Crossing the species barrier - viruses and the origins of AIDS in perspective

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Species specificity

Viral species tend to be restricted to the host animal species which they infect. They have evolved to fill a particular ecological niche which they cannot readily leave, and typically they are not very pathogenic to their long-established host. There are formidable natural obstacles preventing a virus crossing the species barrier to become established and persist in new species. First it must reach and infect cells of a new host and replicate within them. Second, and much more difficult, the virus must be shed in quantities adequate to infect regularly target cells in other individuals of the new host species. If this is not achieved the virus will die out in the new species. On the other hand, if it is successful, the virus will adapt, evolve and may become species-specific in its new host.

Many viruses which infect other animals, and have also infected individual humans sporadically for millenia, have still failed to become fully human-adapted by regular direct transfer from person to person. Many arboviruses readily infect humans when injected into them by infected insects, but they fail to be shed from humans in quantities adequate to infect other people directly. Rabies virus infects humans bitten by an infected animal, but fails to be shed and dies with the human host. These viruses have cleared the first obstacle but failed to clear the second.

Other viruses clearly have been successful. Species-specific acute viral infections of humans which are followed by life-long immunity, such as measles and smallpox, cannot survive in an isolated population of less than about 200 000. They could not persist in small groups of hunter-gathering peoples. These human viruses have evolved from viruses of other animals which have crossed the species barrier successfully and become human-specific within the last few thousand years, after the foundation of cities.

The opportunities for cross-species transfer of mammalian viruses have increased in recent decades. Relevant factors include rapid transport of people and animals, new techniques of animal husbandry, extensive use of live viral vaccines, deliberate infection of experimental animals, growth of viruses in cell cultures, search for biological weapons for war or pest control, and the new biotechnology. Viruses which succeed in infecting alien hosts tend to be more pathogenic to the new host than to the natural one.

20th century cross-species transfer

There are several examples of well documented, spectacularly successful, crossing of the species barriers in the 20th century by viruses affecting non-human mammals assisted by human action - whether by chance or by design. The movement of the domestic pig to Kenya brought it into close contact with its near relative the wart-hog (*Phacochoerus aethiopicus*) and its tic (*Ornithodorus moubata porcinus*). African swine fever virus, which causes a persistent but harmless infection of the African wart-hog, was transferred to European pigs with the help of the tics, and has now been successfully established in them for 70 years. The initial epizootics killed 99% of pigs within two weeks of infection, but as the virus has spread to become enzootic in domestic pigs in Africa, Europe and America, strains have evolved causing persistent but less lethal infections[1].

The myxoma virus was used deliberately to infect rabbits as a means of pest control in Australia and Europe in the early 1950s. The virus has caused minor pathology in the South American forest rabbit (*Sylvilagus brasilliensis*) probably for millions of years, but injected into the European rabbit (*Orystolagus cuniculus*) initially killed 99.8% of them. Myxomatosis was introduced into the wild rabbit population of Australia by government action and into Europe by the action of a single private citizen[2]. Now that powerful evolutionary forces acting on virus and rabbit for more than three decades have greatly reduced the mortality, attempts are being made to restore the viral virulence to earlier levels by genetic engineering.

Canine parvovirus (CPV) appeared abruptly in dogs in 1977 and within a few months had become panzootic on all continents causing an entirely new form of canine enteritis and myocarditis[3]. Within a couple of years a large section of the world's domestic canine population had been infected. CPV is genetically very similar to the long recognized feline panleukopenia virus (FPLV) against which many live modified viruses have been used to vaccinate cats[3]. The dog virus is genetically even closer to some of the vaccine viruses than it is to the naturally occurring cat virus[4]. Several virologists have suggested that canine parvovirus evolved 'under selective growth conditions, for example, in the course of deliberate or accidental adaptation of FPLV strains to replicate in canine cells', during live virus vaccine production[4]. The epizootic originated from a single source[5], though the precise source has not been identified, and the new virus rapidly spread world-wide assisted by jet transport. This is the most plausible explanation for a remarkable and explosive cross-species transfer from cats to dogs, after millenia of domesticated proximity during which the parvovirus failed to infect dogs.

Bovine spongiform encephalopathy (BSE) has appeared since 1985 on more than 1000 farms scattered throughout Britain as an entirely new disease of cattle, with unique clinical features, which has never been reported from any other part of the world[6-8].

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Less than one case per week occurred during 1986[9] but the weekly incidence now exceeds 80 and is rising rapidly[10]. Once symptoms develop the disease is steadily progressive, always fatal, and caused by an atypical virus which produces no immune reaction similar to those which cause scrapie in sheep[11,12], and kuru and Creutzfeldt-Jakob disease in humans. The mean incubation period is about four years with a range from 2.5 to over 8 years[9]. The epizootic has the characteristics of a cross-species transfer from sheep to cattle of a new, slow virus disease originating from a single source[8,9].

It has been suggested that the outbreak of BSE may have been caused by feeding calves with meat and bone meal as feed supplement prepared from scrapie-infected sheep[9]. Experimentally, however, cross-species transfers of these atypical viruses and the diseases they cause usually have been achieved by inoculation; adaptation of the new strains of virus to new host species was then perfected artificially by serial passage by further inoculations[13]. Scrapie has been known to affect sheep for more than 200 years, has a world-wide patchy distribution, yet has never affected cattle before. It is indeed strange that so many cases of BSE should occur so abruptly and be so widespread in one country alone, merely by changes in the preparation of meat and bone meal from sheep as feed supplement, which had been taking place gradually over years and in many countries. If this explanation is correct, it confirms that the cross-species transfer is artificial, not natural, because cattle do not normally eat sheep. However, if the origin of the epizootic is artificial, it follows logically that it was not necessarily accidental, and the scrapie agent may first have been bovine-adapted artificially.

The precise origin also is not known of the new morbillivirus of common seals (*Phoca vitulina*) which in 1988 started a highly lethal epizootic in the Baltic and North Sea[14]. It had apparently been preceded, by a few months, with the appearance of a similar virus infecting the fresh-water seals (*Phoca siberica*) of Lake Baikal in the Soviet Union[15]. Morbilliviruses do not appear to be enzootic in sea mammals, and clearly the virus is spreading in seals as a 'virgin-soil' epizootic. It is closely related to canine distemper virus[16] but is even closer to rinderpest virus of cattle[17]. Modified live morbilliviruses have been used for many years to vaccinate humans against measles, dogs against distemper and cattle against rinderpest. There is no difficulty in principle in modifying, by artificial selection, a morbillivirus from some other species to kill seals, though igniting a panzootic is much more chancy. Seals, like rabbits, have been culled legally as an economic pest for decades. The fact that myxomatosis panzootics in rabbits were started deliberately, and justified economically, is not evidence that the seal epizootic was started likewise; but it is a possibility which cannot be ignored.

Influenza

Influenza type A is particularly interesting as the only major virus of humans which quite often and naturally appears to cross species barriers. Several mammals and numerous birds are host to many sub-types of influenza A which, particularly amongst birds, may jump species. Reassortment of the genes of an influenza virus from humans with those from another animal species, seemed to have been the source of the abrupt appearance of new sub-types which produced the pandemics of 1918, 1957 and 1968[18].

The unexpected appearance on 4 May 1977 in Anshan, in northern China, of the H1N1 sub-type (which had been extinct in humans for more than 20 years) with a molecular structure virtually identical to the virus which caused an influenza epidemic in 1950[19], has been described by scientists as mysterious[20]. However, several virologists postulated that the 1950 strain which, along with many others, had been kept deep-frozen in laboratories for 27 years, had escaped[21] and the epidemic 'resulted from a man-made event'[22]. According to a writer in *Nature*: 'Chinese and Soviet scientists have denied (this) possibility as the origins of the.... epidemics in their countries'[23], and most authors writing after 1978 have been content to write off the event as a 'complete mystery'[19]. However, artificial freezing in 1950 of this rapidly evolving RNA virus, its artificial storage and subsequent release, is the only plausible scientific explanation for its reappearance genetically unchanged 27 years later. The only genuine remaining mysteries are precisely which laboratory the virus came from and the circumstances of its release.

Virologists have been concerned for decades about the possibility of pandemic spread of a new sub-type of influenza A, created by chance reassortment of viral genes with a virus from another animal, with a mortality comparable to that of the original H1N1 sub-type which killed 20 million people (about 2% of those infected) in 1918-1919. In 1979-1980 about 20% of the harbour seal (*Phoca vitulina*) population of the north-east coast of the United States died from a primary viral pneumonia and encephalopathy caused by an H7N7 sub-type of influenza A closely related to a strain of fowl plague virus A/FPV/Dutch/27 (H7N7)[24,25]. This strain is almost universally fatal in chickens, but had not been found previously in mammals. Studies suggested that the virus had only recently been introduced into seals[25]. 'What would happen if such an event occurred in man instead of seals?'[19] asked leading authorities on influenza A virus. And what would happen if the mortality approached that in chickens? If the event was man-made, whether by mistake or by design, would virologists explain the catastrophe as just another 'complete mystery'?

Retroviruses (oncornaviruses)

Retroviruses of the cancer-causing sub-family, oncornavirus, in experimental situations often readily infect cells from different species in cell culture. When a retrovirus first infects intact animals of a new species, the virus is not integrated into the germ line; it is said to be exogenous. Its continued survival in the new species depends upon infectious transmission. With time, if successful, the virus may be incorporated into the DNA of the germ line, enabling transmission to take place genetically within the host; it is then said to be endogenous. When cross-species infection of a retrovirus is dependent only upon chance, and natural selection, as opposed to artifical selection in the laboratory, cross-species infection appears to be a rare historical event.

An endogenous Type C retrovirus is present in all species of baboon, and its precursors seem to have persisted in their ancestors for at least forty million years[26]. About three million years ago, somewhere in

north Africa or the Middle East, an ancestor of the domestic cat seems to have been infected with the baboon retrovirus, and its descendents are present today in all cats as the endogenous feline retrovirus RD-114[27], which is now harmless to its feline host. Between five and ten million years ago, an endogenous Type C retrovirus from a mouse infected the common ancestor of the domestic pig[28]. More than thirty million years ago another endogenous Type C retrovirus from the common ancestor of lions and domestic cats infected the ancestor of the macaque[28].

Set against this geological time scale, some endogenous retroviruses have been transferred to other species very much more recently. The gibbon ape leukaemia virus is an infectious, exogenous retrovirus which caused an epidemic of leukaemia and lymphomas in gibbons in a research colony in Thailand in the early 1970s[29]. The virus has since been detected in several colonies of captive gibbons, but it is not yet known if wild gibbons are infected - which, according to a leading authority on primate retroviruses, 'is an extraordinary oversight in our research efforts'[29]. The gibbon virus seems to have originated from an endogenous retrovirus of mice, and the cross-species transfer appears to be very recent. It possibly occurred, unintentionally, in the 1960s, when gibbons were inoculated experimentally with tissue from other species - including humans.

Retroviruses (lentiviruses)

Lentiviruses are a non-oncogenic sub-family of retroviruses of which the human immunodeficiency virus Type-1 (HIV-1) is now the most notorious. All known naturally occurring lentiviruses are exogenous, being transmitted by infection and not in the germ line. The existence of endogenous, genetically transmitted, lentiviruses has not yet been demonstrated in nature. Recently, however, a breeding colony of transgenic mice was created in which the genome of HIV-1 had been integrated artificially into the chromosomes of fertilized mouse ova. HIV-1 proviral DNA was present in all cells of the offspring, and in some mice infectious virus was expressed[30]. Lentiviruses are highly species specific in nature, readily transmissible only to closely related species of mammal.

Experimentally, maedi-visna virus of sheep, the prototype lentivirus first grown in cell culture in 1959, will cross-infect the goat[31]. The genetically closely related caprine encephalitis arthritis virus of goats will cross-infect sheep[31]. Equine infectious anaemia was, in 1904, one of the first diseases shown experimentally to be caused by a virus. Its virus will cross-infect donkeys and mules[31]. The recently discovered lentiviruses of cattle[32] and cats[33] have not yet been shown to cross-infect other species. No successful experimental infection of small laboratory animals with any of these lentiviruses has yet been reported. Infection of cells from other species has proved difficult or impossible, although there were reports in the 1960s and 1970s of infection of human cells in tissue culture by maedi-visna virus from sheep[34] and the lentivirus of cattle[35].

In the case of human lentiviruses, HIV-1 will infect chimpanzees and gibbons experimentally though none has yet developed any significant disease. All attempts to infect other primate species have failed. Within the last few months infection with HIV-1 of rabbits with chemically induced peritonitis has been reported[36]. On the other hand, infection with HIV-1 of cell cultures from many primate species, has been achieved[37] in spite of failure to infect intact animals. HIV-2 infects experimentally a wider variety of primate species than HIV-1, including baboons[38] and macaques.

Several non-human primate lentiviruses, the simian immunodeficiency viruses (SIVs), have been identified since 1984. SIVmac, which is very similar to HIV-2, started an epidemic of AIDS amongst macaques in a primate research colony in the late 1970s[39]. The virus has not been found in macaques in the wild, which all come from Asia. However, a closely related virus (SIVsm) infects a high proportion of wild sooty mangabeys[40,41] - which come from Africa - in which it causes no disease; but when injected into macaques causes AIDS[42]. The original apparently spontaneous epidemic of AIDS in macaques in the research colony seems to have been the unexpected, and unintended, result of injecting tissues from mangabeys into macaques. The only other primate lentiviruses so far identified are from African green monkeys (SIVagm) and mandrils (SIVmnd)[43]. They appear to be non-pathogenic to their hosts and have not yet been transmitted experimentally to other species.

Available evidence suggests that the primate lentiviruses SIVsm, SIVagm and SIVmnd are naturally occurring species-specific viruses which have infected their hosts harmlessly for a very long time[43] and may have evolved in concert with the evolution of their hosts[43]. By contrast, HIV-2, which is particularly closely related to SIVmac, seems to have infected humans only recently, probably after virus-containing blood or tissues from another primate species were injected into humans by accident or by design. HIV-1 in humans also has the hallmark of a virus which has only recently infected its host - like African swine fever in pigs, myxoma virus in rabbits, canine parvovirus in dogs, scrapie 'virus' in cattle, morbillivirus in seals, leukaemia virus in gibbons and simian immunodeficiency virus in macaques. The theory popular amongst many molecular biologists[43-45] that HIV-1 has been endemic, and largely non-pathogenic, in an isolated group of people in Africa for millenia, is not scientifically credible[46].

No precursor genetically nearly identical to HIV-1 has been found in any other species. The nucleotide sequence of HIV-1 is little closer to HIV-2 than it is to the naturally occurring primate lentriviruses of green monkeys, mangabeys and mandrils[43]. It is possible that a naturally occurring lentivirus much closer genetically to HIV-1 may yet be discovered in some other species. On the other hand, HIV-1 may have evolved rapidly from known animal lentiviruses replicating in the highly artificial, selective conditions, of serial passage in human cell cultures. It is highly relevant that all lentiviruses so far identified in non-human primates (green monkeys, macaques, mangabeys and mandrils) have been obtained by culturing them, not in cells from their natural host species, but in *human* cells[41-43]. As all the primate lentiviruses readily grow in human cells, it is possible that any of them may be adapted to infect intact humans.

Conclusion

It would appear that the AIDS epidemic may be just one of the latest of several mammalian cross-species viral transfers triggered by the techniques of virology developed in the 20th century, which subsequently spread out of control in the new host species. It is certain that in at least one example, myxomatosis, the creation of the panzootics was deliberate. For 35 years myxomatosis has been the prototype of a perfect but ruthless biological weapon, universally lethal to the 'enemy' (the rabbits) but harmless to one's own side (humans) and allies (sheep and other domestic animals). The immense progress in biotechnology since the early 1950s has opened up the possibility of producing viral epidemics in man or domestic animals nearly as lethal to a single species as the hydrogen bomb, yet the source of the epidemic might be untraceable. The principles and techniques involved are simple, requiring neither large plant nor many personnel. It took only one man and a couple of friends to ignite the myxomatosis panzootic in Europe.

In humans highly virulent viruses with short incubation periods and poor transmissibility, like the haemorrhagic fever viruses, are easily controlled by quarantine, but the greatest threat is posed by slow virus diseases, like AIDS and BSE, which can spread silently far and wide before sounding any alarms. It is of interest that one of the co-discoverers of HIV-1, warned of even more virulent infectious agents than HIV-1 which now threatened mankind. 'The greatest danger lies', he said, 'in non-conventional viruses that produce no immune reaction'[47]. Could what is happening in British cattle today to cause BSE be happening in people tomorrow?

It is inevitable that further epidemics and epizootics of new lethal viruses will occur in the future. It should be mandatory that all outbreaks of new major viral diseases should be thoroughly investigated, as soon as they are identified, in an attempt to ascertain the origin. The attitude that there is no importance in attempting to track down the origins of the AIDS epidemic will be held as highly irresponsible and unacceptable by the public.

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