Specialist report for the Penrose enquiry  AML Lever  10th April 2011

I am currently Professor of Infectious Diseases at the University of Cambridge and Honorary Consultant physician at Addenbrooke’s Hospital.

I did my undergraduate medical training at the University of Wales and after general medical training in Wales, London and Newcastle I did research for an MD thesis with Dr David Webster at the Clinical Research Centre in Harrow studying patients with primary immunodeficiency. During this research project we trialled a new preparation of gammaglobulin for patients with hypogammaglobulinaemia. These individuals had up until that time been treated with intramuscular injections of Ig concentrate which only allowed for relatively modest elevation of their circulating immunoglobulin levels. It was felt that intravenous products would be better as the volume administered could be higher resulting in better immune reconstitution. A new Ig product had been prepared at the Blood Products laboratory in Elstree and we carried out the first clinical trial of this. Whilst it undoubtedly improved IgG levels and the general health of the patients receiving it in terms of reduced respiratory infections, it became apparent within the first few months that patients receiving this preparation had developed abnormal liver tests and it turned out eventually that the process by which the intravenous product was produced did not inactivate what was subsequently discovered to be hepatitis C. All patients receiving this blood product acquired hepatitis C.

Following this my interest in infections was ignited and I went on to a Wellcome Trust funded lectureship in infectious diseases at the Royal Free Hospital. After that I moved to the United States to the laboratory of Drs Joe Sodroski and William Haseltine where I worked on the basic molecular biology of the newly discovered HIV. We identified a critical functional RNA region within the virus which has been the focus of my research since then.

I returned from the United States in 1989 to a Senior Lecturer post in infectious diseases at St George’s Hospital in London and in 1991 moved to Cambridge first as University Lecturer and honorary consultant physician. I was promoted to Reader and then to a personal Chair in Infectious diseases in 2000. I am clinically active and see patients, both inpatients and outpatients, with a wide variety of infections including HIV.
Preamble

To put this in context it is worth beginning by noting that retroviruses had already been identified as human pathogens in the early years of the events described in the Penrose enquiry. The events narrative in the report is largely taken from the Preliminary Report and passages in italics are quotations from documents referred to in that report and those which have come to light since the Report was published.

In 1977 the Japanese identified a retrovirus, later called HTLV-1, as the causative agent of an unusual leukaemia and an unusual neurological disease. The virus itself was later isolated in the laboratory of Robert Gallo in 1981. It was understood that this virus could be transmitted by blood products and also vertically from mother to child; there was also evidence of sexual transmission.

Thus it is not surprising that when the first reports of a new and unusual illness began to appear in 1981 the concept of a pathogenic retrovirus as a possible disease causing agent in humans was very prominent and topical. In fact much of the research work that had been undertaken in isolating and characterising HTLV-1 was absolutely critical in facilitating the rapid discovery and identification of HIV. The discovery and usage of certain cell lines for isolating viruses and the discovery of growth factors for human cells were all essential prerequisites for retrovirus isolation. If HTLV-1 not been identified when it was then the identification of HIV might have been delayed by several years.

Although the discovery of HTLV-1 might have been expected to provide a significant alert to the medical community when HIV was being sought, and when it was subsequently identified as the cause of AIDS, it is important to remember that during the late 1970s and 1980s evidence was emerging that HTLV-1 only caused disease in a very small percentage of carriers. Around 95% of carriers of the virus appeared to have no symptoms at all despite being infected for many years. Thus the only exemplar of a pathogenic human retrovirus was one which was benign in most infected persons.

When HIV was identified as a lentivirus, and thus in a different virus group from HTLV-1, there were however animal models of lentiviral disease already known including Maedi-Visna in sheep and Equine infectious Anaemia Virus in horses (FIV in cats was only identified later). The name ‘lentivirus’ was given to this class of virus because of the slowness with which disease developed in infected animals. There was thus circumstantial evidence that lentiviruses were not excessively pathogenic. Indeed our own DNA contains many copies of other retroviruses which are relics of past infections and which, as far as we know, currently cause no disease other than extremely rare events where the retrovirus moves to another part of the DNA and disrupts a gene. Lentiviruses were by implication low pathogenicity organisms which, if they caused disease, did so after a long incubation period.

Against this ‘benign’ hypothesis must be set the fact that this was a new disease. It was not clear whether it was newly arrived in the human race or had been ‘reactivated’ by changes in human behaviour or if it was a zoonosis (a pathogen transmitted from another vertebrate species). Zoonoses are typically very severe infections in the early period in their new hosts often causing a high morbidity and mortality. Over a period of years (generations) pathogens and hosts commonly adapt to each and the disease they cause lessens in severity. For HIV which is a zoonoses from chimpanzees the pattern of causing a severe disease in the new host pertains, and it has been suggested that ‘lentivirus’ is an inappropriate description for a virus which is relatively rapidly pathogenic. However in the early 1980s there was no information that HIV was a zoonosis and HTLV-1 the only similar pathogen seemed to be a uniquely human infection.

Also against this backdrop the NANB hepatitis story was emerging. Here the risk of infection with an increasingly clearly defined transmissible agent was being elucidated but the consequences of infection and
disease appear to be a much less worrying or dangerous option for those people with haemophilia compared to the clear disadvantages of discontinuing treatment with clotting factor concentrates.

Apart from the virus which turned out to be hepatitis C, and HIV, another virus was under study at the time of the early years of this report. This was a superinfecting virus called hepatitis D or Delta (HDV). This had first been identified in 1977 and was a virus which in some fields was getting as much publicity as the above-mentioned agents. HDV could only infect people who were already infected with Hepatitis B (HBV) as HDV borrows the coat protein of HBV to transmit from cell to cell and person to person. It causes a more severe and rapidly progressive liver disease than HBV alone.

This group of newly identified viruses, discovered largely through the advances in technology, notably monoclonal antibodies and cloning, probably also diluted the perceived impact of AIDS initially as this was just one of a number of new human pathogens.

**Timeline of emerging infections since 1980**

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<td>Kaposi's sarcoma reported</td>
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<td>2013</td>
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The emergence of AIDS

(8.5) In June of 1981 the MMWR reported 5 cases of an unusual pneumonia, Pneumocystis carinii (now termed Pneumocystis jirovecii), in members of the gay population. (8.6) One month later the same Journal reported 26 cases of Kaposi's sarcoma, again appearing in the gay population. (8.7) By August 1981 there were a total of 70 cases of either KS or PCP all of which had appeared in the gay population.

There was speculation at the time that Cytomegalovirus or Hepatitis B, possibly a new more virulent strain of one or the other, might be responsible for this disease as all of the individuals were positive on testing for both of these viruses.
At the end of 1981 through the beginning of 1982 three prominent journals, the New England Journal of Medicine, the Lancet and the British Medical Journal all carried reports about this new syndrome and noted that not only were members of the gay population affected but also intravenous drug users.

In June of 1982 MMWR now reported a total of 355 individuals with this new immunodeficiency syndrome and the range of at risk populations had extended with 41 males and 13 females affected all of whom were heterosexual.

An MMWR report at the time suggests that street/recreational drugs used by the gay population may be the cause. Amyl Nitrite is a strong candidate.

In July of that same year (in MMWR) three individuals with haemophilia were identified in the US as having a very similar syndrome two of whom had died by August. The editorial suggested that blood product related transmission was a possibility. Wide publicity to relevant bodies in the US followed.

A memo from the Department of Health in July 1982 identifies the breaking news concerning the safety of American factor VIII and it is noted that about half of the factor VIII bought from commercial companies in the UK is imported from the USA.

In 1982 evidence of AIDS in Denmark in gay men shows that the disease can be acquired without visiting the USA. A case is also described in Italy.

In September 1982 a meeting of the UKHCDO comments ‘there was a remote possibility commercial products were involved ’ the minutes were not sent out until May of 1983.

SNBTS/HCDO met in January 1983. AIDS was mentioned. A letter and questionnaire had been sent to directors. In the meantime in December of 1982 transmission of the immunodeficiency syndrome by blood transfusion to a baby in California had been documented.

In January 1983 at a meeting to discuss NANB hepatitis it was noted that there had been ten haemophiliac cases of the newly named Acquired Immune Deficiency Syndrome-AIDS and five deaths. Overall there had been 800 cases of AIDS reported and there appeared to be a death rate of about 45%. One or two cases of AIDS had been documented in the UK.

Anecdotally this latter figure is likely to be an underestimate through lack of recognition and lack of a test. I personally saw two cases of what was in retrospect probably AIDS at this time. However there was no diagnostic test available. Thus the perceived rarity of the condition is understandable.

In the Lancet it was suggested that a blood-borne virus is a likely cause and even in the ‘popular’ scientific press (New Scientist) a blood-borne virus is suggested as a likely cause. The unification of cases in people with haemophilia and other risk groups was generally accepted by this time although it was noted (inexplicably at the time) that haemophilia population were not presenting with Kaposi’s sarcoma whereas this had been an early and ongoing feature of AIDS in gay men. This is now known to be transmitted by another virus HHV6 (Human herpes virus type 6) otherwise known as KSHV (Kaposi’s sarcoma Herpes virus) which was finally identified in 1994. Presumably KSHV was inactivated by blood product preparation techniques. Thus a difference in the pattern of disease presentation and probably contributed to the belief that there were indeed different aetiological agents behind the disease in patients with haemophilia and that seen in other patients with AIDS.

Based on epidemiology a blood borne virus was suggested as the cause in the New England Journal of Medicine in January 1983. This was echoed by the Lancet in January 1983. The US Public Health Service
issued blood donor screening guidelines in March 1983 stating that AIDS high risk groups should not donate blood. (8.23) US derived commercial Factor VIII concentrates were implicated in AIDS cases in Spain. The connection between AIDS and blood products, particularly commercial blood products from the US appears to be very strong.

Dr Spence Galbraith of the CDSC recommended in May 1983 that US derived blood product usage should be suspended pending investigation. From an individual whose approach to the situation was coloured by his infectious diseases background this is an understandable and rational suggestion.

(8.25) The response from the Haemophilia Society at the same time is aimed to reassure. The comments that ‘..AIDS...has not been proven to result from transmission of a specific agent in blood products.’ whilst true appears to ignore much circumstantial evidence and consensus opinion in the majority of doctors that a transmissible agent, almost certainly a virus, is the most likely aetiology.

The response at this stage urges caution because of the very severe effect this would have on supplies of factor VIII and factor IX to the UK patient population. Notably the Society requests a meeting with the government to include the concern about ‘not banning’ imported concentrates from the US.

In May of 1983 Dr Barre-Sinoussi and Prof Luc Montagnier in Paris publish that a retrovirus from a patient who had the Acquired Immune Deficiency Syndrome and it is termed lymphadenopathy associated virus (LAV). There is a strong suspicion that this is the virus which is responsible for AIDS. However there is some scepticism at this point particularly from the USA as US scientists have as yet been unable to identify any virus in these patients despite considerable efforts. In fact there are suggestions at the time that although the virus had been discovered some months previously publication had been delayed by adverse reviewers, reputedly from the US who were also hunting for the cause of AIDS.

(8.28-8.33) In the UK and at the SNBTS specifically there is discussion of a questionnaire for blood donors including details of those who might be at risk of transmitting the ‘agent’. There is a mixed reaction to this including decisions not to act on this and a concern about discouraging donors and offending people by questions about their sex lives. Doubt about the diagnosis of AIDS cases in the UK is expressed. The theory about ‘repeated infusion of foreign protein’ is raised (Lancet paper from Edinburgh group published). This theory however is in contrast to the implicit acceptance that a transmissible agent is likely to be involved, both from the suggestion of restricting categories of donors and also from the comment that ‘...it was important to assure staff that management were striving to deter possible carriers from donating blood’.

Up until now the haemophilia directors in the UK and in the SNBTS have had several conflicting pressures. Firstly there is the overwhelming success of factor concentrates in treating patients with haemophilia and the enormous reluctance for withdrawing or even threatening to withdraw these from a patient population whose lives had been immeasurably extended and improved in quality. The patient population included many who had been under treatment before concentrates and even before cryoprecipitate had been available and they would be extremely well aware of the highly undesirable consequences of returning to pre-cryoprecipitate days. To maintain the factor concentrate availabilities the directors knew that they had no option but to continue to source blood products from the USA. There was still some doubt as to whether the disease in patients with haemophilia was the same as in other groups and whether it was a virus or not. Any measure which reduced the availability or willingness of donors to give blood was also something which was a pervasive threat.

It is true that at that time society was considerably more homophobic than it is now. Homosexuality was much more rarely discussed than now and had an even greater stigma as representing some sort of deviant behaviour than it still has in the 21st-century. One of the early descriptions of AIDS called it the ‘gay plague’ and one proposed acronym before AIDS was adopted was ‘GRID’ gay related immunodeficiency. The scenario of a group of potential blood donors being given literature to read as they sat waiting to donate
blood and then one of them having to get up and leave and thus identify themselves as a high risk individual can easily be imagined. It could be envisaged that somebody would, rather than identify themselves, simply go ahead and give blood so that they did not appear to be a high risk individual.

Although AIDS itself clearly had a very bad prognosis there had not been enough longitudinal data to say what percentage of individuals who were infected with the putative agent actually went on to get disease. It might, as with some diseases for example HTLV-I, be a very small percentage who became ill, and the risk-benefit ratio of being infected versus not receiving clotting factor concentrates was not clear cut.

The period of May and June 1983 in the UK is a transitional one where an international consensus emerges that AIDS is caused by a virus that is transmissible within blood products. This was no doubt enhanced by the discovery of a putative agent in France together with the fact that AIDS has been diagnosed in a UK patient with haemophilia.

(8.34-8.36) By July of 1983 there have now been 16 US haemophilia patients diagnosed with AIDS of whom eight have died. Overall in the UK there have been 14 AIDS cases including one with haemophilia. In June the haemophilia directors decide on stratifying treatment for different patients to minimise risk to patients with mild disease by restricting usage of clotting factor concentrates sourced from the US in this group. However there appears to be no motivation in the UK (or the US) to withdraw concentrates for those patients with a high requirement. Despite informed discussion amongst the medical fraternity that the weight of evidence was in favour of a transmissible agent, there are mixed messages being presented to the public in terms of the risk with some comments designed to reassure appearing rather overly optimistic (8.42). There was also a disparity in the message being given by the UK health departments and the Scottish office (8.47). In September of 1983 the UK health departments issued a leaflet saying that AIDS can almost certainly be transmitted by blood and blood products at the same time the Scottish office press release states that no case of the disease has occurred in Scotland and that there was no conclusive proof that the disease could be transmitted by blood or blood products. (8.49) In England although information is available to blood donors about who should not give blood it is not being distributed to every donor. (8.50) In September 1982 there is failure to agree on leaflet distribution policy to donors in SNBTS discussions.

The period between June and October 1983 gives the appearance of some lack of coherence and organisation in the response to the possibility of blood product transmitted AIDS. There was also delay in providing information to potential blood donors in the form of leaflets; this appears to be largely due to the ongoing existence of differing opinions about the aetiology of AIDS and the actual threat posed by infection.

Whilst in retrospect the authorities appear to be indecisive, one has to recall again that nothing like HIV had been experienced by the human race within living memory and the scenario that unfolded in which an infection kills virtually 100% of people that it infects was completely unknown (and is still unique). Had one consulted any authoritative body of medical opinion at the time, even those who were experienced in infections, no one would have predicted either that pattern of disease or the high mortality rate.

There had been serious viral infections experienced in the 1960s and 1970s such as Lassa fever, Ebola fever and Marburg virus infection so the concept of virus infections causing high mortality was familiar but only in the context of viruses which were transmitted rapidly person-to-person and where infection was accompanied by a dramatically acute severe disease swiftly followed by death. HIV portrayed a completely unprecedented paradigm whereby an individual could be seemingly completely well for five or 10 years, or even more, whilst being highly infectious and carrying an agent which was certain to kill him or her. No other infectious agent has killed as high a percentage of people that it infects as does HIV. Even severe infections which cause pandemics like influenza may be associated with a death rate of 5% or less and only
in conditions like Ebola virus infection would one see mortality rates of 80% or more. The haemophilia doctors were thus balancing a known good (clotting factors) against an, at the time, inconceivably bad evil (~100% fatal transmissible virus).

Thus although the MRC meeting in October 1983 noted a probable 6 month doubling time for AIDS cases and that AIDS had a high mortality and a long ‘incubation time’, the percentage of individuals infected with the unidentified agent was unknown and hence the mortality rate of infection could not be calculated and any estimates would very probably have been much lower than turned out to be the case.

\((8.51-8.54)\) A variety of meetings are scheduled in the UK in October 1983 including groups such as the central blood laboratories authority and the MRC. These together with other groups such as the WHO appear to be focused mainly on fact-finding exercises. Also in October 1983 \((8.62)\) there appears to be a slight disparity in opinion between the haemophilia doctors and patients represented by comments in a meeting describing a scenario in which patients had started to refuse to take up commercial factor VIII concentrate because of the AIDS scare.

This should not be over interpreted as being representative of the patients being necessarily better informed and making better judgements than the medical profession. The general public is often very much influenced by media coverage of events particularly epidemics and other infectious episodes. Perhaps however it may reflect the fact that the previous few months had been characterised by a relative paucity of information from the professionals to the patients and some mixed messages. Even this may be overstating the case since with the best available information the general public may often believe the sensationalism of the media over the balanced reassurance of professional organisations. Recent experience with Herpes, Toxic shock syndrome, flu, SARS, bird ‘flu, recent bioterrorism threats etc. demonstrate the extreme anxiety producing effect of a new infection appearing in the human race.

In October 1983 the WHO suggests that a C type retrovirus may be responsible for AIDS and note the very poor prognosis of those infected. At a subsequent WHO conference \((8.65)\) it is noted that the length of the incubation period was causing underestimates of the frequency of infection and that case fatality rate was high. It is recommended that patients with haemophilia and their doctors should be informed of the potential hazards of Factor VIII and IX products including the risks related to AIDS. \((8.66)\) Voluntary self exclusion of donors is thought to be the only approach and the Haemophilia Society publication states ‘...haemophiliacs have no reason to be worried about using commercial concentrates.’

This is perhaps over optimistic under the circumstances and presumably represents a strong desire to reassure people who have little choice but use concentrates.

A mitigating comment might be that unless there is a test which clearly distinguishes infected from uninfected donors there is no absolutely safe way of excluding infection from the products. Conceivably one can use surrogate markers and the US had used repetitive abnormal elevation of liver enzymes as one such surrogate. However agreeing that surrogate markers should be used, which was extensively discussed as a way to limit infectivity of concentrates, is also implicitly an admission that the concentrates which have not been screened by surrogate markers may be from donors who have a high chance of being unsafe.
By February of 1984 there have been 21 haemophilia patients who have AIDS and 31 in whom it was acquired by blood transfusion. Heat treatment of commercial concentrates is in place for some products by early 1984 but they were not licensed in the UK. The SHHD (May 1884) opines that SNBTS not pursuing heat treatment would be difficult to defend.

In April of 1984 Robert Gallo's lab claims to have identified the virus that causes AIDS. Later analysis shows that this is the same virus which they have obtained as a sample from the laboratory of Prof Montagnier this discovery however is hailed as being the definitive evidence that the virus, initially termed HTLV III, is the cause of AIDS. The evidence is based not simply an identification of the virus but also on the presence of antibodies to the virus in the serum of every patient with the syndrome tested and the absence of the antibody from otherwise healthy control subjects.

Despite some ongoing suggestion that this was not the cause of AIDS and that the disease in the haemophilia population might be different the tide of opinion at this point swung almost completely to acceptance that HTLV-III, later called HIV was the causative agent of AIDS. The remainder of 1984 is marked by publicity and some controversy about development and choice of HIV testing kits. Detection of LAV in patients with haemophilia from Denmark in July 1984 was a landmark in showing that the virus was present in European patients with haemophilia treated with commercial factor concentrates.

In October of 1984 a letter from Dr Craske indicates that NHS factor VIII contains HTLV III. It is suggested at that stage that the number and proportion of patients who contracted the infection and went on to develop AIDS would be the order of 1 in 500. In November a communication from Dr Ludlam confirms that factor VIII from the Scottish National blood transfusion service is HIV positive. By December there have now been 6000 cases of AIDS described including 52 recipients of factor VIII of whom 30 had died.

In December 1984 the subject of heat treatment becomes prominent and plans are made to heat treat all NHS and SNBTS products. Throughout 1985 much discussion is given to the introduction of testing of donors for the presence of HIV. A number of American testing kits are available but ultimately a test developed by Wellcome is introduced in October 1985.

One further reflection is merited about testing for HTLV-III/HIV. The tests were all based on detecting antibodies to the virus as evidence of infection. Similarly when a blood donation was said to be ‘infected’ it was because of the presence of such antibodies. Antibodies in many illnesses are evidence that the body has mounted a successful immune response and has cleared the virus and they remain as protection against a future challenge (which is their ultimate purpose). There was and in some cases still is a belief that antibodies could provide such protection in HIV infection. It has become clear over the years that the virus is so variable that it can change its proteins and make new ones which are no longer recognised by the antibodies that are present. The idea of a ‘broad neutralising’ antibody being produced by a vaccine is still pursued despite continued evidence that such a thing, if it exists at all, does not provide long term protection against all HIV variants. However in the early days of HIV, antibodies were felt to be useful. In fact there was a reasonably widespread belief that those patients with haemophilia in whom antibodies were detected were actually better off than those who did not have them. It was assumed that many more people might be infected and that those without antibodies would ultimately do worse.
The faith in antibodies being protective led to several groups giving treatment to an infected person of plasma from another infected person. The plasma was heat treated to inactivate any residual virus. It was felt that this boost of additional antibodies would help control the virus but there was never any good evidence that this was efficacious.

The time between the acceptance that the virus HTLV-III/HIV was the causative agent of AIDS and the institution of donor testing and heat treatment of concentrates seems prolonged. Even at this stage it was not clear what proportion of those patients infected with HIV would go on to develop AIDS as there had not been a long enough period to study the natural history. It was not until between 1985 and 1988 that the evidence accumulated slowly that virtually 100% of infections would progress to the fatal end stage condition. Nevertheless there are suggestions that funding to progress the development of tests was not fast. For those already infected there was little that could be done, as drugs to treat HIV were introduced only in 1987 and highly active antiretroviral therapy which was the first effective treatment did not come in until the late 1990s.

Years in which new drugs for HIV were introduced.

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Thus for the individuals infected during the early years whose cases have prompted the Penrose enquiry testing and donor screening and treatment are not strictly pertinent. It is the case however that any delay in introducing testing and screening will have led to a risk of further infections in other individuals.

Additional comments

Comment on Chapter 4 – witness statements

Several important issues emerge here. There is a recurrence of the theme that doctors did not tell the patients that they had been tested and on occasions appeared to request consent for a test when the result was already known. The amount of information given to individual who had contracted a blood borne virus was variable in quality and in who gave the information and the understandability of the information given.

In 2011 this sort of approach would be unthinkable. Patient empowerment has moved on hugely, and diagnostic tests for diseases with major influences on the patient’s life would now routinely only be done with discussion and consent of the patient. This is a relatively recent phenomenon which was to a large extent triggered by the emergence of HIV and the profound implications that being ‘HIV positive’ carried in the early years of the epidemic. Doctors have for many years done blood tests without explaining the exact ramifications of every possible result. Pregnant women had for many years (and still are) tested for syphilis at antenatal appointments to identify possible transmission to the fetus. This had been done without formal consent. The proactive nature of the gay HIV positive population was in large part responsible for the new
approach of giving detailed information to patients and formalising consent procedures. This was in part because individuals would expect to live with the virus for a number of years but the level of infectiousness to others was very unclear initially and there was an enormous stigma attached to the label, apart from major ramifications on issues like insurance, house purchase etc. The case of Ryan White the boy with haemophilia in the US who in 1984, due to protests from parents of children in his class was actually expelled from school exemplifies this.

In the 1980s there was still a detectable paternalistic approach to medicine which was largely accepted by patients and doctors alike as being the norm. In haemophilia this must have been much more overt. The doctor wields huge ‘power’ (literally of life and death) over the patient who relies on his/her distribution of clotting factors, and also over their parents. Thus any patient or parent of a child with haemophilia would naturally seek advice from the most respected ‘life saving’ source of opinion within medicine. The stigma of a positive HIV test was such that in Birmingham (I am informed by a doctor who worked in the haematology department there at the time) in the early 1980s parents of children with haemophilia agreed that their children should be tested for HIV but that the result should not be given to the family. This allowed the doctor to carry out any appropriate treatment whilst absolving the patient and family from any possibility of accusation of concealing the truth about the patient’s status.

Suggested corrections to text

1.19 aplastic anaemia not plastic anaemia

1.20 In addition, other white blood cells (lymphocytes) modulate the immune function: that is, they use different ways of dealing with something that is foreign.

Suggested replacement:-

In addition, other white blood cells (lymphocytes) modulate immune function. Some produce antibodies, others attack infected cells and others control these responses.

1.22 (ii) immunoglobulins (Ig) needed in blood for a normal immune reaction to foreign bodies; and (iii) albumin, a normal protein in the blood which helps to build muscle tissue.

Suggested replacement:-

ii) immunoglobulins (Ig or antibodies) needed for a normal immune reaction to infections and foreign material; and (iii) albumin, a normal protein in the blood which helps to carry other molecules around the body and helps regulates the consistency and volume of the blood.

Suggested rewording of section 2.51-2.67

The references can remain the same as in the current version.
Biology of HIV

2.51 HIV can only replicate (make new copies of itself) inside human cells. The process typically begins when an HIV particle attaches itself to the surface of a cell bearing the protein known as CD4 on its surface. This can be one of the protective cells in the blood that ingest infectious agents known as macrophages or a particular type of lymphocyte the T-helper lymphocyte (a type of white blood cell that plays a crucial role in maintaining the function of the human immune system). After attaching to the cell, the virus then enters the cell and converts its RNA into DNA by the use of an enzyme called reverse transcriptase. The viral DNA is transported to the cell’s nucleus, where it is spliced into the human DNA. Once integrated into a cell, the virus may begin replicating immediately or may lie dormant within the infected cell for months, or even years.

2.52 When the cell becomes activated, however, it treats the HIV genes within it in much the same way as its own (human) genes. The result is that new HIV viral particles are formed and released, thereby starting the replication process all over again. HIV can replicate rapidly with several billion new viruses made every day in an infected person.

2.53 During replication HIV also mutates and evolves. Reverse transcriptase (by which viral RNA is converted into DNA) often makes random mistakes in the transcription of viral RNA into DNA. As a result, new types or strains of HIV (with slightly different DNA) develop in a person infected with HIV. Because of changes in the DNA the proteins of the virus will be different, making it harder for that person’s already compromised immune system to ‘recognise’ or to respond to and deal with the virus.

2.54 Every day, the virus destroys billions of CD4 T-helper lymphocyte cells in the infected person, eventually overwhelming the immune system’s capacity to regenerate itself or to fight infection.

Transmission

2.55 HIV is found in the blood, semen or vaginal fluid of those infected with the virus. It cannot survive for very long outside the body. The main modes of transmission are sexual intercourse, IV drug use (through the use of shared, contaminated needles), receiving a transfusion of infected blood or blood products and perinatally (i.e. from infected mothers to their children at or around the time of birth, from infected maternal blood or through breast feeding).

Symptoms and pathology

2.56 In the first few weeks after infection with HIV most people will experience few if any symptoms. Within a month or two after infection, individuals may experience a flu-like illness, including fever, headache, tiredness and enlarged lymph nodes in the neck and groin area. The symptoms usually disappear within a week to a month after their onset and are often mistaken for another viral infection such as glandular fever or influenza (flu). During this period, people are highly infectious. There then follows a period during which the body’s immune system fights the virus and the disease remains clinically inapparent (clinically latent).

2.57 Over time, however, the immune system eventually deteriorates to the point at which it is unable to fight off other infections. The rate of progression to symptomatic disease (i.e. AIDS) varies greatly from person to person and may take many years. When the disease was first reported it was estimated that only a minority of patients with HIV would go on to develop AIDS. It is now known, however, that, if untreated, the vast majority of patients who contract HIV are likely to go on to develop secondary ‘opportunistic’ infections or tumours which, in the absence of treatment, are likely eventually to result in death.
2.58 The secondary infections that may develop include a variety of fungal, viral and bacterial infections of the mucous membranes and skin. However, a type of pneumonia, caused by an infection called Pneumocystis Jirovecii (previously known as Pneumocystis Carinii — and still often abbreviated to PCP), remains the most common life-threatening secondary infection in patients who progress from chronic HIV infection to AIDS. In addition, due to a failure of the body’s ‘immune surveillance’ of possible cancer cells, secondary cancers may develop over time, including Kaposi’s sarcoma, non-Hodgkin’s lymphoma and primary cerebral lymphoma.

2.59 The disease may also affect the nervous system with the development of secondary infections such as cerebral toxoplasmosis (leading to the formation of abscesses in the brain), or directly as in HIV encephalopathy. Patients may also suffer psychiatric disorders including depression.

2.60 Eventually, patients develop end-stage disease when they have little immunity and death becomes inevitable from one or more of the above or related conditions.

Testing

2.61 When an individual becomes infected with HIV, antibodies to the virus are produced, but unlike the case in most other infections, these antibodies have little or no ability to neutralise the virus. The antibodies are, however, used in laboratory tests as a marker for the presence of HIV. The antibodies include enzyme-linked immunosorbent assay (ELISA) and Western blot tests. Detectable antibodies are usually produced within two to six weeks of infection, although sometimes the period may be up to three months. Accordingly, the ELISA and Western blot laboratory tests may not detect HIV antibodies in an individual who has been infected very recently with HIV (i.e. up to three months after infection). The change to a state where antibodies are detectable is known as ‘seroconversion’.

2.62 PCR tests detect the presence of HIV itself, through detection of its genetic material, rather than the presence of antibodies to HIV. PCR testing may be undertaken to detect the presence of the virus before as well as after seroconversion, and therefore may be used in the ‘window’ between the time the individual acquired HIV infection and seroconversion (the appearance of anti-HIV antibodies in the blood).

Treatment

2.63 In the early 1980s, when the HIV/AIDS epidemic began, after an initial relatively asymptomatic period lasting for a variable number of years, people were unlikely to live longer than a few years from the development of AIDS. Today, the prognosis for those infected with HIV is much better as a result of the availability of antiretroviral medication. There are five main groups of antiretroviral drugs presently available to treat the disease, each of which attacks the virus in different ways. If only one drug was taken, HIV would quickly become resistant to it and the drug would stop being effective. Therefore, two or more classes of antiretroviral drugs are prescribed at the same time, thereby reducing the rate at which resistance will develop and making treatment more effective in the long term.

2.64 These treatments do not cure people of HIV or AIDS and the virus is not completely eliminated from the body. Rather, the drugs suppress the virus either by stopping the virus from replicating itself, or by preventing it from binding to or entering human immune cells. Suppression of the amount of HIV in the body stops further weakening of the immune system and allows it to recover from any damage that HIV might already have caused, thus allowing people infected with HIV to lead longer and healthier lives.

2.65 People undergoing treatment can still transmit the virus, however, and must continuously take antiretroviral drugs in order to maintain their health. There is currently no vaccine to prevent HIV infection nor is there a cure for HIV/AIDS.
Numbers of people affected

2.66 In 2006, the 25th anniversary of the emergence of AIDS in Western countries, there were close to 40 million people around the world living with HIV and over 20 million people had died. In the UK since 1996, there have been around 30,000 HIV diagnoses. As at May 2009, as reported to the National Haemophilia Database, 1382 patients with bleeding disorders in the UK were known to have been infected with HIV. Of those, 72 were registered to Scottish centres. It has been reported that 12 patients in Scotland contracted HIV as a result of a blood transfusion. Other data suggest that the cumulative total of HIV-infected haemophilia patients registered in Scotland to 30 September 1999 was 87. Resolution of a more precise figure will have to await the final outcome of the Inquiry.

Caution

2.67 It has to be emphasised that the information contained in this chapter reflects the state of knowledge current at the date of publication of this preliminary report. Almost none of this would have been known before 1991.

Miscellaneous comment

Chapter 6

6.114 replace 'cytomegala' with 'cytomegalovirus'