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The History of HIV Infection

My talk is about various aspects of the history of HIV infection: HIV/AIDS as it is now commonly called. Some parts of it may involve my memories and no one else's. Lest you are in danger of believing everything I claim to remember, I'll begin with a quote, over 100 years old, from HH Munro, a Burmese born Englishman who wrote short stories under the pen name of Saki:

"The young have aspirations that never come to pass,

The old have reminiscences of what never happened"

So with that small cloud over my head, let me tell you some stories from that time as I, a solitary infectious disease physician, saw and lived them.

It was 1981. I was 40, born in 1941, half my present age. Our family of five had returned from my post graduate training in the UK and Jamaica in 1975, six years earlier.

When did I first hear of this illness? On Thursday July 30th, 1981 at about 1:40pm, I was crossing Park Road, going from Auckland Hospital to the Medical School to lecture 4th year medical students: how lucky they were! Coming towards me from the Medical School was Peter Herdson, Professor of Pathology. He called out to me, raising his hand in a soft stop sign. " Rod, have you read these extraordinary accounts of homosexual men in New York and Los Angeles in MMWR? It seems like they might have some new infection. It could end up in your court?" I told him I hadn't seen them and we passed by. How right he turned out to be.

After my lecture I went to the Med School library. There were no computers, internet, or smart phones in 1981. I found the two articles. MMWR stands for Morbidity & Mortality Weekly Report. It was the weekly written output of the Centers for Disease Control and Prevention, a US government funded institution centred in Atlanta, Georgia since 1930. To quote its website: "It provides public health and safety through the control and prevention of

disease, injury and disability in the US and internationally. It publishes (unrefereed) public health research and recommendations derived from Science based research."

To give you a flavour of its content, recent articles are : Childhood lead exposure linked to apple puree. Nth Carolina 2023: Treatment for opioid use disorder, US, 2022. After the two initial 1981 articles, MMWR was for many years, rarely without an article about HIV/AIDS.

1981. The first article was from June 5 1981. It begins, verbatim, in the language of the time "In the period October 1980 to May 1981, five young men, all active homosexuals, were treated for biopsy confirmed *Pneumocystis* pneumonia at three different hospitals in Los Angeles, California. Two of the patients died. The article finished "The fact that the patients were all homosexuals suggests an association between some aspects of the homosexual lifestyle, or disease acquired through sexual contact, and *Pneumocystis* pneumonia in this population." They were right with their second suggestion. This was indeed a disease acquired through sexual contact, but at that time, we had absolutely no idea of what it was.

Pneumocystis jirovicii pneumonia is an extremely rare sort of fungal pneumonia seen only in those with severely damaged immune systems: the immunocompromised as we say. I had only seen it twice before, but along with patients with HIV/AIDS and all involved in their care across the world and including NZ, it became depressingly familiar to all of us.

The second MMWR article came out on July 3, 1981: it described 26 homosexual men with Kaposi's sarcoma. KS was a rare, violet coloured tumour of blood vessels which spread slowly across the skin anywhere and everywhere, including very commonly, the face. If severe, it spread to internal organs as well. There were no curative treatments. I had never seen it before: it was however, a 'once seen, never forgotten', diagnosis.

Years later, it was, surprisingly, found to be caused by another virus, Human Herpes Virus 8, related to cold sores and chicken pox viruses. It became very common. The non-official story told over coffee or beer at conferences was that two dermatologists in New York were chatting before an evening meeting of New York dermatologists. One said to the other, "I saw two homosexual men with KS the other day. How about that?" Back

came the reply, “You can’t be serious, I saw one this very morning”. And so, in so many small ways, the pandemic was underway.

From all across the world came an increasing number of reports of both common and unusual infections and cancers, particularly of lymph nodes, arising in various groups of patients. Homosexual men, those with haemophilia, those with heroin and other intravenous drug addictions, blood transfusion recipients, pregnant women, new born babies and of course heterosexual people. The cause had to be a blood borne infection and so it came to pass. In May 1983 Luc Montagnier’s research group from the Pasteur Institute in Paris published the causative virus with pictures in Science. There followed subsequently some scientific unpleasantness when Robert Gallo, a US based research virologist from Baltimore made the same claim in 1984. In 2008 Luc Montagnier and Francoise Barre-Sinoussis from Paris were awarded the Nobel Prize in Medicine and Physiology with the Nobel Committee very pointedly saying, “they had no doubt about who had made the fundamental discoveries”. The Swedes at least saw it all very clearly. Professor Luc Montagnier died in 2022 aged 90 years.

Back to NZ: it was decided appropriately enough that any patients with or suspected of AIDS in Auckland, would be admitted to Ward 9C, which had always been where infectious disease patients had been admitted, along with general medical patients. Even at the peak of the pandemic in the late 80’s and early 90’s, there were always many more general medical patients on the ward than ID ones. Nevertheless, Ward 9C became known as ‘the AIDS ward’.

I saw the first two NZ patients with AIDS in late 1983. I was rung by a physician colleague at St Vincents Hospital in Sydney, late on a Friday afternoon. They were caring for a young homosexual New Zealand man with cryptosporidial diarrhoea. Cryptosporidia are protozoa, roughly similar to amoebae and well recognised as pathogens in farm animals. Once again I had never seen a human with this infection. He was carried off a routine Air NZ flight the next day, Saturday, with an IV-line in. He was skeletal, wasted and dehydrated. We rehydrated him and he returned to his parents in Taranaki where he died on April the 4th, 1984, the first death of a New Zealander, of AIDS in New Zealand.

The second patient was a New York attorney off the liner, the Queen Elizabeth, which was in Auckland Harbour. He was vomiting blood, haematemesis. He was literally covered in KS and one of these was bleeding in his stomach. He stopped bleeding spontaneously, cancelled his cruise and flew back to New York. After these first two patients, we were anxious about how this epidemic would pan out in New Zealand. In the event I never saw anyone with cryptosporidial diarrhoea again and internal bleeding, indeed any sort of bleeding from KS was extraordinarily rare.

In 1985 the Labour politician Fran Wilde, later Dame Fran Wilde, finally ushered through the NZ parliament "The Homosexual Law Reform Bill". It followed after a great deal of public posturing, particularly by Norman Jones, a somewhat rabid, anti-male homosexual, National politician from Invercargill. It passed by 49 votes to 44. The then Governor General, Sir Paul Reeves signed it into law the following year. For the first time in New Zealand's history, homosexual men could enter into a sexual relationship without fear of prosecution.

To give you a feel now, for the epidemic, then, in NZ, we published a paper in the NZ Medical Journal in July 1986 called "AIDS in Auckland in 1985". We described the illnesses of the 11 patients admitted to Auckland Hospital in 1985: by the time we published it, six of the 11 had died. AIDS killed everyone then. All were homosexual men: their median age was 31 years. Five had KS, three had *Pneumocystis* pneumonia, and one a lymphoma. They averaged 14 days in hospital over the period. The median time from diagnosis to death in those we cared for then was 9 months.

Over the subsequent years, the numbers needing admission increased, so that in the peak admission years of the late 80's and early 90's, it was not uncommon for there to be eight or nine patients on Ward 9C with HIV/AIDS. Mostly these individuals had *Pneumocystis* pneumonia and about a third would have complicating pneumothorax when holes appeared in the lung tissue, air escaped into the thorax and the lung collapsed. It was often very difficult to re-expand the lung which often led to prolonged and painful hospitalisation.

A blood test, the HIV antibody test, was developed in America in early 1985 and it was registered and used in NZ from late 1985. Using this test, it was possible to diagnose HIV infection before symptoms developed. It was of

course a game changer. By the end of 1988 there had been 101 New Zealanders diagnosed with AIDS in NZ, 99 men, predominantly gay men and one woman. Of those tested for HIV antibodies that year, 385 New Zealanders tested positive, of whom 376 were men and nine women. So the notion in the West at least, that HIV infection was still skewed powerfully in numerical and proportional terms towards gay men was not a false one. It was argued by many, particularly in the US, that the widely expressed public homophobia had powerfully impaired the initial appropriate public health responses. One ranking US scientist is quoted as saying to a colleague before a meeting on AIDS in 1986, "Whatever you do, don't offend the gays and don't inflame the homophobes". Indeed it wasn't until mid-1987 at a time when more than 36,000 Americans had been notified with AIDS, of whom the vast majority were males, and more than 20,000 had died, that President Ronald Reagan, then in his second presidential term, actually said the word AIDS in public.

I went to an International meeting in Jerusalem in 1989, eight years after HIV/AIDs was recognised. One of the papers presented exemplifies, in some ways, this Western gay male fixation. The paper was from Belgium. In summary it discussed an account of a black heterosexual male Zairean engineer (remember Zaire was formerly the Belgian Congo) who spent a few months in Brussels : with contact tracing among his female sexual partners he was found to have infected five of them and to use the exact language "five non-promiscuous females in Brussels over a brief period". All the women were professionals in the lawyer, engineer, medical doctor sense. That a simple and obvious paper about bog standard heterosexual sexual transmission like this could be accepted as important at a big international conference in 1989, eight years after this pandemic began, reinforces the Western gay male bias. And I freely acknowledge now, while I was, by then, fully aware of all the issues about the HIV epidemic in heterosexual people, I was still somehow naively surprised by this account.

In 1987 the first placebo controlled trial of an anti- HIV medicine was published in the New England Journal of Medicine. The medicine used was azidothymidine also called AZT or zidovudine. It was a structural analogue of the nucleic acid, thymidine. It had had a disappointing career. It was originally developed and evaluated as an anti-cancer medicine by the makers, the British firm Burroughs Wellcome, but failed in this role. It was

then tested as an antiviral medicine, but only had action against a viral genus called Lentiviruses within the viral family Retroviridae, retroviruses. Lentiviruses were known to cause slowly developing, generally fatal specific viral diseases in a very wide range of vertebrate hosts but only one that affected humans. As an example, the retroviral Lentivirus called caprine - encephalitis – arthritis -virus makes goats a bit stupid with sore knees. Given the cheapness of bullets, the likelihood of farmers and vets trialling AZT in their dizzy goats was never going to be a winner and development stopped. But AZT existed, metaphorically 'sitting on a shelf' waiting. And the story goes, the very day HIV was pictured in Science in 1983, some B-W scientists immediately recognised it as being a Lentivirus said, "remember AZT" and enabled what turned out to be the first effective anti-HIV medicine, to begin evaluation somewhat more quickly than usual.

Back to the trial. It was planned to run for 20 weeks but stopped after 16 because of the clear efficacy of AZT over placebo. But, as widely predicted, the principal reason for AZT failure was the rapid development of AZT resistance. Consequently, many more anti-virals were developed and tested with clear evidence accumulating that two anti-HIV medicines taken together dramatically reduced the development of resistance. There were many trials around the world, to which the Auckland ID Service contributed and eventually three medicines were shown to be better than two. This philosophy became, and more or less remains, the basis of new treatment regimens. There are now a large number of available anti-HIV medicines, so both prophylaxis and treatments are simpler, generally better and easier to take and manage. Treatment on early HIV diagnosis, now spells a normal life span.

To the second part of my talk: the back story of this pandemic and a bit more complicated

Let's start in Africa. About 2000 years ago, the Roman General and author, Pliny the Elder said, in Latin of course, "Semper aliquid novi, Africanam adferre". "There's always something coming out of Africa". It doesn't matter tonight what he was talking about then, but given both simian (that is monkey and ape) immunodeficiency viruses and human immunodeficiency

viruses came out of Africa, as after all did we, *Homo sapiens*, he was certainly correct. I'll just call them SIVs and HIVs from now on.

A small zoological side-step. Monkeys and apes are very different. There are very many more monkey than ape species. If one of them is coming for you in an unappealing way, remember, apes are generally bigger, don't have tails but do have an appendix; monkeys are therefore generally smaller, do have tails and don't have an appendix. Monkeys and apes are both found in Africa and Asia, and monkeys, but not apes, are also found in Central America.

SIVs are found in the wild only in Africa. There are no SIVs anywhere else in the world.

Firstly, monkey SIVs. There are 416 monkey species in Africa at last count. So far, more than 45 species of African monkeys when tested are infected with their own species specific SIVs, to which they are completely immune. These SIV infected monkeys are healthy and suffer no ill effects even though millions of their own SIVs stream through their bloodstreams all the time. The prevalence of viraemia in these specific monkeys lies between 20 and 80%.

There is nothing biologically outrageous about these events. After all, for example, bats carry rabies virus or covid virus in the same way without illness. Most kittens, including those in Auckland, have the same issue: they are completely well but the bacteria called *Bartonella henselae* which cause cat scratch disease, fill their bloodstreams. These states of being are the long term result of host and parasite co-evolution which ends up with a comfortable compromise solution for both host and parasite.

It is reckoned that these African monkeys were infected mainly between 25,000 and 200,000 years ago .

So, that's the monkeys done and dusted with regard to SIVs.

Now to the apes of Africa. There are four African apes; humans, bonobos, chimpanzees and gorillas. To be complete the apes of Asia are orangutans and gibbons but, remember no SIVs in Asia: forget them for the moment.

No SIV infected bonobos have been found. Gorillas and chimpanzees have been relatively recently infected, but are now geographically widely so

within central Africa: both predominantly directly from monkeys called sooty mangabeys during fighting and chimpanzee predation. The SIVs of both chimpanzees and gorillas are considered by some authorities to be commonly mosaic viruses; viruses formed by viral mixing in several previous hosts. One of, if not the earliest discovery of a living wild SIV infected chimpanzee was in the famous Kombe Park, by lake Tanganyika in Tanzania where Jane Goodall carried out her famous studies of chimpanzees beginning in the 60s.

Gorillas and chimpanzees experience broadly the same outcome as humans with HIV, a prolonged AIDS like illness and ultimate death. Like us, they have not been infected in the ancient past and become adapted to each other. Many others of the Kombe chimpanzees and other wild ones are now infected, dying or dead, as are gorillas.

There are two principal types of HIV: HIV-1 and HIV-2. HIV-1 is the cause of 95% of human HIV/AIDS and the cause of the pandemic. Both arose in West and Central Africa. HIV-2 is a less pathogenic variant remaining principally but not exclusively in West Africa.

The genetic data now unequivocally shows that HIV-1 spilt over into humans on four separate occasions, two definitely from chimpanzees, the other two less securely sourced. HIV-2 on the other hand came directly from sooty mangabeys at eight other separate spill over events.

How did humans become infected? 'Bush meat' in Africa is exactly that: it is the general term given to meat acquired from the capture and butchering of almost any animals, but including sometimes, and importantly, chimpanzees, monkeys and gorillas. This meat is then sold at markets across Central Africa. Butchering is not a simple task. Chimpanzees and gorillas are big. During butchering there are many opportunities for transfer to humans of SIV infected simian blood through multiple cuts and abrasions. At some point an SIV isolate genetically capable of survival in a human environment presumably then 'persisted' and the evolution from SIV to HIV was underway. Further transmission between humans created further evolutionary opportunities. We know from antibody studies that bush meat butchers commonly have antibody evidence of infections with multiple different SIVs. This suggested mechanism is widely known as 'The cut hunter' theory.

The best estimates for the timing of the first chimpanzee spill over into humans is somewhere between 1900 and 1940.

Now to Retroviruses: HIVs and SIVs are retroviruses. They carry their genetic material as RNA ; RNA viruses. They are called retroviruses because they carry a reverse transcriptase gene which codes for an enzyme of the same name, reverse transcriptase.

The usual direction of biological genetic flow is from DNA to RNA. However having this enzyme enables the retrovirus to reverse that flow: so their viral RNA once in a host cell is reverse transcribed back to viral DNA. This new viral DNA is then reintegrated back into the host cell's DNA somewhere, anywhere, randomly. It is then part of the host genome and the fate of this viral DNA is then absolutely tied to the host cell's DNA. With every host doubling cell division, so the viral DNA divides too. If by chance this retrovirus enters what we call a 'germ line cell', either sperm cell or ovum and is lucky enough to be involved in fertilisation, then of course the retrovirus will be tagging along in every single foetal cell. We now, rather clumsily, say the retrovirus is endogenized. However, over eons of copying and doubling, this endogenised retroviral DNA becomes irreversibly damaged and incompetent: hacked, neutralised and domesticated, or as I prefer, simply because of the alliteration, mutated, mummified, munted and marginalised. These retroviral invasions or infections of vertebrates are reckoned to have occurred some 25 to 50 million years ago and now constitute about 8% of our total human genome. Every single vertebrate studied has these retroviral fragments and generally in roughly similar percentages as the human genome. We now call these ancient fragments endogenous retroviruses. In contrast, retroviruses which infect a somatic, non germ line cell and infect locally, eventually dying with the host, we call exogenous infection.

In the last 15 years or so, we have learned that, despite what I have just said, a very, very small number of these retroviral remnants have, incredibly, not lost their function over the eons, but are still competent and

carrying out important functions in their vertebrate hosts: an even smaller number may contribute to disease. The most famous and longest studied are a group of genes called syncytin genes , (spelled s y n c y t i n s) which have a critical developmental and functional role in the mammalian placenta. There are two of these syncytin proteins used in human placentatation, syncytin 1 and syncytin 2. They are retroviral envelope genes, coopted by the host and responsible for the development of the syncytiotrophoblast which is a long name for the single cell shiny layer on the outside of the placenta, the side which faces the internal wall of the uterus. In this site, it is easy to understand that this structure is ultimately responsible for the entry of nutrients and excretion of waste products to and from the foetus.

All mammals work in this way, though there are variations on the basic model.

Without these retained ancient retroviral genes, mammals as we know them, would not be and could not be. We are mammals because in our ancient past, our ancestors' DNA was infected by retroviruses.

Finally to Australia and koalas.

As I have said, every vertebrate tested has been found to have endogenized archaic retroviral remnants from millions of years ago, and transmitted vertically from mother to child. But there is, seemingly, as always, one exception. Koalas. Koalas have somehow not been endogenized by retroviruses in the millennial past and are actually in the process of both exogenous and endogenous infection now.

There are 9 subtypes of koala retrovirus, KoRV. Their history shows KoRVs entered Australia in the NE in Queensland and began endogenization sometime between 22,000 and 49,000 years ago, not millions, and it continues now. This process in the koalas is 'moving' down through the eastern seaboard of Australia and spreading now along the southern

seaboard. Some koalas have only exogenous KoRV infection, some only endogenous infection, some both and some none. These viruses are not taxonomically Immunodeficiency viruses. Nevertheless, exogenous or endogenous, these infections do damage and impair koala immunity causing both lymphomas and leukaemias and a chronic infection which I will discuss in a minute.

The original source of these KoRV infections is reckoned to be an Asian gibbon (there are some at Auckland zoo) an ape which carries a Lentivirus, the Gibbon- ape- leukemia retrovirus, which is genetically extraordinarily close to KoRV.

I first met koala illness when at an Australasian Society for Infectious Disease Annual Scientific Meeting in the early 1990s. An Australian veterinarian presented data on widespread *Chlamydia pecorum* sexually transmitted infection in koalas which affected their eyes and genitals. Given *Chlamydia trachomatis* is the commonest human sexually transmitted infection, veterinarians expected our society to have some ideas for them. Apart from some poor taste, insensitive jokes, including the obvious one that we were surprised that creatures this sleepy could ever stay awake long enough to acquire an STD, we had little to offer. In the event, we now know this chlamydiosis epidemic is occurring on the background of and because of high rates of KoRV disease with its accompanying immunosuppression within the wild koala population

Australian authorities have now formally declared koalas an officially endangered species with the three 'C's being the principal threats. They stand for Canines (dogs which kill them), Cars (which run them over) and Chlamydiosis, implying KoRV infection because that is why they get chronic chlamydial infection so commonly and die from that or malignant haematological tumours.

In finishing, we have come a long and perhaps rambling way from dying koalas and the placentas of mammals back to the HIV/AIDS pandemic. But all these events are linked by the consequences of the extraordinary behaviours of parasitic retroviruses deep within the genomic DNA of their vertebrate hosts.

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