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REFLECTIONS ON THE VIRULENCE OF INFECTIONS

Heirlooms and Temporary Exhibits

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Abstract

Infection has played a crucial role in human evolution – from the ancient acquisition of vital organelles such as mitochondria to the 'fossil' viral elements that constitute so much of our genome – but we usually focus on pathogens. When a virus infects a new host species, large changes may occur in pathogen-host ecology and virulence. Some viruses with RNA genomes (e.g. influenza viruses, henipaviruses and severe acute respiratory syndrome (SARS) coronavirus) can leap across relatively large host taxa, causing epidemics in the naïve population. This phenomenon is exemplified by changes in the mode of transmission and virulence of influenza A viruses when they move from waterfowl to chickens, and from chickens to mammals. Increasing virulence is also evident with retroviruses such as human immunodeficiency viruses (HIV) and the leukaemia virus of koalas. Viruses with DNA genomes (e.g. poxviruses, herpesviruses and papilloma viruses) usually have a greater fidelity to their host, but may devastate a closely related host species provided they gain access to it, as when the New World myxomatosis virus was introduced into European rabbits in Australia. Other virulent pox- and herpes virus infections occur when a host species or populations separated by geography and time regain contact through globalisation or through artificial introduction as captive or invasive species. The epidemics among humans indigenous to the Americas and the Pacific islands following the arrival of Europeans serve as a model for the likely fate of Neanderthals and Denisovans when modern humans reached them out of Africa.

Introduction

> No scientist is admired for failing to solve problems that lie beyond their competence. If politics is the art of the possible, research is surely the art of the soluble. Good scientists study the problems they think they can solve. (Medawar, 1967)

Medawar exhorts us to dismiss insoluble questions – when the intellectual and practical means to answer them are not yet available – as idle speculation. All too often, however, we take refuge in asking small questions that are too easily soluble and which will never lead to Kuhnian paradigm shifts (Kuhn, 1962). An exception was Tony McMichael, who had the art of asking penetrating questions before others had formulated them, but for which at least partial answers could be provided. I first met Tony when he was at the London School of Hygiene and Tropical Medicine and I had moved to University College London, 400 metres up Gower Street. Tony had that freshness and clarity of mind that crossed easily between social sciences and medical sciences, and despite our different backgrounds, we established an easy rapport. I was privileged to speak at the launch of Tony's book, *Human Frontiers, Environments and Disease* (McMichael, 2001).

In 2001, the Royal Society invited me to deliver the Leeuwenhoek Lecture and I rashly chose to speak on the origin of human infectious diseases at the London School. The Australian President of the Royal Society, Bob May, looked bemused as I donned a yellow biohazard suit while he introduced me. I asked the audience to imagine that I had recently received a heart transplant from a pig, in order to illustrate the potential infection hazards of xenotransplantation (Weiss, 1998). My purpose was to explain that novel infectious diseases did not always emerge from 'backward' parts of the world. Consider the transmissible spongiform encephalopathies: while kuru, a form of Creutzfeldt–Jakob disease (CJD), did emerge from certain ritual cannibalistic practices in Papua New Guinea, advances in medical technology such as human pituitary transplants gave rise to iatrogenic CJD, and 'advances' in food technology such as mechanised extraction of neural tissue from beef carcasses led to mad cow disease and to variant CJD in humans (Schwartz, 2003).

The editor of *Nature Medicine* attended my Leeuwenhoek Lecture and later invited me to contribute an article to an issue devoted to emerging infectious diseases. She wished me to address broad aspects of the emergence of infections rather than remain in my comfort zone of the cellular and molecular biology of HIV/AIDS. Feeling ill-equipped to write a review covering this degree

of breadth, I realised that there was one person above any other who could co-author the article, and I was delighted that Tony (by then back in Canberra) agreed to do so. It is reprinted in this volume (Weiss and McMichael, 2004).

In homage to Tony, I shall raise some questions on the origins, spread and virulence of infectious diseases in the hope that the time is ripe to consider how to solve them. We have the exciting prospect of bringing together social aspects of infectious diseases with their molecular biology (Pulliam, 2008; Wood et al., 2012), and neither discipline should ignore the other.

The Human Body as an Ecosystem

What constitutes an infection? The vast majority of microbes that live in and on the human body are not classified as infections, merely as fellow travellers, and we depend on some of them for good health, the beneficial strains of *Escherichia coli* for instance. As a 'metagenome', our human body contains a minority of human cells (Table 29.1). The human microbiome comprises immensely diverse species, representing about 3 kg of our body mass. The bacterial biofilms in our mouths alone contain upwards of 1,000 species. Moreover, the invasion of the human body goes deeper: some 8 per cent of our chromosomal DNA sequences represent fossil retrovirus genomes. Most, but not all, are defunct. The placental fetal–maternal interface depends on the expression of ancient retroviral envelope glycoproteins to form the syncytiotrophoblast (Weiss and Stoye, 2013). There are DNA traces of RNA viruses such as bornavirus in our chromosomes, too (Feschotte and Gilbert, 2012). If we include retrotransposons among the virus-like fragments that have invaded the human genome, then we carry more DNA derived from infective processes than the genes encoding human proteins (Weiss and Stoye, 2013).

Table 29.1 The human metagenome.

10^{13} human cells	1 sp.
10^{11} eukaryotes	~10^{2} spp.
10^{15} bacteria	~10^{4} spp.
10^{17} viruses	~10^{3} spp.

Source: Author's work (multiple sources).

The numbers listed represent a very rough estimate because the tally and load of organisms in the healthy human body is still incomplete. The eukaryotes include fungi, protozoa and helminths. Less than 1 per cent of the species (spp.) are known pathogens.

Eukaryotic (nucleated) cells themselves represent a successful evolutionary outcome of invasion by different microbes. Mitochondria (and photosynthetic plastids in plants) derive from once independent microbes. Then, eukaryotic cells learned to form multicellular organisms in which cells and tissues could evolve different functions. Nick Lane believes that the emergence of eukaryotic cells is a rarer event than the evolution of microbial life (Lane, 2010), which might explain why we have not yet come across signals of intelligent life on other planets.

On the other hand, pathogens can emerge from normal tissues that have never previously followed an infectious lifestyle. Prions causing transmissible spongiform encephalopathies are encoded by a normal gene but acquire self-propagating epigenetic 'chain reactions' that lead to disease when a misfolded protein triggers similar misfolding in neighbouring molecules (Schwartz, 2003). Genetic predisposition to prion disease is evident where a single amino-acid residue in the protein sequence renders it more liable to misfolding. The cancer that threatens the survival of the endangered Tasmanian devil is derived from an escaped somatic cell originating from one animal (Murchison et al., 2012). A similar but more ancient transmissible pathogen of dogs, canine transmissible venereal tumour, is a somatic cell clone that probably originated ~11,000 years ago and which has spread worldwide (Murgia et al., 2006). As a sexually transmitted infection, it is hardly surprising that it is most prevalent among lower socio-economic canine communities such as pie dogs in India.

What is a Pathogen?

Among the plethora of micro-organisms cohabiting with us, a few are pathogenic. And many of these are conditional pathogens, behaving as harmless companions most of the time but exerting a disease profile when the host is out of condition owing to other factors. Several epidemic and endemic diseases are caused by conditional pathogens. Paradoxically, some infectious diseases have increased in incidence as the prevalence of the pathogen diminishes. Once common infections of infancy have become rarer, and the age of first infection is therefore delayed. The mid-20th-century epidemic of poliomyelitis is an example. When almost all of us acquired poliovirus infection early in infancy when maternal antibodies were present, the virus seldom spread from its natural home in the gut to damage the central nervous system. But, clean, middle-class children acquiring delayed infection when they went to swimming pools were more susceptible to paralysis. Similarly, the gamma-herpes virus, Epstein–Barr virus (EBV), engenders little more than a sore throat in infancy, but can cause infectious mononucleosis when acquired at a higher dose by teenagers. These examples are

reminiscent of the 'hygiene hypothesis', whereby early exposure to infectious agents and to antigens may, by influencing the direction of maturation of the immune system, be protective against later infectious and autoimmune diseases.

Some of the chronic diseases of adults may also have an infectious component in their aetiology. Until Barry Marshall famously swallowed *Helicobacter pylori*, epidemiologists did not regard gastric ulcers and stomach cancer as infectious diseases. As molecular methods of microbial detection become more sophisticated, other common microbes may prove to be pathogens for diseases prevalent in the ageing population.

The Power of Molecular Phylogenetics

Until recently, the origin of viruses and other parasites was based on data from historical and ecological surmises. With the development of powerful forensic DNA sequencing technology, we can apply more stringent methods to investigate origins. Analysis of simian immunodeficiency virus (SIV) genomes reveals that four distinct transfer events to humans took place because each of the four HIV-1 groups has SIV relatives in chimpanzees, which are genetically closer than the human HIV-1 groups are to each other (Figure 29.1). Only one virus lineage, HIV-1 group M, has become pandemic and has diverged into the diverse clades (subtypes A–K) and the recombinant strains we see today (Ndung'u and Weiss, 2012). Thanks to molecular phylogenetics applied to urine samples from painstaking field studies, the geographic origin of group M could be located to a small area in south-east Cameroon, because that was where chimpanzees with SIV of similar sequence were found.

Molecular sequencing proved that the HIV strains infecting children in Benghazi in Libya pre-dated the arrival of the Bulgarian nurses who came to care for them, and who were accused under the Ghadaffi regime of deliberately spreading AIDS (de Oliveira et al., 2012). The same technique demonstrated conclusively that the *Vibrio cholera*e strain causing the cholera outbreak in Haiti following the 2010 earthquake really was introduced, albeit unwittingly, by UN emergency forces from Nepal (Frerichs et al., 2012). Ironically, 40 years earlier, Haitian UN peacekeeping forces returning from the Katangan war in the Congo were probably the vector that introduced HIV subtype B to the West (Pepin, 2011). If John Snow, born 200 years ago, came back today, I think he would delight in applying molecular epidemiology to tracking transmissible diseases.

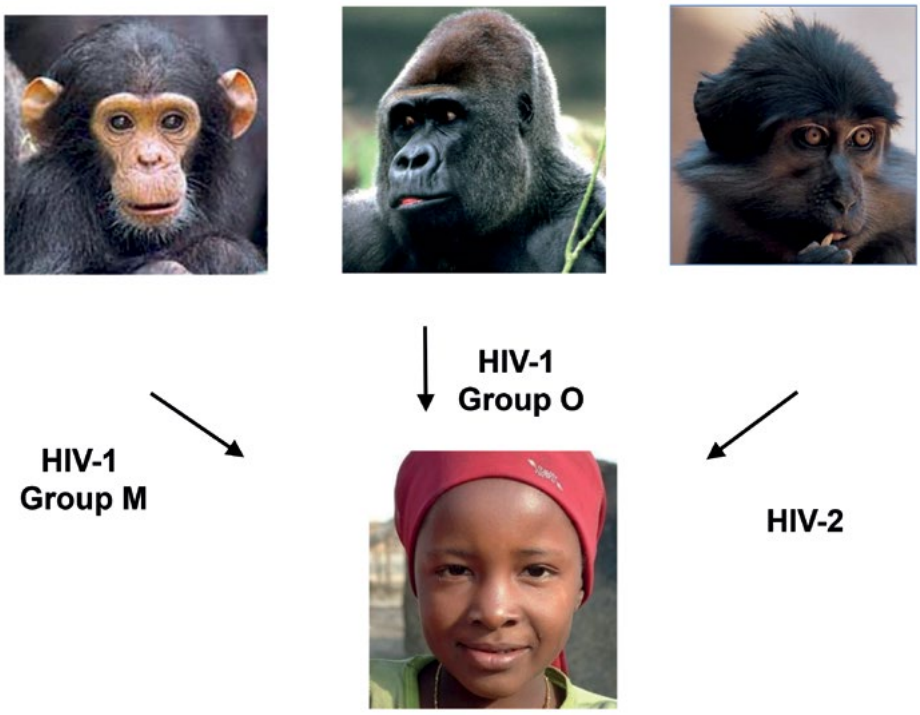

Figure 29.1 Multiple cross-species origins of human immunodeficiency viruses (HIV).

The pandemic strain of HIV-1 group M came from a specific population of chimpanzees (*Pan troglodytes troglodytes*) in Cameroon about 90 years ago and has infected approximately 65 million humans to date. HIV-1 group O came either from gorillas (*Gorilla gorilla*) or chimpanzees and has infected about 10,000 humans, while two other SIVcpz transfers have spread to only a handful of humans each. HIV-2 has been introduced from sooty mangabey monkeys (*Cercocebus atys*) to humans in West Africa on at least six separate occasions. It has spread to Europe and India, but its prevalence is waning, for poorly understood reasons. See Ndung'u and Weiss, 2012.

Source: Author's work.

Molecular sequencing of complementary DNA from the RNA of influenza A virus genomes showed that during the recent epidemic of swine-origin H1N1, the virus was imported several times into the UK (Baillie et al., 2012). Temporal and geographical movements of viruses can be tracked through phylogenies, and deep sequencing can reveal the evolution of virus populations within one infected individual. Sequencing and rescue of the influenza virus from archival specimens from the 1918/19 pandemic helped to pinpoint its origin as an avian virus, and may explain why it was highly pathogenic (Taubenberger et al., 2001).

With increasing refinement of DNA amplification and sequencing from ancient specimens, it is becoming possible to determine origins previously based on historical studies; for instance, whether the virulent form of syphilis that appeared in 1493 really came from Hispaniola (Harper et al., 2008). The Justinian

Plague in 541 CE and the Black Death in Europe in 1347/8 were discussed by McMichael (McMichael, 2010), and it has been confirmed that the latter was caused by *Yersinia pestis*, perhaps by two distinct clades (Haensch et al., 2010). It may soon become possible to elucidate which particular pathogens lay behind more ancient plagues through the molecular analysis of archaeological specimens.

A caveat is that as DNA sequencing techniques become ever more sensitive, allowing single cell and microbe amplification, the greater the danger becomes of contamination by extraneous DNA fragments. For example, much publicity was given in 2009 to a virus related to the xenotropic murine retrovirus putatively detected in blood samples from people suffering from chronic fatigue syndrome, but the whole edifice crumbled on more detailed and objective analysis (Weiss, 2010). Thus, candidates for viruses possibly contributing to other chronic diseases like multiple sclerosis need to be examined with genuine curiosity mixed with healthy scepticism.

Family Heirlooms and New Acquisitions

The title of this section is a metaphor first coined by Tony McMichael (McMichael, 2001). *Family heirlooms* are the human infectious agents that have co-evolved with us ever since we and the other great apes diverged from each other. The gamma-herpesviruses, EBV and Kaposi's sarcoma-associated virus, KSHV, are maternal heirlooms; they are typically transmitted from mother or grandmother to offspring via saliva, but can also be transmitted sexually or by sexual kissing later in life. Our closest extant relative, the chimpanzee, carries a virus closely related to EBV, while other apes and monkeys harbour more distant relatives of EBV in parallel with the evolutionary distance of the host (see Figure 29.2).

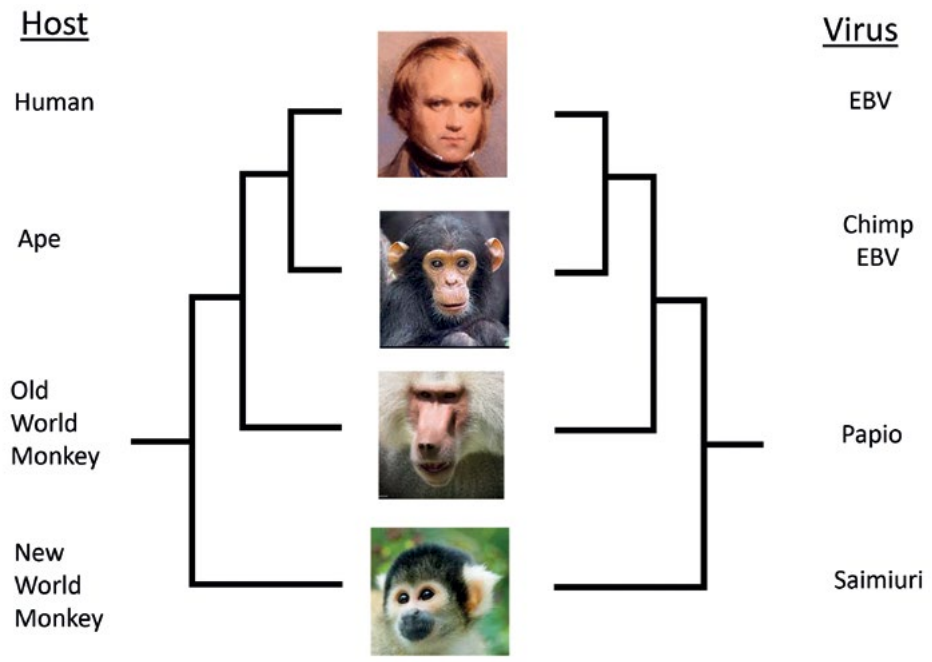

Figure 29.2 Co-speciation of lymphocryptic herpesvirus (EBV) genomes and their hosts. The estimated time back to the most recent common ancestor is broadly the same for virus and host.
Source: Author's work.

I used to assume that each of the eight known human herpesviruses came down to us adhering strictly to host lineage, but now it appears that there has been more horizontal exchange of family heirlooms within families than we formerly imagined, including the EBV lineage (Ehlers et al., 2010). Such horizontal transfers may lead to large changes in virulence, as argued below. There remain puzzles: humans harbour two distinct herpes simplex viruses, HSV-1 and HSV-2. Phylogenetic analysis of HSV genomes indicates that HSV-2 is much closer to chimpanzee herpesvirus than to HSV-1 (Luebcke et al., 2006). This observation raises the question whether humans have always had the two types on board (separated in their anatomical silos) ever since the viruses diverged about eight million years ago, or whether HSV-1 has been acquired horizontally (Luebcke et al., 2006; Weiss, 2009).

New acquisitions are the infections that we have picked up in 'recent' times, such as measles about 10,000 years ago and HIV less than 100 years ago (McMichael, 2001; Weiss and McMichael, 2004). Tony McMichael documented different episodes in the emergence of pandemic infections and the changing patterns of human migration, ecology and behaviour that promoted their emergence (McMichael, 2001). Many prehistoric and historic disease agents came from

domesticated livestock, or from animals which themselves found a suitable habitat in becoming our companions, such as dogs and rats. In contrast, recent outbreaks of novel virus infections tend to originate in wildlife (McFarlane et al., 2012). The SARS coronavirus, Hendra and Nipah paramyxoviruses, and Ebola and Marburg filoviruses came from exotic species such as primates (Ebola) and civet cats (SARS), although the paramyxoviruses came from bats via horses (Hendra) and pigs (Nipah). But, all these animals are temporary amplifying vessels for viruses that have their long-term reservoir in bats (Wood et al., 2012). Extending McMichael's metaphor, we can regard outbreaks that naturally peter out as *temporary exhibits*.

The challenge is to ascertain which novel outbreaks are likely to become long-term acquisitions or disappear like Ebola. SARS engendered enormous fear and economic damage, although less than 1,000 persons worldwide died as a result of SARS infection (McLean et al., 2005). In contrast, the World Health Organization's (WHO) figure for annual human mortality from rabies is 55,000, and this figure may well represent a substantial underestimate of actual deaths. Yet, each human is a dead-end host for rabies, so there is no fear of a rabies pandemic.

Although WHO claimed that intelligent surveillance controlled the SARS epidemic, it probably played a minor role (McLean et al., 2005). What saved the SARS outbreak from becoming a major pandemic was more mundane biology. In contrast to influenza, people infected with the SARS coronavirus only become infectious to others after they develop serious symptoms and retire to bed. Moreover, only a minority of those with SARS were what became known as super-spreaders. As with Ebola virus, those at greatest risk for acquiring secondary infection were carers – family members and nurses. In other words, SARS transmission was inefficient and the overall reproductive rate of the virus was low, $R0 = <1$.

It might have gone otherwise for SARS. A novel, highly pathogenic coronavirus (Van Boheemen et al., 2012) arising in Saudi Arabia in mid-2012 had killed 6/13 infected people in the Middle East and Europe by February 2013, and we do not yet know what the outcome will be. HIV initially struggled to take off (Pepin, 2011), and as mentioned, only one of the ten transfers from apes and monkeys has become pandemic. This is not because the environmental or social conditions differed for each transfer. Rather, subtle differences in the properties of the virus strains themselves determined how efficiently they could adapt to their new host. Despite Colin Butler's timely warning (Butler, 2012) that overemphasis on novel emerging pathogens diverts attention from other important health problems and determinants, the example of HIV/AIDS shows that to ignore them altogether would be foolhardy.

Our burgeoning understanding of the molecular biology of species-specific host restriction factors (Duggal and Emerman, 2012) that a virus has to overcome to establish itself in a new species may help in forecasting which new outbreaks pose the greatest threat to become pandemic. Moreover, analysis of the amplification and reduction of genetic sequences within the viral genome can reveal past patterns of adaptation in the Red Queen evolutionary race between virus and host (Elde et al., 2012).

The Concept of Virulence

I regard disease caused by viruses as collateral damage to viral replication. True, there are a few pathological symptoms that may be induced specifically to aid onward transmission, such as the behavioural changes induced by rabies virus. In most cases, however, disease is only indirectly related to transmission dynamics. For instance, the paralysis induced in a small proportion of those infected by poliovirus is related to high viral load, but the neurological effects are not themselves relevant to polio transmission. Some symptoms of illness are a sign of a healthy reaction to the infection, such as the fever and aches induced by interferon. But an overstimulation of such an innate immune reaction, often referred to as a 'cytokine storm', may in itself be fatal. Severity tends to be associated with novel infections where there is no immunological memory and no previous selection in the host for survival.

Virulence is neither positively nor negatively related with the efficiency of epidemic spread. There is a tendency for initially highly virulent infections to become attenuated over time, as Girolamo Fracostoro observed for syphilis in the 16th century and Frank Fenner witnessed for myxomatosis (Fenner and Ratcliffe, 1965). In contrast, the virulence of untreated HIV-1 infection over the past 25 years appears to be increasing (Herbeck et al., 2012). Virulence in the individual has little impact on the population when it occurs at the extremities of lifespan – in infancy and in old age. However, viruses newly introduced into a host population (like the 1918–19 influenza pandemic and HIV) are virulent at all ages – which has greater consequences for society (Weiss and McMichael, 2004).

Cross-species Virulence

The virulence of infection in a new host species is difficult to predict. Most zoonoses are barely detectable, being ill-adapted to the new host, yet some are devastating. I shall reflect on a few virus examples.

Influenza and other avian viruses

In public health terms, we rightly fear the emergence of a highly pathogenic virus that is also highly transmissible. That is why there has been so much concern about the highly pathogenic H5N1 influenza virus that kills chickens and humans alike. Luckily, the H5N1 virus has not yet adapted to efficient human-to-human transmission and remains a zoonotic infection. While the public health experts were looking eastwards in trepidation, the H1N1 influenza virus quietly escaped from pigs in Mexico and spread rapidly across the globe. The mortality of this virus is low and is restricted mainly to a rare human genotype (Everitt et al., 2012). However, a reassortant virus between H5N1 and H1N1 might be quite a different matter.

Why do chickens and humans alike suffer from influenza virus infection when the natural hosts, waterfowl, do not usually become ill? There is no clear answer, but it behoves us to consider the ecology of the infection in different hosts. In ducks and geese, influenza is an enteric, waterborne infection, whereas in both chickens and humans, it is respiratory. Thus, the mode of transmission differs, as well as virulence. The transfer from duck to chicken may well involve a more drastic change for the virus than that of chicken to mammal. However, we understand the avian to mammalian switch better at the molecular level because the stereochemistry of the sialic acid receptors differs for influenza virus in these two classes of host.

It strikes me that the social dynamics of different species of birds is being largely ignored in discussions of avian reservoirs of potential human infection. Migratory birds have an enormous geographic range. We do not know whether it was a stowaway mosquito or an imported bird that brought West Nile virus to New York in 1999, but we do know that it took only two years to reach the US West Coast. Apart from migration, there is 'epideictic' behaviour, whereby some avian species live for part of their life cycle in extraordinarily crowded habitats while they may be highly dispersed and sparsely distributed at other times (Wynne-Edwards, 1962). Large avian colonies, such as seabird nesting sites or the mass roosts of starlings in cities like London, resemble the dense human habitation that facilitates the spread of epidemic infections, whereas dispersed birds (such as the jungle fowl progenitors of the domestic chicken) are more like hunter-gatherer humans whose viruses need to establish persistent infections to be passed vertically through generations. It would be interesting to investigate whether the species exhibiting crowd behaviour are more effective reservoirs for the emergence of viruses. Likewise, many species of bats live in huge colonies when not on the wing, and they are the reservoirs of many types of RNA virus (lyssa-, filo- and henipaviruses) that do them little harm but are highly pathogenic for terrestrial mammals (Wood et al., 2012).

Poxviruses

Poxviruses typically establish short-lived, acute infections. If the host survives, it becomes immune to reinfection, and a relatively large population of naïve subjects is needed for maintenance of the virus. Some like smallpox virus are highly pathogenic, and this may be a marker of its relatively recent introduction into humans, about 2,000 years ago (McMichael, 2001). Myxoma virus is an endemic, low pathogenic virus in American lagomorphs such as the jackrabbit (*Sylvilagus* spp.), but it became a mass killer when introduced by accident or deliberately into European rabbits. This is the most famous example of high virulence upon cross-species transfer (Fenner and Ratcliffe, 1965). But, high virulence in cross-species infection is not inevitable. Cowpox is not virulent in humans, but as Edward Jenner demonstrated, it confers acquired immunity to smallpox (Weiss and Esparza, 2015). This lack of virulence may be due to the large evolutionary distance between bovines and humans. More closely related species show a similar pattern to myxomatosis in rabbits. For instance, the dieback of indigenous red squirrels in the UK since the introduction of American grey squirrels 100 years ago appears to be due less to competition for habitat than to a grey squirrel poxvirus (Sainsbury et al., 2008).

Retroviruses

Some retroviruses represent the extreme family heirloom in being transmitted as chromosomally integrated DNA genomes in the host. As already mentioned, ~8 per cent of human DNA is derived from retrovirus infection. In this way, the virus gets a free ride through the generations, but intact genomes can re-emerge as infectious agents (Weiss and Stoye, 2013). The host carrying the endogenous virus often evolves resistance to reinfection at the cellular level, so that viral load remains low, but such viruses can infect foreign species and hence are called xenotropic. An example is an endogenous gamma-retrovirus transmitted through the germ line of Asian species of mice. In the 1970s, it spread to gibbons held in captivity in Southeast Asia, and it has also spread to koalas in Australia. It causes acute leukaemia in both the new hosts. Interestingly, it is becoming newly endogenous in koalas in colonising their germ line (Tarlinton et al., 2006) (see Figure 29.3).

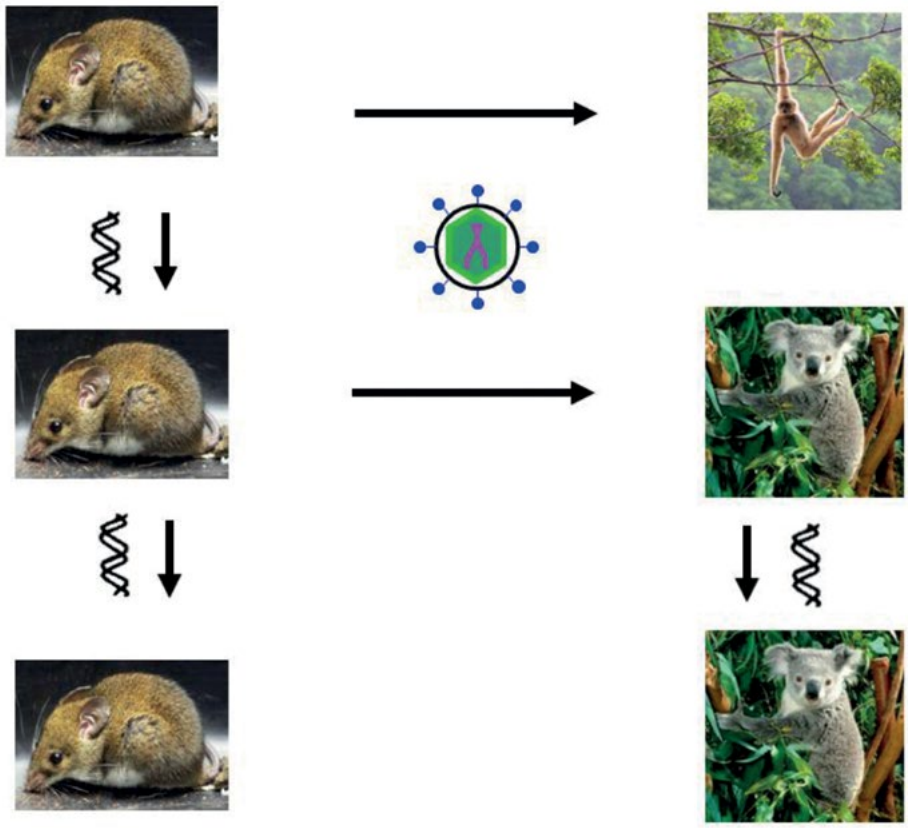

Figure 29.3 Gamma-retrovirus genomes can be transmitted either vertically as Mendelian traits or horizontally as infectious virus particles.

The evolutionary dynamics of such contrasting modes of transmission are drastically different. Two Asian species of mouse, the Ricefield mouse (*Mus caroli*) and the Fawn-coloured mouse (*Mus cerviclor*), carry closely related Mendelian retroviruses that are more distantly related to the leukaemia viruses of house mice (*Mus musculus*). The similarity in genomes of the two murine retroviruses indicates that this genome reservoir has been present in Southeast Asian mice for tens of thousands of years before these species diverged. During the 20th century, this virus gave rise to two distinct infectious epidemics causing leukaemia, one in gibbon apes and another in koalas. The koala retrovirus is in the process of becoming endogenous in the koala genome. It may be significant that the lar gibbons first known to be infected were captive animals held at ground level, where they would have had more contact with mice than in the canopy of the rainforest. How the Asian mice gained contact with koalas in Australia is not known, but it may have been through the importation of rice and other goods by ship.

Source: Author's work.

Herpesviruses

Herpesviruses are heirloom viruses that set up long-term persistent infections ideally suited to maintenance in small, isolated host populations like hunter-gatherers. The virus can be activated decades after initial infection and transmitted to the next generation. Although human herpesviruses such as herpes simplex, cytomegalovirus and EBV cause disease in some individuals, infection is not commonly fatal. Like poxviruses, however, herpesviruses can be lethal to related but distinct host species. This has long been known for human exposure to herpes B virus of macaques. More recently, this phenomenon has come to light in elephants held in zoos. An alpha-herpesvirus of African elephants is lethal to Indian elephants, while causing nothing more serious than a cold sore in its own host. Conversely, the Indian counterpart is highly pathogenic to African elephants (Richman et al., 1999).

Conclusion

I have argued that the virulence of cross-species virus infections can be devastating. RNA viruses often cross into quite unrelated hosts. Modern-day examples of novel viral diseases in humans tend to come from wildlife, and particularly from species that associate with humans (McFarlane et al., 2012; and discussed by Ro McFarlane, this volume). One factor of this wildlife origin may be that humans have already had ample time to acquire infections from livestock, such as measles from rinderpest of cattle.

Cross-species infections by DNA viruses are more likely to originate in species closely related taxonomically to their new host, and also often show a marked increase in virulence. The separation of species or populations halts selection for attenuation for the other species' virus, so that when related species meet again, their herpesviruses and poxviruses may present a disastrous situation in the new host. If Indian elephants unwittingly acted as bioterrorists to their African counterparts (and possibly to Hannibal's 'third' species and mammoths, too?), and if myxomatosis was so lethal to European rabbits, we could surmise that when modern humans met Neanderthals and Denisovans, they almost certainly introduced them to lethal viruses (Weiss, 2009). Our hominid cousins would have been just as susceptible to human diseases they had not previously encountered as the Indigenous Americans and Pacific Islanders were to Old World viruses exported by European colonisation.

Of course, the transfer might also have gone in the opposite direction. We do not know what infections modern humans acquired from Neanderthals and Denisovans, but we certainly had contact because we acquired some of their genes (Meyer et al., 2010). Today, ecotourism can threaten endangered great

apes if they acquire infections such as common colds and measles from humans. Such 'anthoposes' may account for more ancient animal infections; it seems as if bovine tuberculosis may have come from humans (Brosch et al., 2002).

Overall, in this dynamic world where climatic change, human expansion and habitat destruction continue, we should expect to witness further surprising episodes of novel infections with curious origins and threatening virulence.

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This text is taken from *Health of People, Places And Planet: Reflections based on Tony McMichael's four decades of contribution to epidemiological understanding*, edited by Colin D. Butler, Jane Dixon and Anthony G. Capon, published 2015 by ANU Press, The Australian National University, Canberra, Australia.