every reason for optimism. While that spirit and courage might, in retrospect, appear naive, it was also laudable.

To them their aims were not unreasonable and they fought very hard to achieve them. It is tragic that their lofty ideals were not altogether realized. Perhaps it reflected, in part, a regrettable separation of clinicians from basic scientists.

In fact those people whose living depended upon a study of microbes, of their potential and durability, were never deluded. A prescient few, such as René Dubos, warned us openly that the optimism was unjustified.[4] But on the whole people were not inclined to listen. Most doctors, never mind members of the public, were infected with the prevailing hubris, hardly perceiving the growing threat of social changes such as the 'global village'. They seemed unable to grasp the new potential afforded to a very ancient peril, arising from global travel. Diseases that once took months to cross the Atlantic with Columbus or the Pilgrim Fathers, could now circumnavigate the globe in a single day.

Today, as one after another of the dismissed plagues returns to haunt us, as new plagues every bit as deadly as anything seen in previous history threaten our species, it is obvious that it was an age of delusion. It was comforting, a very understandable delusion, but a delusion nevertheless.

At first glance, there is something very curious about this ability to delude ourselves. Until the discovery of antibiotics most of the human race, even

in developed countries, died from infection, often the so-called 'common' infections. Common these might have been, but that did not imply insignificant. Deaths from these infections were often very unpleasant. How was it possible, therefore, that we had forgotten this? It is every bit as strange as if humanity had within a generation lost its fear of war.

Perhaps, in the words of Matthew Arnold, 'we forget because we must' and not because we will. There is an understandable human need to forget misery and embrace happiness. The average member of the public has little real conception of microbes, their ubiquity and the vital role they play in the cycles of life on earth. Television advertisements in the 1960s had tidy housewives banishing germs from the home with a flourish of a spray or bottle of bleach, as if humanity were at last embarked upon a world of inner cleanliness, a world in which bacteria and other microbes were banished into the sewers of history. In science also, a dramatic metamorphosis of attitude, born out of understanding, was also taking shape. The discovery of DNA had triggered the change. Virology, at its intellectual cusp, would move closer to the developing world of molecular biology and its scope would expand far beyond the domain of doctors.

Gone was any residual simplistic notion of a static chemistry of life – in its place a mysterious and much more complex tapestry, a hybrid picture not static at all but constantly changing, with the most subtle implications. The real landscape inhabited by viruses was perceived to be the landscape of the genome. And the genomes, or books of life, were far from the stable monoliths once envisaged.

Viruses it now seemed were much more than parasites. 'Our view of a virus as a parasite is complicated by that of a virus as a genetic element, a two-way channel.'[5] It was the business of viruses to weave in and out of the genomes of every form of life on earth. As a result, terrestrial life had become a dense web of genetic interactions. The relatively simplistic notion

of host and parasite was eclipsed by this more complex and far more interesting world. Yet it was nevertheless a world in which viruses were as dangerous as ever, perhaps all the more dangerous for their being less predictable. But one should not allow oneself to be seduced by the reductive rationalizations of molecular biology. To understand plague viruses, it is equally important to remember the other landscape: this wonderful diversity of life on earth, in which the human expansion and colonization must be just as intimately linked with viral behaviour.

While people might, in their naivety, dream of a perfect world in which there were no microbes, in reality, a world so sanitized as this is more than just an impossible dream, it is a nightmare. Early in this century, the Russian scientist, Vladimir Veradsky, invented the 'biosphere' as a holistic concept that embraces all of life on earth, together with its interactive atmosphere, soil and oceans. Microbial life is an integral part of this living whole. A world devoid of microbes would mean death to all life on earth. The cycles of life would stop, plants would cease to grow, and with the death of plants, oxygen would slowly disappear from our atmosphere and the animals that depended directly or ultimately on these symbiotic cycles of nature would become extinct.

Several years ago, a scientist called George Poinar teased out germs from a 30-million-year-old bee preserved in amber. The world was astonished at this miracle of survival, a miracle that was all the more profound for the fact that the germs were almost identical to those found in bees today.[6] In September 1994, scientists working on ocean sediments off the coast of Japan reported the finding of hitherto unknown species of bacteria living in sediments at depths of 520 metres under the ocean bed, in a world devoid of oxygen and at pressures that would seem to preclude life. The bacteria were similar to primitive types already known to inhabit mud but the extent of the seas and the depths at which the germs were found meant that they significantly increased the diversity of life on earth.[7] In another extreme example of fecundity, others have found bacteria two miles beneath the earth's surface, eking out a precarious living in the

Stygian dark between the very grains of the rocks.[8]

Three and a half billion years ago, microbes were the earliest evolution of life on earth. For aeons they colonized and ruled every habitat, from the sea to the sulphur-laden air, from the beds of the oceans to the primeval mud of shore and lake, where higher forms of life began. Unlike the dinosaurs, those smaller and simpler elements never became extinct, always prepared to modify their genetic book of life, through natural selection, to hold their occupation of every ecosphere on earth.

We live in a world that teems with microbial life. They swarm in unimaginable numbers and variety in the soil, in the manure heaps, in the hedgerows and the floors of forests, in the waters of river, lake and sea. Perhaps even more importantly they swarm over and through every known form of life. Two thirds of the bulk of human faeces are made up of enteric microbes, living within us in an age-old symbiosis. These are not harmful. Quite the contrary, they appear to play a benign role in human health.

Infection, in the sense of an interaction between our lives and a small minority of microscopic life forms, is a fact of life on earth as solid as the mountains and as predictable as the seasons and tides. Not only is nature not benign, nature cannot be benign. You cannot watch a nature programme on TV without becoming rapidly aware of the tenuous nature of existence for very many species on earth. The governing relationship is often that of predator and prey. A big cat pounces on a gazelle or a wildebeest, sinking its canines into the vulnerable neck. Within seconds it seems the prey's eyes glaze and as if anaesthetized, it sinks from life, choked in a manner that is a daily routine. We live in a predatorial world. No species is exempt from this fear of predation, just as no species, including our own, is exempt from the threat of extinction.

The microbes that kill people, particularly those that kill huge numbers in sweeping epidemics, follow, in many ways, the same universal law of predator and prey. It is part of this complex gestalt that the balance is shaped by the behaviour of the prey. If the prey moves, the predator must

move with it – if it changes, if its numbers increase or decrease, if its ecology alters. To understand what is now threatening us, we must look to ourselves. In what way have we, the prey, changed?

Throughout the developing world, assisted by the beneficent efforts of organizations such as the WHO, the United Nations, and the social revolutions that have resulted from advances in agriculture, speed of international travel, and remarkable achievements in engineering, such as the Aswan Dam, the result has been a massive burgeoning of population. At present close to 6 billion people inhabit a world where there were no more than 1.5 billion a century ago. The resultant human needs, the exploitation that necessarily derives from them, have put the world's ecology under threat. Plagues spread a good deal more easily in overcrowded surroundings. And the greatest expansions of population are in the poorest countries, where the medical infrastructure and money spent on health are at their lowest.

There are signs that can only appear ominous. The present generation has seen a proliferation of new plagues and a frightening recrudescence of old ones. The burgeoning human population, the ease of spread through international travel, the changing patterns of human behaviour, including the sexual liberation that began in the 60s, have all put great strains on our ability to cope with these new and renewed demands. In the face of such massive new demands, how justified is optimism over science's ability to cope with the threat of epidemics? A question, unpalatable, perhaps even frightening, as it might seem, that must nevertheless be asked.

Could the genuine miracles of science, the very real benefits of the social revolution, the mass production of food, the miracle drugs such as antibiotics and vaccination, fail us?

TWO

Unexplained Deaths

> The harmony within the universe is such that everything lives within the balance of the whole. Man is not at the top of the pyramid but is a part of it. When a Western doctor says an illness is caused by some infectious agent, the Navajo will say there is a disturbance to the *hozhon*.
>
> Conversation with Ben Muneta

1

Shy and inward-looking, with intense dark eyes, Michael[1] was more comfortable speaking Navajo than English. His family home was the small town of Torreon on the 25,000 square miles of Navajo reservation, the Navajo Nation, that straddles the Four Corners states of New Mexico, Arizona, Utah and Colorado. Like many young Navajos he left the reservation and completed high school in 1992 as a boarder at the Indian school in Santa Fe. But after graduation, he returned home to his friends and people and the old ways.

Friends would describe him as pleasant and sensible. They would also

describe him as athletic, a very good runner. In photographs, Michael is usually shown running, a handsome young man, his face filled with concentration and his thick black hair swept back by the wind. He liked to test himself out in the dry sunny hills of home rather than on the artificial surface of field or track. Just twelve months after he had finished school, he was three times runner-up in the state marathon championship.

Michael had first met Rosina[1] when they attended the same junior school. She was two years older, always a class or two ahead. Rosina was pretty. She was a little more outgoing than Michael, a happy-go-lucky sort of person, full of energy and given to joking in Navajo and English. Later they met again when she was manager of the high school track club. Michael and Rosina had fallen in love and planned to marry. In the tradition of the Navajo, Michael had gone to live with Rosina's family in their compound in Littlewater. Relatives and friends would describe theirs as a very happy relationship. In January 1993, when Michael was nineteen years old and Rosina twenty-one, she had their first baby, delighting Michael with a healthy son.

In time, it would be this aspect that would shake the community around Littlewater: they seemed so young and happy, only recently blessed with a baby, a couple who had a good and fruitful life ahead of them.

New Mexico, where Michael and Rosina lived, is the fifth largest state in America. It is sparsely populated, with a statewide total of just 1.6 million. There is one large city, Albuquerque, accommodating a little more than half a million people. This population is rapidly expanding with influxes from all of the major ethnic groups, immigrants from Mexico, young Navajos from the giant reservation and Anglos from California, fleeing the fear of earthquakes and the after-effects of the Los Angeles riots. To get to Gallup, the 'Indian Capital of America', you take the Interstate 40 westwards from Albuquerque, a journey of 135 miles. Travel on a little further and you arrive in Arizona at the eastern cliff face of the Grand Canyon.

Michael and Rosina travelled this road every time they left home for

Santa Fe. The landscape is hauntingly beautiful. It varies from arid flatland to mountains and seasonal river valleys, or arroyos, that are parchedly

beautiful and deceptively rich in a variety of wildlife. Buttes of rock, of every gorgeous shade of red and gold, soar out of the desert, worn and fissured in the furnace of the sun, towering sandstone cliffs that change colour with the dawn and sunset, wooded canyons with blue-green foliage bathed in heat haze, the emotive backdrops of a thousand Westerns. To the Navajo, whose 25,000 square miles of reservation encompass Gallup, this land is sacred, their ancestral homeland. For them it is the fifth world, the world of *hozhon,* or harmony, into which First Man and First Woman brought soil from the disharmonious third world that would be forged into the four sacred mountains. You pass directly by one of these landmarks at Grants on the Interstate – Mount Taylor, to the Navajo *Dzil Dotlizi,* or the Turquoise Mountain. Here it is easy to imagine that you are close to that creative enchantment.

On 4 May Rosina felt ill. Her symptoms resembled flu, but there was more stomach upset than usual. A few days after her illness began, she deteriorated and was admitted as an emergency to the Indian Health Service Hospital in Crown Point. Michael could not believe it when she died there, only a day or so after her admission. Even the doctors were mystified.

He was so upset he felt out of sorts himself. He felt sick, with a vaguely flu-like illness, starting with headache, then progressing to a fever with aching in his muscles. He lost his appetite. His bowels turned loose. By 12 May he felt so much worse he drove to the clinic in Crown Point where the examining doctor diagnosed flu overladen with grief over the loss of his fiancée. When the doctor offered to admit him to the hospital for observation, Michael refused. With no regular job, he had little money and he needed to visit relatives and friends to raise the cost of Rosina's funeral.

On 14 May, at about nine in the morning and still feeling ill, he

climbed into the back seat of Rosina's father's car, to be taken into Gallup for her funeral. Starting out from their home in Littlewater, near to Crown Point, their journey took them southwards along the broad and dust-blown Route 371 that would join up with the Interstate at Thoreau. Along the way, Michael became progressively more distressed. What had appeared a minor if distracting illness was rapidly worsening. The muscle aches evolved to a constant torment, he felt lancinating pains in his chest and he was becoming more and more breathless.

The deterioration was frighteningly rapid. Within ten or fifteen minutes, his hands and lips were blue and he was gasping for breath. He could not sit still. He would straighten up, then hunch over, try to stretch out through the window of the car. It made no difference. Nothing seemed to ease him. Rosina's father, alarmed at his condition, pulled up the car in the town of Thoreau, veering onto the dirt parking area at the side of the road.

In the lazy heat of mid-morning, the B J Kountry Store was Thoreau in microcosm: a broad, low gable, friendly and unpretentious, with its naive mural of jousting stags, framed by the coral-red cliffs of the Mesa de los Lobos. The matching sun-bleached boards of its neighbour carried the Navajo title for Thoreau, *Dio-Ay Azhi,* which means prairie dog town. As the helpful shopkeeper dialled the emergency ambulance on the old-fashioned black telephone, Michael was rapidly deteriorating. Confused and struggling to breathe, he staggered and paced restlessly about the car park before collapsing on the sun-baked dirt outside the store.

In the ambulance screaming westwards, Michael continued to deteriorate. Throughout the 30-mile journey, the crew performed cardio-pulmonary resuscitation.

Half an hour later, with emergency lights still flashing, the ambulance reversed into the admission bay of the Indian Health Service Hospital in Gallup. They had already called the Hospital switchboard on their radio and the emergency staff were waiting by the entrance as the rear doors of the vehicle burst open and Michael was rushed through the double swing

doors, then left into the emergency room, where he was transferred by metal gurney into the resuscitation area. Curtains were hurriedly drawn round him as all the while the cardiopulmonary resuscitation measures continued. The emergency bleeper sounded on the breast pocket of the medical internist on call.

There are six primary care internists working at the hospital, each with their own separate interests. That morning the senior internist, Dr Bruce Tempest, was conducting his round when the intern on duty was called away. As soon as the round finished, Dr Tempest hurried down to see what was going on.

Resuscitation measures were tragically unsuccessful. Michael was pronounced dead at 11.53 a.m.

2

Gallup is a small city of 20,000 people and the IHS Hospital caters exclusively for Native Americans. It is small, as city hospitals go, but well equipped and friendly, with its brightly painted corridors, decorated with Native American patterns. Most of the staff of the hospital are recruited locally so there is a powerful sense of community. Losing somebody under such circumstances is distressing, even for the most experienced of doctors and nurses. It was into this emotionally charged atmosphere that Bruce Tempest arrived after the ward round.

After some discussion with the emergency room doctor and the admission nurses, who were understandably shaken and upset, Tempest walked over to an illuminated wall viewer to inspect Michael's chest x-rays. What he saw startled him. Instead of the feathery translucency of healthy lungs, all he could see was a solid opaque white. The delicate air-sacs, or alveoli, of Michael's lungs had been flooded, leaving no room at all for air to get in. Michael had literally drowned in his own body secretions.

With a pang of apprehension, Tempest remembered a similar case at the hospital only a month earlier.

At that time a 30-year-old woman, also a Navajo, had been rushed to the emergency room unable to breathe. She too had suffered from an illness that vaguely resembled flu in the few days before her admission. She had also died soon after admission, with a 'whiteout' on her chest x-rays. At autopsy, her lungs had been so laden with fluid they weighed more than twice the normal. The pathologist had been so baffled by the strange findings she had been unable to issue a death certificate. Like Michael, the young woman had drowned in her own secretions. At the time, her death had been attributed to 'adult respiratory distress syndrome', familiar to doctors under the acronym ARDS. This is far from a precise diagnosis. It is a blanket designation that covers many possibilities, including heart failure, overwhelming infection in the lungs, shock from inhaling heat or fumes or from massive lung injury, for example as a result of being close to an explosion. No such explanation had been found.

In New Mexico all unexplained deaths are reported to the Office of the Medical Investigator, which is situated in Albuquerque. The Investigator works with a group of forensic pathologists, who perform autopsies on accidental or criminal deaths and who also investigate non-criminal deaths where a doctor cannot give an adequate explanation. In the more outlying rural areas, the Investigator employs local policemen or detectives who are deputized to investigate their own territories. The deputy examiner for McKinley County is Richard Malone.

Malone is a young-looking man with neatly trimmed dark hair, a moustache and calm brown eyes. He has a gentle voice, an expressive face, a tendency to wrinkle his forehead and narrow his eyes while pausing a moment for thought before replying to questions. His office is in the McKinley Courthouse, a striking brown-pink pueblo on Hill Street, which stands like an island in a sea of dusty cars and pick-up trucks. At 12.35 p.m. that Friday, he received a call from a physician at the hospital asking if he could take jurisdiction over the young man's death. Needing an autopsy,

the doctor anticipated legal technicalities in getting permission. The doctor told him that he had absolutely no idea why this young man had died.

Malone's office is about two miles from the Indian Health Service Hospital. When he arrived in the emergency room, he listened to the disturbing story of the young man's presentation and the emergency room doctor showed him the dramatic chest x-rays with their whited-out lungs. Then Malone went to look at Michael's body.

A graduate in criminology in the campuses of New Mexico and Indiana, Richard Malone was an experienced officer, who had worked as a police investigator before taking his current post with the Medical Investigator's Office. In fourteen years, his work had never lost its fascination for him. It did not take him long to inspect Michael's body. Sometimes you get clues from the skin colour, the colour of the whites of the eyes, obvious bruises, wounds, lacerations. But there was nothing to be deduced from this superficial examination. There was no jaundice of the skin and eyes, as might be seen in a death from alcoholism, no untoward bruising, none of the puncture tattoos above the veins that expose the clandestine horrors of intravenous drug abuse, nothing at all, apart from the common findings that result from the emergency resuscitation measures themselves. Malone could only shake his head.

He was no wiser than the doctor as to the cause of death and that presented him with a sensitive and rather difficult problem. Michael's family were now gathered in a hallway outside the emergency room. He needed to formulate his thoughts for a few moments before going out to talk to them.

Michael's parents were so stricken by the suddenness of events, they could not believe that their son was really dead. How could this happen, when Michael was a good enough track athlete to have represented his high school as a marathon runner? Malone sat down with them and patiently enquired about their circumstances, where Michael lived, the necessary probing of occupation, hobbies, social life and habits. 'Could you just try to

carefully retrace the last few days of Michael's illness prior to the collapse?' They could add little to what he had heard from the doctor.

Malone was born in Thoreau. He has had plenty of opportunity to get to know the Navajo and understood their culture. During his interview with Michael's parents, he expressed his condolences and then, out of courtesy, asked them where Michael was headed today on his journey. They told him he was coming into town to attend the funeral of his fiancée, Rosina, who had died five days earlier.

'I'm real sorry to hear that,' Malone commiserated. 'What happened to Rosina?'

To his amazement, the family described identical symptoms to those of Michael's illness.

Malone felt a sense of growing shock as he continued to ask questions, eliciting more and more worrying information. The details of Rosina's illness matched Michael's, symptom for symptom. 'At that moment, I realized we had a major problem. I didn't know what was going on but whatever it was, we were dealing with something very serious.'

Two young, healthy people, living in the same household, had suffered identical symptoms. Rosina had lived on the reservation, a sovereign and self-governing body, which was not required by law to report deaths on Indian land. In practice, the Navajo Nation were very good about reporting homicides, suicides and deaths by accident. But this had been regarded as a death from natural causes.

On the wall of his office, Malone has two certificates awarded to him for outstanding service. There is a large street map of Gallup with pins fixed wherever somebody has died of exposure. His mind is by nature methodical. He is a man who studies patterns, the algorithms of human behaviour, the geography of their deaths. Now he thought back to a month earlier when he had been puzzled by the death of another young woman who had died from a similar illness as this young man and his fiancée. At the time, her case seemed to be an isolated one. It was also still unresolved. As he reflected on her detailed symptoms and findings, he realized that she

too appeared to fit the strange pattern, symptom for symptom, of what he was seeing here.

'When is the funeral?' he asked the family.

'It starts in fifteen minutes.'

Malone excused himself and hurried to a telephone within the hospital, then called Patricia McFeeley, the pathologist working in the Medical Investigator's Office in Albuquerque. It was Dr McFeeley who had performed the autopsy on the young woman in April. Malone gave her a summary of what he had just discovered. He asked her if she remembered the other woman's case from a month ago. She remembered it very well. She agreed that they needed to stop the funeral. They had urgent need of those two more autopsies. In Navajo culture, great importance is placed on privacy and religious tradition. During the customary four-day mourning period, when the *chindi* or spirit of the dead is still wandering the earth, the deceased is not even spoken of. Gazing on the body of the dead is frowned upon. Any irreverence might cause the spirit to linger, leading to disharmony, tragedy or even worse. Autopsies are particularly unwelcome.

'You can't imagine the thoughts that were going through my mind as I realized I would have to go across the street and tell her family, only fifteen minutes away from the service, that they couldn't have a funeral – that they couldn't have a burial.'

Malone called the mortuary to give them notice of his intentions, so it wouldn't appear to be an ambush when he arrived. Perhaps they could gather together the essential family members in the arrangement room? Walking across the parking lot of the hospital to the mortuary, he met with Rosina's family in the silent room. He introduced himself, then explained that he had just come from the hospital where Michael had just died. Expressing his sympathy, he allowed some moments for them to come to terms with this additional grief. Then he said: 'Unfortunately, we have a problem here because, as far as I can see, all of Michael's symptoms match the symptoms of Rosina's illness.'

With tact and sympathy, Malone explained the possibility of a contagious illness. 'We need to do an autopsy because there is a very real danger that the rest of your family could be in jeopardy from whatever has happened to these two young people.'

The surviving relatives lived together as an extended family on the Navajo reservation, Rosina's mother and father, her siblings, perhaps even grandparents. Malone outlined how, if this proved to be contagious, everybody close to them, including the parents themselves, the infant and their neighbours, were at risk. In spite of their shock and grief, the family listened to him and were courteous in reply. His words frightened and concerned them. They consented to Rosina's autopsy. Malone suggested that they should go ahead with the funeral service but then instead of going on to the cemetery for burial, the family should go home, leaving the body at the mortuary.

Malone returned to the hospital. By now Dr McFeeley and her team were standing by in Albuquerque. He made arrangements for two bodies to travel down Interstate 40.

3

Bruce Tempest had first arrived in the Indian Health Service as long ago as 1967, starting work on the western end of the reservation, where the people were more traditional. 'When I came out here I realized that I could put to use here all the things that seemed important in my life up to that time. I really felt needed.' He found himself fighting life-and-death battles against the old-time infectious diseases, rampaging tuberculosis, epidemics of diphtheria, pneumonia and dysentery. Not only had he come to know and like the Navajo, he knew their illnesses. Michael's sudden death, those bizarre x-ray findings, troubled him greatly. Back in his office, Tempest began a parallel investigation, talking it over with his colleague Larry Crook, compiling his own litany of disturbing similarities, evolving to further

enquiries. He got on the phone to Crown Point about Michael's investigation and treatment. The recorded history confirmed that muscle pains had been a prominent symptom. The doctor had wondered about an obscure infection called mycoplasma, caused by a microbe halfway between a bacterium and a virus. He had prescribed a suitable antibiotic.

Tempest now thought mycoplasma unlikely. He already knew about the death of the young man's fiancée and that of the 30-year-old woman in April. Now he remembered being consulted about a strikingly similar case by a colleague in Arizona the previous November.

There are eight small rural hospitals scattered throughout the vast area of the Navajo Nation, each responsible for different geographic regions, and these hospitals work closely together. It is not uncommon for other doctors to approach the experienced Tempest for advice. He now thought back to the details of when a colleague at one of the other hospitals had called him after the death of the young man's fiancée. It had only been a few days ago and he remembered his puzzled colleague asking his opinion. He knew he had not been of much help: he just could not make any real sense of it. Today, with the death of the young man, he picked up the phone and called his colleague for more detailed information. With totally whited-out lungs, a particular diagnosis played on Tempest's mind. He was considering the possibility of plague.

Plague is of course the most infamous epidemic disease in history, the cause of the Black Death that swept through Asia and Europe in the Middle Ages. Such a diagnosis might seem exotic, but the disease is endemic in the New Mexico area and a handful of cases occur each year, particularly in the spring and early summer. There are two clinical patterns of plague, bubonic or septicaemic, both caused by a germ, *Yersinia pestis*. The two forms vary in their clinical evolution. In one, there is a big swelling of lymph glands in the region draining the bite. This swelling, called a bubo, localizes in a matted collection of infectious pus, giving the disease its name, 'bubonic plague'. In the other form, it doesn't localize at all but

spreads through the blood stream with a clinical picture like septicaemia or blood poisoning. If caught early enough, the disease is still potentially curable using modern antibiotics. But speed of diagnosis is essential, particularly in the much more dangerous septicaemic form, where if not diagnosed early, it progresses to an overwhelming blood-borne spread. The septicaemic form can seed the lungs, giving rise to a whiteout on the chest x-ray. In this 'pneumonic' form, the plague can spread from person to person through coughing, making it extremely contagious.

Tempest called his colleague to ask him if they had screened the patient for plague. In fact they had looked into this possibility and seemingly ruled it out.

The other young woman had come into the Gallup Medical Centre six weeks before. She had arrived in the hospital about midnight, was intubated and put onto a ventilator yet she died just four hours later. In his mind, Tempest located her geographically. Unlike Michael and Rosina, who had lived northeast of Gallup, she had lived a good distance south of the town. If it was a contagious infection, it was extending over a wide territory. He made some more phone calls, confirming what Malone had also recalled, that they had managed to obtain an autopsy on this woman. But the pathologist, Patricia McFeeley, had come up with no new information from examination of the internal organs. No more had the bacterial or viral cultures subsequently grown anything. The implications were becoming more and more sinister.

While Tempest was requesting her records, he remembered yet another occasion, where he had been asked to review the case notes and observation charts of a patient who had died about six months before. Another young and previously fit woman, she had come into a reservation hospital fifty miles west of Gallup. Her presentation was a carbon copy of the others, with fever and severe muscle pains. She hadn't seemed very sick at all on admission. Four days later, and despite every measure to save her, she was dead. Tempest remembered studying the details of her hospitalization, which had lasted several days. Her physicians had treated

her with broad-spectrum antibiotics, so they were convinced they were dealing with an infection. From the sounds of it, they had done all the right things, yet she had deteriorated and died.

Sitting at his desk, Tempest knew he had the case histories of four people, all of whom sounded very much alike. He picked up the phone again and called the hospital that had looked after this woman. Doctors often request tests, such as viral cultures, that take a long time to produce results. These might not have been included in the charts they had sent him. His colleague could offer no new information on the woman but during the conversation he suddenly volunteered a new statistic to add to Dr Tempest's growing compilation. 'Well listen –! There was this guy that died here last week who sounded just like her.'

Hearing this description of yet another case, Doctor Tempest was alarmed. In just a couple of hours on that Friday, 14 May 1993, he had identified five people who lived within the Navajo reservation, all of whom had contracted a mysterious illness. They sounded so very much alike they had to be suffering from the same illness. He had no idea what that illness was. All five people had been young and previously fit. All five had rapidly deteriorated and, in some cases despite hospitalization and urgent medical treatment, all five had died.

4

The Office of the Medical Investigator (OMI) stands in a discreet corner of the campus of the University of New Mexico Hospital in Albuquerque. The entrance doors are of smoked glass and the front elevation is garlanded with bougainvillea.

On Friday, 14 May, Doctor Patricia McFeeley was the pathologist on call for the weekend. At three in the afternoon, she was sitting in her office when Richard Malone called. McFeeley has a deep respect for Malone: in

her opinion he is one of the most experienced of the investigators attached to the department. This was why, when Malone gave her brief details of the two unexplained deaths, she sanctioned his request for the autopsies.

A few minutes later, worried they might be dealing with something contagious, McFeeley called her friend and colleague, Dr Edith Umland. Umland was Chief of the State Public Health Laboratory, two floors above in the same building. She was also a good pathologist, somebody McFeeley had worked with closely in the past and whose opinion she trusted. Now Patty drew Edith's attention to the similarities between the puzzling autopsy a month earlier and the deaths of the young couple, similarities that had been shrewdly spotted by Malone. In their discussion, they probed those similarities and what they might mean, the differing ages of the young couple and the thirty-year-old woman, where these people lived. The thirty-year-old woman lived more than a hundred miles from Littlewater. It seemed unlikely they had ever come into contact with each other.

While waiting for Umland to come down to her office, McFeeley had called the State Department of Epidemiology, which is based in Santa Fe. The call was logged at 3.35 p.m. The message was essentially anticipatory: 'We may have something of a problem.'

Patricia McFeeley is a tall, slim woman in her forties, with fair hair and light blue eyes. She enjoys her work in the Medical Investigator's Department. 'What you do makes a difference to people. It really matters to the family of the dead person, certainly to a person who may be on trial and in whose case I am giving evidence.' She gets a particular satisfaction in counselling the parents of children who have suffered violent or accidental deaths. On that Friday afternoon, when Patty McFeeley called up the Department of Public Health in Santa Fe, the officer she spoke to was the medical epidemiologist on call. At this time McFeeley and Umland were convinced they were dealing with plague. There were other possibilities, some more or less improbable, but they weren't really considering anything dramatically out of the ordinary. The epidemiologist was interested but could add nothing to their investigations. He would wait for the result of

the autopsies. He also gave McFeeley the name of his colleague who would be covering over the weekend. 'If you find something, give us a call.'

The bodies arrived late that night. Patty was enjoying a night out with her husband and daughter, having dinner at a friend's home. After taking the call, she drove back into the department, arriving at about nine o'clock. She was joined in the mortuary by Edith.

Given the late hour and anticipating a readily demonstrable diagnosis, the two doctors performed only limited dissections. McFeeley opened both chests just enough to get lung biopsies that could be tested for infection and examined under the microscope. In Michael's case, she also took blood that could be used for serology. They worked quickly, extracting samples that were as fresh as possible. Then, back in their two laboratories, they began an extensive series of tests. They examined blood, mucoid smears from the lungs and from throat and nasal swabs. They spread the smears over slides and stained them for bacteria. Edith arranged fluorescent antibody tests that would detect the presence of *Yersinia pestis,* the bacterial cause of bubonic and pneumonic plague.

The test is technically finicky and takes about two hours to perform. Essentially you smear lung tissue onto a slide, then apply specific antiserum to the *Yersinia,* which has been labelled with a fluorescent dye. The slides are then washed to remove unattached antibody before being allowed to dry. You inspect the results using a fluorescence microscope when, if present, the plague bacilli light up a bright apple green.

When, with her senior technician, Edith inspected the slides, no yellow-green fluorescence showed.

She performed Gram stains on the smears – these would show up most of the common pathogens – and she set up routine bacterial cultures for plague and a host of other germs. She included another bacterium which occasionally causes a fatal pulmonary disease, *Legionella.* This causes Legionnaire's disease, a novel infection that had been first diagnosed in America in 1976 amongst army veterans. It seemed prudent to inoculate

tissue cultures for likely viruses, particularly influenza.

The tests had taken them a good deal longer than they had anticipated. All of the quick readings had proved negative though the cultures might yet prove revelatory. About midnight, Umland called the epidemiologist in Santa Fe, who had been anticipating her call. The people in the Public Health Offices became a little more concerned. They too had been convinced it would turn out to be plague. It was close to one in the morning when the two exhausted women headed for home.

The following morning they returned to read the overnight cultures. Edith brought the news downstairs to Patty: they had all drawn a blank. McFeeley knew now that she would have to perform full dissections on the two bodies. On her arrival, she had found a large number of other autopsies waiting so she asked some residents to take over the routines. Summoning up a renewed vitality, she started work again on the bodies of Michael and Rosina. It was now 8.30 a.m. as Umland stood by, watching the operations and accepting specimens. McFeeley began the crude but formal incision, from the throat to the pubic bone, prising open the entire chest and abdominal cavities. It is normal practice at autopsy for the pathologist to cut out each individual internal organ and weigh it. Michael's lungs felt heavy. When she put them on the scales, they weighed more than a kilogram each, more than three times the normal.

Where somebody has died of an overwhelming bacterial pneumonia, from plague for example, the lungs would be full of pus. Michael's lungs were not full of pus. They felt and looked rubbery. They had the consistency of a good quality sponge, allowed to soak until it was turgid with water. In medical language, this is termed 'oedematous'. McFeeley considered these lungs 'very oedematous'. When she cut into their firm rubbery mass with her long-bladed knife, a watery fluid seeped out, frothy, bubbling up from the sliced surface and lacing the stainless steel blade with fine pinkish bubbles.

Patty McFeeley felt a powerful sense of *déjà vu*. Michael's findings were exactly the same as the thirty-year-old woman's a month previously. His

lungs were waterlogged. The air sacs, through which oxygen crossed into the capillaries of the blood and carbon dioxide diffused out, were flooded.

In medicine, pathology is said to be the final recourse to the truth. She was gazing at that truth, the pathological confirmation of the whiteouts on the x-rays. Michael had literally drowned in his own secretions.

'Drug overdose' flickered across McFeeley's mind: you certainly saw oedematous lungs like these in some cases of death from drug overdose. In Michael's case, there was also some free fluid in the pleural cavity, the space between the lungs and the chest wall. This also seemed to fit with the oedematous lungs.

In Rosina's case, the embalming process ruled out any meaningful bacterial or viral cultures. Any likely tissue effusions that might have given useful information had been removed by the undertakers. It was still useful however to perform the autopsy since tissue samples could still be examined under the microscope. At the very least, that histological examination might show up commonalities between her disease and Michael's, a clue to the cause of their deaths. In the gross pathology McFeeley did discover a feature the young couple had in common. They had both suffered bleeding from the lining membrane of the stomach. To the pathologists, it seemed to confirm the possibility of a drug- or poison-related cause of both deaths, what medically would be included under the umbrella term 'toxins'.

Certain drugs, sometimes taken as part of a suicide lovers' pact, will cause bleeding from the lining of the stomach. Aspirin is notorious for this and it is also a common self-prescription in these tragic circumstances.

McFeeley saw little else that would point to any particular disease. She saw nothing even remotely helpful. In particular, the spleens were not enlarged, as would be found in an overwhelming bacterial infection, such as blood-borne plague. She cut out chunky samples from various organs, more than enough to search for microscopic evidence of every possible obscure disease and for chemical analysis for potential drugs and poisons.

The diagnosis was as elusive as ever.

By Friday night, Patty McFeeley and Edith Umland had already gone a long way towards excluding plague as the cause of death. By Saturday morning, they thought a viral pneumonia due to influenza unlikely. They were already wondering if they were dealing with a much rarer infection, such as inhalational anthrax. McFeeley called the histology technicians at their homes. She explained it was an emergency and asked them to come in and run the specimens through so they could get slides out the next day. By Sunday McFeeley and Umland had micron-thin sections of the tissue samples mounted on slides and stained, to look for any unusual pathological change, for the odd, the curious and the rare among bacteria, protozoa and fungi.

By Sunday they had found no organisms of any description on any of their tests. Routine cultures had ruled out the commonly invasive bacteria, the aerobes, like the abscess-causing staphylococcus and the beta haemolytic streptococcus, which would subsequently become notorious in the flesh-eating bug scare. They had ruled out chlamydia and Legionnaire's disease. They had dry runs on anaerobes, the bacillus that causes anthrax, the bacterium that causes the milk-associated brucellosis, the epidemic germs of whooping cough, diphtheria, the intestinal pathogen, *Campylobacter,* even the fungus-like *Nocardia,* mostly found in the immunocompromised.

That Sunday McFeeley spent hours just looking down the microscope. Umland came downstairs to join her. McFeeley would subsequently remember her colleague sitting there, willing her to find something. By this time they were surer than ever that they were dealing not with two but three cases. McFeeley had pulled out the slides on that previous autopsy about a month before, looking for commonalities in all three cases. Patty turned to Edith in frustration and said, 'Go ahead, use my microscope. Sit here and look yourself.'

Patricia McFeeley and Edith Umland were more than colleagues. They were also friends. Patty was the taller of the two, Edith with slightly darker

hair, also blue-eyed. Where Patty tended to wear contacts, Edith wore wire-rimmed spectacles. They were of much the same age, having first met

when they had attended the UNM med school. They had shared the same pathology rotation in their post-grad training. In their working relationship, their mutual sense of trust, they were comfortable with one another. At this moment, Patty was exhausted from looking down the microscope. Edith had just arrived and her eyes were fresh. Patty had some family business to see to, she needed to pick up the kids and take them somewhere, so she left her office, with Edith rummaging through the slides all over again.

When McFeeley returned, later that same day, Umland had gone home. But McFeeley found a hastily scribbled note, a jotting of her friend's thoughts, which she kept and which she showed me when I interviewed her a year later.

The note is dated 16 May. 'To my eye, all three have the same thing, more or less, whatever it is.' Umland then summarized most of what would ever be demonstrable, under light microscopy, of the pathology in the mystery illness. There was mild damage to the liver and slightly more damage to the kidneys. Her final line was a prediction: 'I sure hope we get a virus out of the lung tissue.'

THREE

The Panic Spreads

> People would hear about somebody they knew dying with symptoms that appeared not much different from an ordinary cold. At the first sign of a headache or mild fever, they jumped to the terrifying conclusion: 'That's me – I have all of those symptoms.'
>
> Conversation with Patricia Guthrie

1

The University Hospital in Albuquerque is an attractive cluster of modern buildings linked through an ironwork bridge with the tree-lined main campus across Lomas Boulevard. A colourful ethnic mix of Spanish, Anglo and Native Americans jostles cheerfully about its wards and corridors, which are shaded by tinted glass from the full glare of the New Mexican sun. Dr Fred Koster is the Professor in the Department of Medicine. On Monday 24 May Gary Simpson, Director of Infectious Diseases for the state, came down from Santa Fe to speak at the weekly departmental case review conference. Simpson had been alerted by Bruce Tempest and now he told the UNM clinicians about the strange cluster of five cases. Fred Koster is six feet tall, grey-haired, with a moustache of the same colour. He wears metal-framed spectacles and is filled with a restless, impatient energy that seems to marry well with his enthusiasm for research into the

immunological defences against infectious diseases. Koster would subsequently remember the reaction to Simpson's presentation: 'We all thought that something very strange was going on.'

A couple of days later, Koster took a call from a doctor at Crown Point Hospital asking him to take over the care of a young man who had come down with a fever. Koster listened to the symptoms of muscle aching, shortness of breath and a cough. Although the patient was not seriously ill, the IHS doctor suspected the new mystery illness.

'Why,' Koster asked him, 'do you suspect the mystery illness?'

'This is the brother-in-law of the marathon runner. His sister also died from it.'

Rosina's brother normally lived in Washington State but had come to stay in the family compound to attend her funeral. Hearing that Frank was now sick, Koster felt it prudent to transfer him to the intensive care unit.

When Frank made his reluctant journey to the UNM Hospital, his wife, Dolores, travelled with him. Frank was very frightened so Dolores refused to leave his side, even when she needed to sleep. Concerned relatives as a rule are offered accommodation on campus. Occasionally, when matters are critical, they will stretch out on a couch in the waiting room of the intensive care unit. But Dolores, who was 34 weeks pregnant, refused even this degree of separation. She took some blankets and made her bed on the floor of her husband's room in the intensive care unit.

Frank was not as desperately sick as Rosina and Michael. Nevertheless, he had a chest x-ray performed every twelve hours. Fleeting shadows would appear and as quickly disappear again. It seemed likely that he had a milder version of the illness that had killed his sister and brother-in-law. He never became breathless and there was no question of putting him onto a ventilator. There was another curious finding. His blood film showed abnormal lymphocytes.

Lymphocytes are white blood cells, circular in outline and with a large nucleus. They do not ingest foreign matter in the amoeboid fashion of the

other white cells. Their role is more subtle, recognizing foreign antigens, helping in the production of antibodies. They also contribute to 'cellular immunity' – part of the body's defences against foreign antigens, such as organ transplants, and long-term infections like tuberculosis. An increase in lymphocytes in a patient's blood film is suggestive of a viral illness.

Each morning at 7.00 a.m. the doctors would arrive to conduct their rounds. Masked and gowned as a precaution against a possible aerosol-spread infection, they would enter the room to talk with Frank. They would listen to his symptoms, examine his chest, look at the charts. Then they would have a few words with Dolores.

'How do you feel?'

'I feel fine.'

Three or four days later, Frank's fleeting exudates had cleared and he was feeling so improved the doctors stopped his oxygen. They were thinking about letting him go home. A medical student who had been chatting to Dolores drew the doctor's attention to the fact that she looked sick.

'Well,' she told the doctors on today's round, 'I've been getting all these backaches and muscle aches but I thought it was just from lying on the floor. I think maybe you're right. Maybe I am sick.'

When they took her temperature, it was markedly elevated. They arranged a chest x-ray and to their consternation the pictures of her lungs resembled a snowstorm. It was apparent that Dolores had the illness. Her lungs were already filling up with the strange infiltrates.

Her illness advanced with a fearsome acceleration. She was admitted into a room further along the corridor and hour by hour the doctors followed her progress. Within eight hours of first noticing she was sick, they watched her crash. She became extremely breathless and her chest x-ray showed a whiteout identical to that of her late brother-in- law, Michael.

Horrified by what was happening to this previously fit young woman, Fred Koster was now certain they were dealing with some very unusual

condition. He talked it over with Howard Levy, the director of the intensive care unit, who was taking immediate care of Dolores. Earlier in the week, they had read through the pathology reports of Michael and Rosina. What baffled them was the fact that so much pointed towards an overwhelming infection yet no infectious agent had been found. Meanwhile, with the close monitoring of Dolores, they noticed another unusual feature.

Her platelet count was tumbling. Platelets are tiny particles that circulate in blood and are vital in forming blood clots. Apart from their role in wounds and accidental injuries, they play an important part in sealing off small leaks and damage to the walls of tiny blood vessels. This is happening all the time through normal wear and tear within the body. So the fall in Dolores's count was significant.

Frank had also shown a plummeting platelet count. Now they noticed that Dolores was also showing atypical lymphocytes in her blood. These were bigger than normal and stained differently, a royal purplish blue. They were immature precursor cells, of a kind normally found only in the spleen, lymph nodes and bone marrow: doctors called them 'immunoblasts' or 'blasts'. In Koster's mind a syndrome, inchoate as yet, was struggling into creative recognition: and those atypical lymphocytes and the low platelet count were an integral part of it.

A 'Dear Doctor' letter had been circulated statewide by the concerned Public Health Offices in Santa Fe a few days earlier and it was already exciting a response. While Frank and Dolores were being treated in the intensive care unit, more cases were being referred into the University of New Mexico Hospital. By the time Dolores crashed there were at least six cases, all thought to have the mystery illness, on the same intensive care unit. At this stage there was a call from Crown Point. Dolores's five-year-old son had a temperature. Crown Point received permission to send him straight to the UNM Hospital for observation.

On Thursday, 27 May, Fred Koster picked up the phone to have an

urgent conversation with Gary Simpson in the Public Health Department in Santa Fe.

Dr Koster's call arrived just as Simpson was attending a crisis meeting with senior colleagues including C. Mack Sewell, the State Epidemiologist. Everybody was extremely tense with the worry that they might be dealing with an aerosol spread of a highly contagious and lethal microbe. One of the technicians in the Medical Investigator's Office, who had assisted in the original autopsies on the couple, had just been admitted to the UNM Hospital with fever and a dropping platelet count. That same afternoon came news that two other health workers who had cared for the original couple were also sick with febrile illnesses of unknown cause.

Howard Levy was considering closing the intensive care unit at UNM Hospital to all cases other than the mystery illness so they could triage suspected cases into there. 'We don't know what we are dealing with,' Koster told Simpson. 'We had better get together and think this through.'

Events were moving at such an alarming pace that Simpson welcomed Koster's suggestion. At eight in the evening of Thursday, 27 May, an urgent gathering of seven or eight senior doctors took place at Simpson's home in Placitas, about 20 miles north of Albuquerque. Those present included Norton Kalishman, the Chief Medical Officer for the State of New Mexico, Edith Umland, Fred Koster, Mack Sewell together with his deputy, Ron Voorhoes, and Jim Cheek, head of epidemiology for the Indian Health Service.

With two decades of experience in public health, Sewell is not easily ruffled. But in the last 48 hours, he had received word of many more suspected cases. Earlier in the afternoon, he had called his colleagues in Arizona, Utah and Colorado. A week ago they had not seen a single case. But now the first reports of suspected cases were arriving into their public offices of health. 'In my position you find yourself sitting there and you have to weigh and to judge what is really going on, how much resources you need to put into an investigation.' Since Tuesday, 18 May, there had been a series of communications between Maggie Gallaher in Sewell's

department and the Centers for Disease Control in Atlanta – the CDC.

The CDC are the most experienced disease investigators in the world.

But their charter does not permit them to interfere in the health affairs of an American state unless invited to do so by the state authorities. That afternoon everybody was agreed they should call them in.

Sewell knew Ed Kilbourne, a senior officer at the CDC, working in the Center for Environmental Health. They had worked closely together during the investigation of an outbreak known as the eosinophilic-myalgia syndrome. Later in the afternoon, Sewell spoke to Kilbourne on the phone and he formally requested the CDC's assistance.

Sewell's presence at the brainstorming meeting at Gary Simpson's home would be constantly interrupted by telephone calls, requests for updates from colleagues in other states and from senior officers at the CDC as the formal request moved through the divisions. While Sewell was fielding the enquiries, his deputy, Ron Voorhoes, briefed the small gathering on a trip he had made to the site of the outbreak. On the Thursday morning, Voorhoes and Jim Cheek had made a special trip to talk with 20 or so members of Rosina's extended family in Littlewater. Aerosol spread was still a worrying possibility and Voorhoes described the atmosphere of alarm now pervading the community around Crown Point.

Fred Koster startled everybody with his description of Dolores's fulminating decline. The small gathering talked about that. Perhaps they should subject her to a lung biopsy? Sometimes this is the only way in which doctors can diagnose a baffling pulmonary illness. But it would involve some degree of risk, and on the whole his colleagues were opposed to it. Again and again the conversation veered back to the question that was on everybody's mind: what exactly were they dealing with?

Was this really something new? Or was it something familiar they were failing to recognize? There were a number of diseases that could behave in just as deadly a fashion if they remained undiagnosed and, consequently, untreated. They spent time thrashing out a list of possible diagnoses. It was

a very long list. Fred Koster felt that he now had the rudiments of a clinical and laboratory picture to go on, enough perhaps to give other doctors in the southwestern states a clearer idea of how to recognize the illness.

Since the circulation of the 'Dear Doctor' letter, the evolution of alarm had greatly accelerated. How could they even hope to keep colleagues updated on circumstances that altered alarmingly from hour to hour? The closer circles within the state were no longer adequate. With cases now suspected in neighbouring states, there was a cogent need to alert colleagues wider afield – but just how wide did the net extend? Certainly to the Four Corners states and perhaps, Simpson pensively wondered, even nationwide? There was a momentary silence as they pondered the ramifications of that. Were they all going to look very stupid when a common explanation eventually turned up?

But Koster's awe was contagious. The illness seemed a virtual death sentence. The eclectic choice of victim in the reservation was frankly terrifying. The pattern was too unusual, too dangerous, not to take the risk. There was no option but to set bigger wheels in motion. The public offices of health would take on the arduous labour of keeping colleagues statewide – nationwide if it came to it – educated on the day-to-day developments.

The problems confronting them were so daunting it was the unanimous conclusion that they needed to hold a major conference, thrown open to every conceivable medical expert in the state. The conference would take place just two days later, on the Saturday of the Memorial Day holiday weekend.

2

On Thursday, 27 May, the same day the small group met at Simpson's home in Placitas, the story broke in one of the state newspapers. The *Albuquerque Journal* carried a front page headline: **MYSTERY FLU KILLS 6 IN TRIBAL AREA**. The report was written by staff writer, Leslie

Linthicum.

A mystery flu-like illness has killed six people on or near the Navajo reservations in the past six weeks and has sent four others to hospital for treatment ... Moving on to describe three cases in the index family, it was ominously complete with photograph of Michael, his real name, the name of his fiancée, the name of their baby and their address in Littlewater.

The State Health Department would subsequently praise the local reporters, who showed considerable sensitivity in their handling of emotive local issues. Yet this very first report gave fair warning. There would be likely conflicts of priorities between journalism and medicine in the coming weeks. This Problem aside, the article was remarkably accurate. Two out of the ten suspected victims of the mystery disease were identified as Anglos; it should have been clear from the very beginning that this could not be specifically a Navajo disease.

The following day, Patricia Guthrie, a staff reporter on the *Albuquerque Tribune,* was out interviewing people on the Navajo reservation. She was in the position to write two separate reports, highlighting the mysterious nature of the illness together with the fact that yet another possible death had been confirmed. The latest victim was a Navajo male in his early twenties who had died on Tuesday at the Zuni Pueblo Hospital after being transferred from the neighbouring Pine Hill health clinic in Ramah. His death, together with another at an as yet undisclosed location, brought the total fatalities to eight. In New Mexico as a whole, the suspected total of infected had now risen to 14. The only glimmer of relief was the fact that Rosina's baby and Dolores's son had each been excluded. All the same Guthrie somewhat pithily summed up the position: 'Officials are not yet sure whether the disease is highly contagious, how it is contracted, what is causing it or how to prevent it.'

By now the story was hitting the US national media. Reporters and film crews from around the country descended upon the Navajos, where, in the words of Duane Beyal, public relations assistant to President

Peterson Zah, 'they trampled the rights and the privacy of these poor families who were already stricken with this scary mystery disease'. While the local journalists understood the traditional reticence of the Navajo culture and their need for a four-day period of quiet mourning, out-of-state reporters had little conception of the culture shock their arrival into the introverted and highly conservative local community would bring. They would go out and swarm around families, photographing funerals, printing victims' names, disturbing customs and invading their privacy.

In a typical incident, a television crew arrived at the home of a recently bereaved family, pulled up outside the hogan in one of their big trucks, set up their link-up vans with satellite on top and then knocked on the door. In more extreme examples, reporters sneaked into funeral parlours and attempted to photograph or to interview relatives in the very intimacy of the church or the service. One went so far as to trick his way into a hospital, where he attempted to interview a woman who was being ventilated in the intensive care unit. The following day the woman died. To the grieving Navajos, it seemed that 'even on your deathbed, you could find no peace'.

The medical authorities in Santa Fe were frantically trying to warn physicians and the public at large that what appeared to be the flu might not in fact be the flu at all. Inevitably, as the symptoms were spelt out in the local newspapers, as the staggering lethality of the disease became more widely known, people would jump to the most alarmist of conclusions. There are two main hospitals in Gallup, the Public Health Service and a private insurance hospital called Rehoboth McKinlay Christian Hospital. By the Memorial Day weekend, the emergency waiting areas of both hospitals were besieged by people, anxious that they had the plague.

The symptoms were so non-specific it was impossible at this stage to placate this mass anxiety. Terror of a malignant unknown, the bafflement of the doctors themselves, fuelled the public panic. In every newspaper article, the symptoms were described as vaguely flu-like. And flu-like symptoms could mean just about anything.

By Monday, 31 May, and the Memorial Day holiday, the tally had risen

to 25 such victims. Most of these were young and previously fit, including 18 Navajos, five Anglos, one Hispanic and a single Hopi Indian. The death rate remained desperately high in spite of the efforts of both the doctors and the press to persuade people to report in early. One patient, who had been sitting up in bed in the morning eating breakfast, was on a respirator by afternoon and dead that same night.

News reports branded the epidemic a 'Navajo Disease'. Before the medical experts had been able to demonstrate that the disease was not spread from person to person, fear of contagion led to the resurrection of old prejudices.

A school bus of Navajo children travelling to Los Angeles to see their pen pals was turned back at the Californian border. Restaurant meals were presented to people on paper plates, or the serving waitresses wore rubber gloves. A car with New Jersey licence plates was seen driving across the reservation with its passengers wearing surgical masks. A Navajo couple were detained at a large airport and kept for a time in quarantine conditions, because the airport authorities feared they might be carrying plague.

Day after day there would be some new horror story, some petty episode of discrimination, some indignity imposed on the frightened people. When Ben Muneta, a Navajo doctor with the Indian Health Service, arrived in Gallup to conduct investigations, people avoided him in the street. 'In the shops in Gallup, they wouldn't touch me. I'd give them money and they would throw it back at me.' The shopkeepers in the small town, highly dependent upon the tourist trade, were blaming the Navajos for the loss of business. In one of the most unpleasant resurrections of prejudice, gangs of thugs roamed some of the border towns, beating up Navajos.

Little wonder that the residents on the reservation began putting up NO MEDIA signs on the approach roads. A more tragic consequence of this circus-like intrusion, coupled with the fear that the medical authorities were

openly cooperating with the media, releasing names and addresses, was the refusal of local people, sometimes even the families and neighbours of victims, to cooperate with the ongoing medical investigations.

The paranoia now gripping the reservation was excusable. The arrival of a plague is one of the most terrifying experiences any community will ever experience. When Doctor Muneta drove out to reassure his mother, who lived in a hogan at the top of Coyote Canyon, she told him about a neighbour who had suddenly taken sick and had been carried off by helicopter to Albuquerque. It was as if a pitiless fate hidden in the crepuscular shadows was throwing the dice and just picking out people at random. The slow swelling ripple of death widened with a seeming inexorability, following that same mysterious pattern it had established that fateful day of 14 May. It was the youngest and fittest in the local population who were dying. As one fearful day followed another, there was a stepwise escalation of alarm.

Panic also bred internecine tensions. People in Littlewater were apprehensive about each other. The Navajo community at large were looking at Littlewater somewhat apprehensively. In turn the Navajo people were being regarded with identical apprehension by the people in the border town areas who suffered the same suspicions from the people in Albuquerque. So the ever-widening ripples extended until, with the arrival of CNN and the national media, they lapped the length and breadth of the United States.

In this invidious mire of fear and mistrust, some Navajos asked themselves if it had been Anglo tourists who had brought the disease into the reservation in the first place. Unlikely as this might seem, history, for the Native Americans, carried some terrible precedents.

In 1763, Sir Jeffrey Amherst, commander in chief of the army in North America, ordered that blankets laden with smallpox should be distributed to the Pontiac Indians, who had been fighting a successful and courageous battle for their lands and culture against the encroachment of the European settlers. This ruthless use of germ warfare destroyed the

Pontiac and, in the explosive contagion that typifies plagues in a virgin population, straddled the Rockies to involve the Sioux and other Plains

Indians in a wholesale slaughter. It is believed that smallpox, measles and a host of other plagues carried with the European settlers, more often introduced accidentally than deliberately, may have wiped out as many as 56 million of the native inhabitants of continental America.[1]

Over the tribal lands, people remembered the odd climatic conditions of the last year. They talked about a greenish-yellow mist that overhung the Southwest. Ben Muneta would remember how the winds would come in from the dry desert bringing a similar haze over Albuquerque. The changes in the weather and local ecology had been so remarkable that some of the Navajo elders, who spent their lives studying such changes, had predicted that people would die six months before the sickness appeared.

If the elders had a long and venerable tradition of wisdom that gave reasonable grounds for their fears, elsewhere the scientific vacuum threw up some rather more arcane and crazy theories. Every oddball psychic and psychotic took the opportunity to ring in with their offbeat theories. Somebody from California called the medical authorities to say that the disease was an effect of earthquakes, which caused micro-fissures in the ground from which coccidioidomycoses spores were escaping from quartz crystals. Another faxed the reservation to say that Russians were going around in UFOs and dropping the illness onto the reservation.

Wild speculation now swept through the community that an Andromeda strain of virus had escaped from some supposed biological weapons bunker at Fort Wingate. More perniciously still, some people were wondering if the Navajos were the victims of some ruthless germ warfare experiment.

The medical intensive care unit (ICU) would bear the responsibility for the urgent care of all suspected cases of the illness arriving at the University of New Mexico Hospital. Howard Levy is the Director of the unit. A youthful man with sweptback dark hair, sensitive features and intelligent green eyes, he wears a white coat, belted at the back, and decorated with a Navajo cross on the breast pocket.

It had been part of Levy's duties when newly appointed to plan the design of the intensive care unit. He was proud of his modern facility of fourteen rooms, each fitted with, multiple channel video monitors, linked to a master network housed in a control room. In this master centre, a hive of space age technology, with banks of monitors, each scrolling four to eight differently coloured traces, followed the vital signs of every patient. Here they could observe 14 continuous EKGs on a single screen, fourteen respiratory rates, arterial gases, or the pressure waves from Swan-Ganz catheters that had been inserted through a subclavian vein and wound through the right-sided chambers of the heart into the capillary bed of the lungs. At a glance you could pick up the moment when somebody was breathless, if they turned over in their sleep, or their life was suddenly threatened with a cardiac arrhythmia.

Howard Levy graduated in medicine at the University of Witwatersrand in Johannesburg, where he took a special interest in pulmonary critical care. He remembers how his colleagues had to go into quarantine when a nurse was infected with a devastating haemorrhagic fever called Marburg disease, which she had contracted from a young Australian backpacking across Africa. The horror and drama of that imbued him with a healthy respect for plague viruses. Now, with the increasing alarm surrounding Dolores, he was very glad that he had included high-grade barrier treatment at a time when those precautions might have seemed extravagant. 'One day,' he had predicted, 'a formidable infection will hit us and we will be prepared for it.'

Levy is gifted with an engaging wit that peppers his conversation. On the afternoon of Friday, 28 May, the senior staff at the hospital called a

meeting to review the situation but Levy knew nothing about it. 'They called the crisis meeting and forgot to invite me.' At 3.00 p.m. his pager sounded and he was instructed to hurry along immediately. He entered a cramped room through a door in the back of the main canteen where 'everybody who is anything in the hospital were there, sitting and waiting. It was kind of terrifying to realize they were expecting me to explain what was happening.' He painted a graphic picture of the cluster of deaths and explained the findings at autopsy. In response to their anxious questioning he assured them that he and his staff were ready and willing to look after these patients.

By this stage two suspected cases had already died here in his unit. The staff were clearly frightened. Since the cause of the disease was unknown, it was impossible to predict just how it was spread. As soon as he returned from the meeting Levy gathered the unit nursing and medical staff together so he could explain what he had in mind. The intensive care unit had been designed with two rooms exhausted to the outside air. With more patients already in transit, this would clearly be inadequate. As soon as he had accepted the fourth and fifth cases, Levy closed the unit to all other cases. All of the beds except four, which needed to be allocated for the more usual purposes of the intensive care unit, were now standing by for the epidemic. From that moment everybody working there was instructed to wear masks incorporating particulate filters, which were designed to trap a virus. Now his nurses gave him reason to be proud of them: not a single member of staff, from senior to junior, asked for leave or resigned.

The interview room was converted to a dressing area, where people would gown up before entering the quarantine zone. On the entrance they placed notices, warning people to gown up and to wear gloves and masks. 'We had no need to place a guard on this door – nobody wanted to come in.'

In the two hours of relative peace, beginning each morning with the 7.00 a.m. ward round, Koster, Levy and another intensivist called Steve

Simpson, would rack their brains in a determined attempt to understand the physiological disturbance that caused people to die. What could be happening in the tissues and organs of the sick patients, the cause of the whiteout, the sudden crashes that overwhelmed the defences of even the fittest victims?

For Fred Koster, there was no one moment when everything clicked. It was a gradual accumulation of small details, beginning with Dolores's astonishing progression right there in front of them, with recognizing that the curious blood patterns were repeating themselves with every victim, with studying very carefully the clinical and laboratory findings and titrating those against the tragic outcome in the fatal cases, when the tissues were subjected to minute examination at the autopsies now being continued by Kurt Nolte.

They had already demonstrated that when you sucked out the fluid from the waterlogged lungs, you obtained a material that looked to the naked eye like straw-coloured water. They had sent this to the lab for analysis and the report had confirmed their suspicion. It was hardly what you might have expected from lungs inflamed with a lethal infection. When the pathologists examined it for pus cells, they found virtually no cells at all. If you took a sample of blood and allowed it to clot, then filtered away all the red and white blood cells, all the solid components of the blood clot itself, this is what you would be left with. This, by definition, was serum. It was both a clue and a puzzle.

It was increasingly apparent that there was some unexplained anomaly in the way their patients were dying. 'Once we tumbled to the fact that this deterioration was extremely rapid, we could aggressively oxygenate them. Yet even though they were very well oxygenated, still they died.' This suggested that although the pulmonary disease was an important part of the crash, there was some other, as yet unknown, component. By degrees the doctors became more convinced that there really was some vital yet mysterious aspect to the shock that killed these people.

On Saturday, 29 May, at the start of the Memorial Day weekend, a task

force of forty specialists parked their cars on the sun-scorched campus of the UNM Hospital, to join the meeting now taking place in a large conference room on the ground floor of the building that housed both the OMI's office and the state public health laboratories. They were joined by an enthusiastic young epidemiologist newly arrived from the CDC, Jay Butler, head of a small team including a fellow EIS officer, Jeff Duchin, and a toxicologist called Ron Moolinaar. As one by one the arriving experts signed the attendance sheet, also de facto joining what was now the working group, people in the university hospital a block away were dying from the disease.

Although the numbers of victims were still modest, the lethal nature of the disease left no doubt that they were dealing with an extremely dangerous epidemic. The mysterious nature of the illness – they still had not the slightest idea what was causing it – stoked the escalating sense of alarm.

At first the possibilities were so confusingly numerous, they had to be tabulated on flip charts. But they moved through this encyclopaedic list very quickly. Many of the possibilities had already been ruled out by the hard work of McFeeley and Umland or during the Thursday meeting at Placitas. Nobody seriously believed they had missed bubonic and pneumonic plague. No more did they believe they had missed any of the other uncommon yet lethal germs that might have caused the picture. The pattern, when you took everything into consideration, just did not fit with anything they were familiar with. They must, therefore, be dealing with something extremely unusual.

They drew up a remaining shortlist of three broad diagnostic categories. One possibility that still worried many of them was a virulent form of influenza. Influenza A, as the virologists reminded them, was still causing serious infection in the community. In 1918 a pandemic strain had killed 25 million people. The second possibility was poisoning. For example some local farmers used phosgene, a First World War poison gas,

to put down rodents in their burrows. If pockets collected underground and subsequently leaked out, it could cause a similar pattern of pulmonary disease. The majority did not believe that this was the explanation. That focused people's minds onto the third diagnostic possibility. People began to openly consider a rather shocking scenario. They were not only dealing with something new, a new plague caused by a microbe nobody had ever seen before, but those negative findings pointed to the most worrying possibility of all – what the scientists now call an 'emerging virus'.

FOUR

Emerging Viruses

A virus is a piece of bad news wrapped in a protein.
Sir Peter Medawar

1

The fundamental principle – the quest if you like – behind this book is understanding. It serves little purpose merely to be scared by viruses. But it serves a good deal of purpose to understand them.

What do scientists mean when they talk of a virus? This is not as elementary as some people might believe. In the Shorter Oxford English Dictionary, a virus is defined as 'a morbid principle, or a poisonous venom, especially one capable of being introduced into another person or animal'. The dictionary takes its cue from the Latin *virus,* which denotes a slimy liquid, poison, offensive odour or taste. It is a colourful definition, redolent of medieval notions of disease origins in evil emanations, but it offers little by way of scientific understanding.[1]

A common confusion is to equate viruses with bacteria. For example, a recent article in a London broadsheet carried a headline about a virus when the offending microbe was clearly a bacterium. Although the

confusion is understandable, it is also misleading.

Both bacteria and viruses are very tiny life forms. They are both classed as microbes. Both may cause human disease. Nevertheless to equate them is rather like lumping together birds with flying insects on the basis that they both have wings. Bacteria are free-living life forms. They imbibe their own nourishment and multiply with a profligate independence. Most bacteria are not parasitic at all but inhabit the soil, making a vital contribution to the cycles of life on earth. Viruses are altogether different.

In the seventeenth century, Anton van Leeuwenhoek was the first to observe bacteria and protozoa, through his invention of the first simple microscope. He did not however see viruses because viruses are invisible to the light microscope. The first hint of their existence was the observation by Adolf Mayer in 1885 that the mosaic or leaf-spot disease of the tobacco plant was caused by a strangely invisible contagious agent. A little later Dimitri Ivanowski, contemporaneously with Martinus Willem Beijerinck, found that the tobacco mosaic disease agent was not only invisible, it would pass through the finest pores of porcelain filters. Beijerinck proclaimed it a 'contagious living fluid'.[2]

The infective agent was not however a fluid but a particulate living entity so small it could readily pass through their porcelain filters. We now call it the tobacco mosaic virus. Twenty-five years would pass before any further advances were made in the study of this extraordinary life form.

Although some viruses may be a fifth the size of small bacteria, on the whole they tend to be orders of magnitude smaller, a hundredth or even a thousandth of the size of bacteria. The flu virus for example is 80 to 100 nanometres (thousandths of a millionth of a metre) in diameter where the bacterial cause of typhoid measures 2 to 4 microns (millionths of a metre). This means that they are not usually visible through the light microscope. It was not until 1933, with the invention of the electron microscope by Ernst Ruska, that their true anatomy could be seen for the first time. For those early virologists, it was an exciting introduction to an entirely new dimension of life.

The ancient Greeks defined beauty as fitness for function: nothing could more adequately describe the austere beauty of viruses, their tendency to symmetry of form, which can give rise to wonderfully aesthetic if geometric realms of perfection.

Even today, there remains a sense of mystery about viruses that seems not to apply to other life forms. If I were to ask a series of different experts what they meant by a bacterium, there would be a pretty close general agreement. Not so with viruses! As I travelled about in many countries and spoke at length with various experts, I would routinely ask them to define what a virus meant to them. Of all the questions I asked, this provoked the longest pauses: it seemed that the more the expert knew about viruses, the less easy the answer. How revealing it was that each expert gave me a somewhat different definition.

As you might anticipate, each had evolved a perspective that tallied with the nature of his or her work. Molecular biologists tended not to perceive viruses as living entities. What they envisaged were nanomachines with their own inbuilt system of replication, controlled by a chemical coding analogous to a computer programme.

There is a good deal of truth to this. Outside its host, a virus does appear to become inert, to behave as a complex organic chemical. Viruses can aggregate to form structures that resemble crystals.

Medical virologists on the other hand see viruses solely as the harbingers of disease. To them, they appear the ultimate in predators, minuscule time bombs of nascent malevolence, invariably parasitic, contributing nothing positive to life on earth. Yet other experts, in particular the Nobel laureate Joshua Lederberg, have a totally different perception: for them viruses are vehicles for genetic exchange between the disparate species that make up the matrix of life on earth. Seen from a particular perspective, every definition contains its own implicit truth. If viruses were human, they would appear to have multiple personalities.

In my opinion, a virus is very definitely a form of life. It has the same

physiology and biological chemistry as all other forms of life on earth. DNA, with its counterpart RNA, is of course the template of life and heredity. It is also the environment in which a virus comes to the full realization of its nascent potential. This landscape, the landscape of the genome, is the world a virus, in human terms, might call home. No other form of life inhabits this extraordinary ecological niche. And in the way of all life, the virus changes the landscape just as the landscape moulds the virus. What power such a primal association would seem to confer!

Viruses are certainly very small. They are so minuscule that billions could fit into a drop of water – or a drop of human blood. They are life honed to the absolute minimum. In the opinion of John Holland, an expert at the University of California, they probably go back to the first origins of life. Though they possess no nucleus, they contain the nuclear template of DNA or RNA, no cytoplasm, but some viruses do contain the absolute minimum of enzymes – chemicals that control and facilitate the everyday processes of life.

Viruses have no processes of locomotion, yet in the words of Stephen Morse, 'they move around the world'. Viruses do not breathe, they do not taste, hear or see. They do however have a single representative of the five senses: they have a kind of sensation that could be classed as intermediate between a rudimentary smell or touch. It is not what you or I would normally mean by either sense. They do not feel or smell through a sensitive skin, with nerve endings that conduct electrical stimulation to a perceiving brain. Viruses have no skin, no nerves and for that matter no brain. But they have a way of detecting the chemical composition of cell surfaces. Every virus has a chosen host cell, whether it is the leaf of a tobacco plant in mosaic disease or the CD4 subset of T-lymphocytes in a human sufferer from AIDS. The virus has the most exquisite ability to sense the right cell surfaces. It recognizes them through a perception in three-dimensional surface chemistry. But then so too does each of our human senses derive ultimately from a similar complex chemistry.

Though devoid of a mind, viruses undoubtedly possess an alternative

means of control, what I shall subsequently refer to as a 'genomic executive intelligence'. Consequently they do not think in a human sense at all. They

are amoral, in the true sense – a complete absence of morality. This is a point that needs emphasis because people so readily project along these lines in relation to plagues and disease.

Of course there is a 'purpose', speaking from an evolutionary point of view, to this extreme frugality of anatomy. It means that the virus does not need a physiology of movement, of breathing, not even of growth. Their plan of life has made all such processes redundant. Everything is honed down, with incredible single-mindedness, to the pursuit of the only function that matters from an evolutionary standpoint: the need to create more viruses like themselves.

2

When compared to the complexity of the cells that make up a human being, viruses do appear structurally simple. But the comparison is misleading. In their behaviour, viruses are far from simple.

The late Dr Bernard Fields, who originated the masterly text, Fields' *Virology*, marvelled at their ability to survive. In their invasion of human victims, he compared them to spaceships voyaging into the most dangerous and hostile of alien worlds. Devoid of even the simplest of vision and hearing, devoid even of their own propulsion, viruses must devise ways of spreading from host to host, of battling their way through powerful defence barriers to gain entry into the body. And once inside these tiny life forms must withstand the unrelenting attack of the cells and antibodies of the human immune system.

Virology is a relatively new field. It is also a rapidly changing field, as important new steps are made both in our understanding of viruses and their ecological consequences throughout the animal and plant kingdoms.

Viruses don't just cause diseases in people, they infect every form of life on earth. There are viruses that infect chimpanzees, whales, molluscs, the bacteria that swarm in the soil or lie on the sunken floors of the seas.

Fred Murphy, Dean of the University of California at Davis, has spent many years of his life classifying them into genera and species. He wrote the taxonomic chapter of Fields' *Virology,* in which he describes approximately 4000 classified species, of which about 150 are known to infect people.[3] On the other hand, the ecologists estimate that there are 30 million species of life on earth, each of which probably has at least one virus species that infects it. In the yawning chasm between the known and the estimate, we glimpse the boundaries of a great unknown, an extraordinary submicroscopic universe that science has hardly begun to explore.

Viruses do not grow, like other forms of life. They are created in an identical assembly, every member at once a replica of the others of its species. When, as part of his Cambridge PhD, the botanical molecular biologist, George Lomonossoff, mixed the separate chemical components of the tobacco mosaic virus in a test tube, the component structures self-assembled to form the virus. They achieved this without the aid of any outside sources of power, without the need of enzymes: an awesome vision of alien potential, scary and thrilling in equal parts.[4]

There are aspects to virus infection that demand explanation if we are to attain any fundamental level of understanding. For example, very many viruses, perhaps the majority, infect people, animals and plants without causing any symptoms of distress or disease. Yet other, admittedly rarer, species of virus are devastatingly destructive in their infections, with a very high degree of lethality. People were aware of the harmful effects of such viruses long before they realized their nature or existence. Viruses have caused some but not all of the frightening epidemics that project like tombstones through the fabric of human history. People were more likely to notice plagues that struck panic and terror in their own communities, perhaps afflicting their own families. Farmers could not fail to notice blights that fouled their crops, or husbandmen the epidemics that swept

through their herds of cattle, sheep, pigs and poultry. Long before the first virus was seen, the elders and doctors of afflicted communities had recognized the contagious nature of such pestilences. Rituals were handed down from shaman to shaman, from doctor to doctor and from mother to daughter, serendipitous observations on coping with such miasmas, rituals of avoidance, of assisting the victims, of purification of the land and community after the evil's passing.

Plagues were named after the animal or plant that was afflicted, or in human terms after the patterns of disease they caused or the place where the tragedy first appeared. The viruses that caused some of these plagues have inherited the same appellations. The yellow fever virus, for example, causes infection in the liver, which gives rise to yellow discoloration of the skin and eyes. The smallpox virus causes holes, or pocks, in skin, smaller than the holes caused by the 'great pox', now believed to have been the epidemic manifestation of syphilis. The common cold tends to infect people in cold weather. Such traditions of naming plagues continue even today. O'nyong-nyong is the Ugandan name for a mosquito-borne virus that was first diagnosed in 1959, causing explosive outbreaks of fever and severe joint pain – the African name means 'joint-breaker'.

But as our knowledge and understanding of viruses increased, these simple designations and classifications were found to be inadequate until finally, the International Committee for the Taxonomy of Viruses (ICTV), an international committee meeting in Moscow in 1966, began the first orderly taxonomic classification. Viruses are 'polyphyletic' in their origins; in other words, different viruses evolved from different origins, so they cannot be grouped under any single kingdom or phylum of life. The notion of a species, in the sense of compatibility of reproduction, has much less meaning for viruses but the term 'strain' and 'substrain' carries a kind of equivalence. Viruses are classed in a number of definitive ways, for example on their size and shape, on the presence or absence of an enclosing capsule, on the properties of their genomic makeup – whether DNA or RNA based,

single or double strand, negative or positive sense – on their serological antigenicity, their component proteins, their manner of replication and other physical and biological properties.[5] This breaks directly into families, their component genera and strains and substrains (species).

For example, the hantaviruses are a genus within the family of *Bunyaviridae,* or Bunyaviruses, and the herpes simplex virus that causes cold sores, *Herpes simplex labialis,* is a member of the genus of simplexviruses within the family *Herpesviridae.* With every discovery of a new virus it is classified on the basis of its similarities to or differences from the large number of known viruses.

And new viruses, indeed new microbes of every description, are still being discovered at an astonishing rate. While the majority do not cause much in the way of disease, a significant minority come to our attention because of the diseases they cause, whether in people, animals or plants. This whole group of new diseases, whether caused by a virus, a bacterium, a protozoan or possibly even a nonliving particle called a 'prion,' are linked together under the heading 'emerging infections'. Emerging infections are one of the greatest dangers facing our world today.

Viruses pose a particular threat, one that is qualitatively different from that of bacteria and protozoa. Few virus infections are amenable to drug therapy. Even vaccines, which were first thought to be the answer to viruses, have controlled only a few. This means that 'emerging viruses', though far less important in the day-to-day fight against disease in hospitals and family practices throughout the world than bacteria and protozoa, nevertheless pose a potentially more dangerous global threat than any other form of infection. Even in the case of viruses, most of the new emergers do not cause epidemics of fatal disease. Roseola, for example, is a ubiquitous infection of children, which manifests with a pinkish rash and a mild febrile illness. Although it has been recognized since at least 1910, the virus that causes it, a herpesvirus known as HHV-6, was only discovered in 1986.[6]

Some emerging viruses are a good deal more serious. Common examples are the hepatitis viruses, B and C. The hepatitis B pattern of

illness was recognized at the end of the nineteenth century, yet the virus itself was not isolated until 1963.[6] The surface antigen of this one virus is being carried by 176 million people globally and the infection causes a vast amount of illness and death, including most of the fatal cases of liver cell cancer. More exotic examples of emerging viruses include Crimean-Congo haemorrhagic fever virus, a member of the family of *Bunyaviridae,* which emerged independently in Africa and Asia, spreads by tick bites and causes 10% mortality in its wide distribution across Africa, the Middle East and Asia. The previously mentioned O'nyong-nyong, a member of the family of *Alphaviridae,* emerged in 1959 to cause a series of epidemics that would eventually infect two million people in East Africa. And the various Ebola viruses will be discussed in detail later.

Another way in which a disease may be regarded as emerging is when one that is already long established changes its pattern and begins to spread more rapidly so as to become a new danger. Dengue fever is a typical example.

The first epidemic of a disease resembling dengue was reported in Philadelphia as long ago as 1780. Today we recognize four different strains of dengue virus that can cause it, all belonging to the family *Flaviviridae,* which also includes many of the most dangerous arboviruses known, such as yellow fever and the insect-borne viruses that cause brain infection, such as Japanese, Murray Valley and St Louis encephalitis. Today dengue fever is one of the most rapidly emerging diseases in tropical parts of the world, with millions of cases occurring each year. Puerto Rico, which suffered five dengue epidemics in the first 75 years of this century, has had six epidemics in the last 12 years.[7] At the same time, there has been a massive increase in the numbers of cases throughout many South American countries, extending to Cuba and the Caribbean. The lethal form of dengue, dengue haemorrhagic fever, is also increasing. And with the arrival of the tiger mosquito, *Aedes albopictus,* into America in shipments of used tyres from Asia, the circumstances favour invasion into the United States.

All of these mentioned viral diseases are regarded as newly emergent or representing a growing threat as re-emergents and the numbers of new diseases, caused by emerging viruses, appear to be increasing: in the words of the authoritative Murphy and Nathanson, 'the list of newly emergent viruses of humans and animals is impressive, indeed, and is seemingly prophetic of more to come in the future'.[8]

Viruses have a phenomenal capacity for mutation – RNA viruses, which have no proofreading mechanism during replication, mutate at thousands of times the rate of human cells. In previous decades scientists were convinced that such viruses appeared largely as a result of mutation. Today however we think that this is much less commonly the case. Emerging viruses do not arise from spontaneous creation any more than any other form of life; they are life forms that have been around a long time but have never been identified with human disease before.

In the words of Stephen Morse, a leading virologist working at the Rockefeller University in New York, 'newly evolved viruses will usually descend from a parent that already exists in nature'.[9] While evolution of a novel strain of virus through genetic reassortment or mutation can be important in emergence, for example with new 'Asian' strains of flu, a more common route to human infection is through a virus that normally infects a very different species. For such species-hopping, Morse has coined the term 'viral traffic'. Whether as a result of such cross-species traffic or mutation, when a virus emerges as a totally new entity or as a renewed assault from a new strain of a previously recognized species, the virus always emerges as it were into human consciousness. And often human behavioural factors play a leading role in inviting the virus to traffic across species.

There appears to be an inexhaustible supply of such new viruses, with a new addition appearing at least once a year and often a good deal more frequently than that. They emerge from every ecological niche of nature, from rainforests to deserts, from the seven oceans to the decorative plants you buy in a garden centre. The vast majority of these are uninfectious to

people, but the list of human viruses is gradually increasing. Some years ago, the Rockefeller Foundation was the fulcrum of eight satellites spread about the world, including Africa and South America, all actively looking for new viruses that had the potential to infect humans. Over the twenty-year period between 1951 and 1971 they discovered no less than sixty new viruses.[10]

It is fortunate that few such viruses infect us: if they did, the human species would be ravaged by an unrelenting series of epidemics. It is actually quite rare for such an emerging virus to cause a global epidemic, what scientists call a pandemic. But it does happen from time to time and some of the familiar viral plagues of history began as emerging infections caused by new viruses in this way. Smallpox and measles, for example, are thought to have emerged as new diseases at the time of the Roman Empire. Both these viruses spread by respiratory aerosol. This is the most contagious route for any infection and when they first emerged, they caused catastrophic epidemics.

Amongst the more serious new viruses seen in the twentieth century, we can list the pandemic strains of influenza, dengue fever and HIV. Another important group of emerging virus infections are known as the 'haemorrhagic fevers'.[11] These have certain clinical manifestations in common, a tendency to high fever and prostration, with bleeding from the body orifices. The haemorrhagic fevers include some of the most lethal viruses known to man. They are caused by a miscellany of different viruses, some new, others all too familiar. A familiar haemorrhagic fever virus, and one which has caused an appalling catalogue of death and suffering for centuries, is the mosquito-borne yellow fever. Many other haemorrhagic fevers are caused by emerging viruses which have erupted into human awareness through lethal epidemics in many different countries over the past half century, from South America to Africa and Asia.[12]

One such genus of haemorrhagic fever viruses is the hantaviruses. These take their name from the prototype, a virus called Hantaan, which

was named after the river that flows through the epidemic area in Korea.

3

Hantaan virus first came to the attention of the US military doctors during the Korean War, when more than 3,000 United Nations troops were afflicted by a mysterious plague. It caused high fever, weakness and prostration, many cases showing signs of haemorrhage, often no more than small bruises under the skin or in the lining of the mouth. But in some cases the haemorrhage could be more prominent. People would bleed into the whites of the eyes, they would develop large bruises under the skin or bleed profusely from the bowels. The epidemic was called Korean haemorrhagic fever. Roughly one in ten of those infected died.

Although the disease was entirely new to the Western doctors caring for the troops, it had long been familiar to the Russians and Japanese. They strongly suspected a virus but in spite of every effort nobody could find it. It was twenty years later that a Korean doctor, Ho Wang Lee, and his colleagues working at the University in Seoul discovered the Hantaan virus.[13]

After two years of searching they found the reservoir of the virus in nature. It was a small rodent, *Apodemus agrarius,* commonly known as the striped field mouse. The mouse, it seemed, was the natural host to the virus, contracting the infection from other mice when young. After infection, the virus seemed to do the mouse little harm, living in some curious accommodation with the animal for the remainder of its life, being constantly shed in the saliva, urine and faeces. Epidemics of the virus were now explained. They broke out at the time of the rice harvest, when people disturbed the mouse's burrows, raising clouds of dust contaminated with dried urine and faeces. That dust, thrown up by the pounding of feet and

flails, was a teeming effluvium of virus, which coated the skin, was inhaled and swallowed by the harvesters.

The striped field mouse extends across most of eastern Asia, throughout all of southern Russia and into the eastern countries of Europe. Since the discovery of Hantaan virus, scientists have recognized similar viruses as the cause of other haemorrhagic fever epidemics in very many countries throughout Asia and Europe. The patterns of illness have been similar to Korean haemorrhagic fever, with fever, haemorrhages and, in a minority of sufferers, death from kidney failure. The syndrome is called Haemorrhagic Fever with Renal Syndrome, the acronymic HFRS.

As early as the 1930s a similar illness was being reported in Scandinavia, where, almost half a century later, they would discover a different strain of hantavirus, named, after a small Finnish town, the Puumala virus. In 1986 another variant was diagnosed in Greece, Albania and parts of what was then Yugoslavia. So it went, new strains of Hantaan and Puumala viruses being diagnosed in localized epidemics afflicting one country after another, including Korea, China, Japan, the USSR, Scandinavia, France, Italy, Belgium, Hungary – even Scotland within the British Isles. Another hantavirus, the Seoul virus, was discovered in a fatal human case in Korea. This was a different strain of virus again from Hantaan. It did not infect rice harvesters. Instead, it caused illness and kidney failure in urban residents. The natural host was again a rodent, not a mouse but a rat – or to be more specific, different species of rats, including *Rattus norvegicus,* the brown rat, and *Rattus rattus,* the black rat.[14] A wave of disquiet began to ripple through biologists working in the great university conurbations. Rats were common city denizens. One or other of the two rats is to be found everywhere in the world with the exception of Antarctica. Tentatively, in a number of different cities at once, biologists started to screen the rats in their own back yards.

In 1982, Ho Wang Lee joined forces with a Nobel laureate, Carleton D. Gadjusek, to look for hantaviruses in America. Gadjusek recruited his

10 adopted New Guinea children to scour his own property on Prospect Hill in Frederick, Maryland, for likely rodents. They quickly discovered a new hantavirus, the Prospect Hill virus, which infected two local species of voles, *Microtus pennsylvanicus* and *Microtus californicus*.[15] Gadjusek and his colleagues at the National Institute of Health (NIH) looked for a related disease in humans but could find no convincing evidence for it.

4

In October 1987 there was a major US military field exercise, close to the demilitarized zone in Korea. It involved a simulated attack by thousands of assault troops including large numbers of amphibious marines. Following the exercise, one of the marines reported sick and he died soon after being flown out to a hospital in Seoul. Within days several other troops fell sick with identical symptoms.

The Engineering Corps seemed afflicted with a relatively high sickness rate, with three cases amongst a group of around eighty. These were advance teams, responsible for the pre-exercise constructions. Their job was to make sure the following marines could get through the natural obstacles. They would lay out platforms for headquarter tents, build bridges, grade small roads, lay down tracks for tanks. During these activities they lived out of doors, sleeping in tents. They also disturbed a lot of soil. By the time most of the troops had returned to base in Okinawa, a total of 13 additional marines had reported sick and three more had died.

In 1983, a tall, bespectacled man arrived to work at the US Army Medical Research establishment at Fort Detrick in Frederick, Maryland – familiarly known as USAMRIID. Lieutenant Colonel Tom Ksiazek was a veterinary microbiologist in the Epidemiology Branch of the Disease Assessment Division. At the time, few medical or scientific centres in the world were interested in funding the kind of research that was taking place at USAMRIID.

Plague microbes have been a familiar threat to armies long before their deliberate use as weapons. It costs very little to develop extremely dangerous microbes, which could be all too readily turned against an enemy. As a result of this, biological warfare offers poorer nations a horror every bit as dangerous as nuclear weapons. In the 1960s, overwhelming public revulsion caused these centres to be abandoned in Europe and America. But it seemed prudent to continue the defensive aspects of this research. One such defensive strategy at USAMRIID was the search for vaccines against dangerous infections, whether of natural origin or the brainchild of ruthless biological experimentation. Tom Ksiazek's role was to discover and improve upon the methods of diagnosis. He had a particular interest in the haemorrhagic fevers, including those caused by hantaviruses.

In the autumn of 1987, when he was attending a meeting for overseas research laboratory staff at the Walter Reed in Washington, a doctor from Okinawa gave him some specimens of serum from the war exercise outbreak. Tom took the specimens back to USAMRIID for testing.

At this time, it was still difficult to diagnose a hantavirus infection. The usual test used an indirect fluorescent antibody assay, the same test that had been developed by Dr Ho Wang Lee, who had discovered the Hantaan virus. This was reasonably accurate but it was subjective and laboratory staff had to maintain a supply of infected field mice, passing the live virus from one generation of mice to another. For scientists working with dangerous pathogens, the greatest risk comes from handling infected animals. They squirm, kick, scratch, bite, introducing the unpredictability of life into an already dangerous situation. German colleagues had devised a safer way of testing for certain virus antibodies but these had not included hantaviruses. At USAMRIID, Tom Ksiazek modified this test for hantaviruses.

His test was called an 'Immunoglobulin Capture Assay'. Since the test would work just as well with a dead virus, they could kill the virus first,

removing the hazard of handling live virus or infected animals. If the person's blood contained antibodies to Hantaan, the dead virus would attach to the captured antibody layer. A dye, attached to a virus detecting system, would show up green in the 'wells' on the plate containing the samples. Tom Ksiazek tested the serum from the first dead marine at USAMRIID and the wells turned green. Now he and a colleague, A. J. Williams, flew out to Okinawa, where they set up a laboratory within the hospital to test the troops.

Three and a half thousand marines were now screened for antibodies. Although the assay was hard work for the laboratory staff, testing of a new case could be completed in four hours. Ksiazek's test system proved dramatically accurate in the field setting. They were able to diagnose cases the same day they arrived at the hospital. But two years later, such optimism for the test would be confounded by experience in Central Europe.

In 1989, there was an outbreak of haemorrhagic fever in Sarajevo, in what was then a united Yugoslavia. To make the situation more difficult, it was known that there were at least two types of hantaviruses infecting local rodents. One was closely related to Hantaan, while a second was a variant of Puumala. When Tom Ksiazek arrived, his immunoglobulin capture test was used to diagnose suspect cases coming into the local hospital. But here in Sarajevo he made an important observation. As anticipated, some patients were confirmed as suffering from Korean haemorrhagic fever. But he also found that a high proportion of these people were not infected with Hantaan virus at all but with Puumala. This created serious diagnostic problems but also an interesting dilemma.

When you get two viruses that are of the same genus, but different strains, you get some degree of cross-reactivity on antibody tests. In other words, a patient infected with virus A will have a weak positive reaction to virus B, and vice versa. Tom, who had hoped his test would screen for all hantaviruses, found that the cross-reaction between Puumala and Hantaan was deceptively weak. There was no problem if he obtained a strong

antibody reaction to the Hantaan virus, when he could confidently diagnose Korean haemorrhagic fever, but in those with a weak positive to Hantaan he could not be sure if it meant Puumala or nothing at all.

A test system designed only for the Hantaan virus was not going to cover the other hantavirus. For the army scientist it had proved a valuable lesson.

But there was an additional, more subtle, implication to these hantavirus researches and discoveries. The genus of the virus was distributed very widely around the globe, where new strains of the virus – the equivalent of species – were increasingly being discovered. Hantaviruses, it seemed, were distributed in a vast archipelago of species throughout whole continents. There was some curious relationship between the virus and its host that must signify an ecological stability, an accommodation with nature, that was tantamount to apostasy from the classic thinking of viruses as simple predators.

In 1991, Tom Ksiazek left USAMRIID to take up a post as Chief of the Diagnostic Section in the Special Pathogens Branch of the Centers for Disease Control in Atlanta.