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Australian Red Cross
BLOOD SERVICE

Provided in Sydney
7/4/04

7 April 2004

Mr Elton Humphries
Secretary
Community Affairs References Committee
The Senate
Parliament House
Canberra ACT 2600

Dear Mr Humphries,

I write to inform you of a typing error that we have discovered in the original written submission presented to the Senate Community Affairs Reference Committee in December on 2003.

The error occurs on page 31, section 3.4, paragraph 5 beginning "Initially, donors...".

The penultimate sentence incorrectly includes a reference to "Factor VIII", rather than "Factor VII". The sentence should therefore have read:

"The reason for this was that the plasma fractionation process was known to inactivate the NANBH agent in all plasma products except Prothrombinex and **Factor VII**."

We would be grateful if you could ensure that this error is noted and corrected in the document you have on record for reference. Should you have any comments or questions please contact myself (on 02 9229 4426 or 0412 717 250) or Julia Herbert (on 02 9229 4455).

Yours sincerely,

Anne Fletcher

Dr Anne Fletcher
Project Coordinator
Australian Red Cross Blood Service

Australian Red Cross
BLOOD SERVICE

Senate Community Affairs References Committee
Inquiry Into Hepatitis C And Blood Supply In Australia

Submission prepared by the Australian Red Cross Blood Service

December 2003

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SUMMARY

Hepatitis C is an infectious illness causing inflammation of the liver. The disease is transmitted through infected blood-to-blood contact. Hepatitis C is unusual in that up to 25% of those who develop hepatitis C will clear the infection and suffer no complications. Of the remaining 75% of people diagnosed with hepatitis C the large majority will remain asymptomatic with approximately 7% developing cirrhosis of the liver within 20 years of infection.

The Australian Red Cross Blood Service (ARCBS) is the sole collector and distributor of blood products within Australia, and in its position as guardian of the nation's blood stocks, understands the misfortune of anyone acquiring hepatitis C through a blood transfusion. ARCBS acknowledges the physical and psychological impact hepatitis C can have on the individual and their family.

In various forms, the Red Cross, as part of an international humanitarian movement, has been supported by generous Australian volunteer donors of blood since 1929 in the provision of safe and adequate supply of blood. The service today is an integral part of the nation's social fabric, supporting its health and wellbeing. Approximately 4% of the adult Australian population makes regular blood donations. As an operating Division of the Australian Red Cross Society, the Blood Service has enabled Australia to access self-sufficient blood stocks for almost all periods of its existence. In doing so, its operations and decisions have been conducted in close partnership with successive State, Territory and Federal Governments.

From the one million donations per year, over 700,000 fresh blood products are issued to approximately 100,000 patients annually, and a further 100,000 patients benefit from plasma products every year. Thousands of blood donations are needed each week in Australia. Many different people need blood - from premature babies to the elderly, from people with life-threatening illnesses to accident victims.

In 1975, a disease named "Non-A, non-B hepatitis" (NANBH) was described to account for hepatitis, which was not due to either hepatitis A or B. For many years the condition was a challenge to researchers and the medical community internationally as it was not known what caused the condition, or whether it was the result of a single specific agent or several agents. The disease was thought by the medical fraternity for most of the 1970s and 1980s to be generally benign with few complications as most people with it were without symptoms and rarely became seriously ill.

In May 1988, the international medical community recognised non-A, non-B hepatitis as being caused by one specific agent – the hepatitis C virus. By 1989, it was confirmed as a virus capable of transmission through blood transfusions. It was at this time, in late 1989, that Australia also identified its first confirmed post-transfusion cases when the first hepatitis C test kits (research only) were used in a Red Cross post-transfusion study.

In February 1990, the first commercial specific screening tests became available and were immediately adopted nationally to protect against the spread of hepatitis C. Australia was a world leader in this regard, being the second nation after Japan to commence this blood screening process for hepatitis C. The development of a specific test for hepatitis C dramatically reduced the problem of post-transfusion hepatitis C in Australia.

The question of the value of a surrogate or non-specific test for non-A, non-B hepatitis prior to 1990 forms a major focus of this inquiry. Surrogate tests, are no substitute for a specific test as they lack sensitivity and specificity, meaning that results can be inaccurate or inconclusive. For NANBH, the two surrogate tests proposed were ALT and anti-core. Few countries, other than the US, utilised these surrogate tests.

Australian management and decision making about blood and its safety has been based on knowledge available at the time, and has been in line with best international practice.

The Australian policy relating to the use of surrogate testing was in accordance with advice from the Council of Europe, Committee of Experts in Blood Transfusion and Immunohematology. This highlighted the need for each country to establish the underlying prevalence rate of post-transfusion NANBH and to then determine the potential contribution of surrogate testing in its own population. It was during the completion of a major Australian prevalence study on post-transfusion hepatitis commenced at this time that hepatitis C was properly identified.

Even today, it is difficult to quantify the value of surrogate tests or the impact on the blood supply of their introduction. The American Association of Blood Banks' *Technical Manual*, 1996, concluded when assessing the use of surrogate testing in the US, that the merit of surrogate testing for hepatitis C today remains inconclusive. Additionally, the decision relating to surrogate testing has recently been reviewed by *The Expert Advisory Group on Hepatitis C and Plasma in 1990* who commented that it would be counterproductive to introduce surrogate testing in countries like Australia where the prevalence of post-transfusion hepatitis C was low.

Justice Krever was appointed in 1993 to conduct an Inquiry into the Canadian blood supply with respect to HIV. He warned against judging actions of the past based on the knowledge of the present. A minor focus of the Krever Inquiry was hepatitis C. In relation to hepatitis C, there are major differences between Canada and Australia. The key being that Australia had a much lower rate of post-transfusion hepatitis C than Canada or the US.

Assumptions and/or inferences about the Red Cross cannot be drawn from the examination of a different system operating in another jurisdiction. The findings of the Krever Commission and the recent criminal charges against the Canadian Red Cross are not relevant in any way to the Australian situation.

In Australia, there has been under-reporting of post-transfusion hepatitis C from hospitals and medical practitioners to ARCBS. There is no formal national reporting system to systematically capture all adverse events (including infections) following transfusion and therefore it is difficult to ascertain the numbers of those affected. The ARCBS from its own resources has estimated that there may be 2,050 individuals living in Australia who may have been infected with post-transfusion hepatitis. Additionally, it could be estimated that approximately 1,350 living patients with haemophilia

Summary of introduction of various tests for hepatitis C in Australia:

February 1990 – Australia started routine screening of all blood donations for hepatitis C virus in Australia and was one of the first countries in the world to do so using the first licensed testing kits available.

May 1991 – A second generation testing kit using a more sensitive detection system became available and was introduced immediately. Successive generation tests have been introduced, keeping pace with emerging technology.

June 2000 – The safety of the blood supply was taken to a new dimension with the introduction of Nucleic Acid Testing (NAT), which identifies the presence of genetic material from the hepatitis C virus. Again, Australia was one of the first countries to introduce NAT technology for routine screening of all blood donations.

may be infected. To put these figures into context, in the past twenty years Blood Services in Australia have issued in excess of thirty million blood products.

The ARCBS has worked with patients, donors, health professionals and organisations in assisting, counselling and offering referrals to blood transfusion recipients who have contracted hepatitis C. Through this experience, the ARCBS has learnt of the impact this disease can have on the person and their family. In accordance with our mission and guiding principles ARCBS remains ready and willing to continue to assist Australian patients within the scope of our agreements with governments.

The ARCBS, like all in the health sector, strives to reduce risks wherever possible. However, all medical procedures involve risk and there have been, and continues to be risk in blood therapy. Blood is a biological material and it is never possible to say that there are no associated risks; accordingly there is inherently a balance of risks and benefits involved in its use.

The current risk of receiving a hepatitis C infection through blood is less than 1 in 3 million. The choice of accepting this level of risk must be weighed against the possibly life threatening consequences of not receiving a transfusion.

The ARCBS extends its sympathy and understanding to each Australian who might have acquired post-transfusion hepatitis C. It particularly extends its understanding to those who have or will develop symptoms and complications. It is committed to continuing to provide services and to working with the Australian and State and Territory Governments to improve options and remedies available to those in need.

ARCBS also thanks the Australian public for continuing to voluntarily donate blood in order to ensure future access to secure National blood stocks.

By way of recommendation, the ARCBS proposes the Inquiry address as part of its findings measures to:

- Improve community education and awareness of hepatitis C and its causes;
- Ensure appropriate personal, medical, and social support services are made available to those suffering complications as a result of post-transfusion hepatitis C;
- Support research into certain aspects of hepatitis C including epidemiological studies;
- Enable doctors treating patients with hemophilia to be able to prescribe recombinant Factors VIII or IX where it is the most appropriate product for the patient;
- Expedite consideration of new anti-hepatitis C drugs for Australian patients;
- Support the timely introduction of a national government-sponsored haemovigilance system in Australia.

GLOSSARY

acute hepatitis	A short-lasting (loss of appetite, nausea, malaise, sometimes jaundice) illness associated with elevated liver function tests such as ALT.
albumin	Albumin is the major protein that circulates in the bloodstream. It is synthesised by the liver and secreted into the blood. Albumin levels can be low in conditions like chronic liver disease, malnutrition and kidney diseases.
alanine transaminase (ALT)	ALT is a liver function test used to determine whether a patient has liver damage. Elevated ALT levels may be a sign of liver inflammation i.e. hepatitis; it does not necessarily indicate the presence of a virus. Other causes of elevated ALT are obesity and alcohol ingestion.
aspartase transaminase (AST)	AST is another liver function test, which is also used to determine whether a patient has liver damage.
antibody	A protein produced by the body as part of the body's immune response (see below). A reactive antibody test for hepatitis C virus means that the person may have at some stage been infected with the virus. It does not necessarily indicate present infection. Depending on the infectious agent, antibodies may be effective at eliminating a foreign invader (e.g. measles virus) or less effective (e.g. HIV, hepatitis B or hepatitis C virus infection).
antibody against surface antigen (Anti-HBs)	Hepatitis B surface antigen (HBsAg) is present in currently infected individuals with hepatitis B. Anti-HBs (Antibody to HBsAg) is present both in those who have been immunised against hepatitis B, and those who have recovered from acute infection and are now immune.
antibody to hepatitis B core antigen (Anti-HBc)	Hepatitis B core antigen (HBcAg) is detectable in the liver (but not in the peripheral blood) of individuals infected with hepatitis B virus. Antibody to hepatitis B core antigen is a useful test indicating that an individual has had contact with hepatitis B virus at some stage in life. This includes people currently infected and those who have had hepatitis B in the past.
"anti-core"/ anti-HBc	Term used in the ARCBS submission for antibody to hepatitis B core antigen.
antigen	A foreign substance that promotes the formation of antibody, as a part of the body's immune response. Tests that detect the hepatitis C virus antigen offer a more direct test for the presence of virus (in contrast to the indirect method of detection of antibodies formed by the body in response to the protein). The formation of antibodies can take many weeks to develop in a hepatitis C virus infected individual; so these tests are more useful in picking up infections earlier than antibody tests.
anti-HBc	Antibodies to hepatitis B core antigen. The hepatitis B core antibody test detects antibodies produced by the body in response to infection with the hepatitis B virus. A positive result means only that some one has been previously exposed to hepatitis B but does not indicate if the person is still infectious. To actually be infectious for hepatitis B, someone has to have a positive hepatitis B surface antigen (HBsAg) test as well.
anti-haemophilic factor (AHF)	An older form of Factor VIII concentrate used in the eighties to treat haemophilia. Nowadays, it is replaced by Biostate for the management of Haemophilia A.
apheresis	The collection procedure which separates whole blood into its components and returns the remaining components that do not need to be collected, to the donor. This term includes collection of plasma, platelets and red cells.
asymptomatic	Absence of any noticeable symptoms.
ARCBS	Australian Red Cross Blood Service, an operating division of the Australian Red Cross Society, established in 1996.
Australia antigen	See HBsAg.
autologous transfusions	Transfusions using the patient's own blood for their own use e.g. collected prior to planned surgery.
background rate (of infection)	In this submission, this refers to the unexplained incidence of post-transfusion hepatitis in a control group i.e. hospitalised patients who have not been transfused. This was observed in up to 3.3% of the controls in the US Transfusion-Transmitted Virus study. This is most likely due to hospital-acquired infection.

Biological False Positive (BFP)	A non-specific reaction in a laboratory test, which is noted in a small percentage of the healthy general population. They do not indicate the presence of an infection.
Blood Transfusion Service	The State and Territory based services operated by each division of the Australian Red Cross Society prior to 1997.
carriers/carrier state	Carriers of infectious diseases are individuals who appear to be free of the symptoms of the disease but are infectious and are able to transmit the disease to others.
chronic hepatitis	Hepatitis present for 6 months or more, often defined by raised liver function tests.
cirrhosis	Irreversible scarring of the liver that may occur with chronic hepatitis, such as with hepatitis C. However, there are many other non-infectious causes of cirrhosis e.g. chronic alcohol overuse.
clinical course	The sequence of symptoms associated with the course of a disease e.g. jaundice in acute hepatitis followed by recovery within 3-6 months in most cases.
clotting factors mentioned in submission	Factors II, VII, VIII (absent in Haemophilia A), IX (absent in Haemophilia B).
co-factors	Other factors such as alcohol, age, other diseases, which may contribute to the progression of a disease.
concentrate	A component or product where the volume has been reduced.
control group	Often in a study where the effect of a particular intervention is studied e.g. the risk of acquiring NANBH by receiving a blood transfusion, the patients are divided into two groups: the study group who receive the transfusion and the control group who do not.
components (of blood)	What is generated from a blood donation including red cells, platelets, and plasma but excluding products manufactured by CSL.
confirmatory tests	Screening tests are never 100% accurate, so they generally need to be verified with additional tests. These additional, generally more specific, tests are sometimes referred to as confirmatory tests where they can give a definitive result. The tests are often more correctly referred to as “supplemental” to indicate that although assisting to establish the laboratory diagnosis, they too are not necessarily always definitive.
core (viral)	The central part of a virus.
core protein	The protein component of the core of the virus.
Commonwealth Serum Laboratories	The name, until 1994, of the Australian government authority responsible for plasma fractionation in Australia.
C S L Limited	The name of the corporation responsible for plasma fractionation listed on the Australian Stock Exchange on 30 May 1994.
cryoprecipitate	A concentrate of plasma containing Factor VIII made by freeze thawing of individual plasma donations.
cut-off level	The level, which separates a positive from a negative result.
Cytomegalovirus (CMV)	A virus, which can be transmitted by blood transfusion. It can also cause a disease similar to Glandular Fever (infectious mononucleosis) and is found commonly in bodily secretions.
delta agent	A unique RNA virus, which can cause acute or chronic hepatitis. It only affects individuals co-infected with hepatitis B.
donor deferral (temporary or permanent)	Action taken on the individual donor whereby they are rejected: a) if they fail to qualify e.g. major illness in the past or carrier of hepatitis B, or b) if their screening tests are reactive and confirmed positive. Donors can be deferred temporarily e.g. if they are found to be anaemic on that particular visit or permanently e.g. if they have a positive viral screening test result.
donor selection	Process whereby a set of criteria are instituted mainly to try and reduce the likelihood of an at-risk donor inadvertently being admitted into the donor pool. Other general criteria are used to ensure the donor’s health is not adversely affected by the donation of his/her blood.

Donor Triggered Lookback (DTLB)	A donor is a person who has given a blood donation. This is a process of going back through records of previous donations of donors identified as hepatitis C reactive in screening tests from 1990. The ARCBS examines the earlier donations made by the donor and investigates the outcome of any fresh blood components made from the blood. In cases where blood components were transfused, the ARCBS contacts the hospitals concerned and through them the recipients are recalled and tested for hepatitis C.
ELISA/EIA	Enzyme-linked immunosorbent assay (ELISA), or Enzyme Immunoassay (EIA) is an immunchemical assay used to detect the presence of antigen or antibody, indicated by a chemical reaction driving a colour change in a reaction mixture. One of the types of test routinely used to detect hepatitis C virus antibodies.
epidemiology	Scientific discipline studying the incidence, distribution, and control of disease in a population. Includes the study of factors affecting the progress of an illness, and, in the case of many chronic diseases, their natural history.
Epstein-Barr Virus (EBV)	A Herpes virus, which can very rarely be transmitted by blood transfusion. It is also a cause of Glandular Fever (infectious mononucleosis).
Factor II (two)	A clotting factor which forms part of Prothrombinex, (a product no longer in use) for the management of blood clotting disorders.
Factor VII (seven)	A more specialised product, this is a clotting factor used less commonly than Factors VIII and IX.
Factor VIII (eight)	A clotting factor that assists in the formation of blood clots. Males who are Haemophilia A patients lack this factor.
Factor IX (nine)	Haemophilia B (also known as Christmas Disease) results from lack of this clotting factor.
false negative	A negative test result, when it should read positive. The test may be very specific in ruling out false positives, but may miss some true positives. The more sensitive a test is, the fewer the false negatives i.e. the less likely it is to miss real positive cases. There is usually a trade-off (inverse relationship) between sensitivity and specificity.
false positive	A positive test result when it should read negative. The test may be sensitive in detecting positive results, but includes some true negatives. The more specific a test the fewer the false positives, and the better the test is at excluding real negative cases.
fractionation	A process for separating blood plasma into valuable blood products by separating plasma proteins. Fractionation involves changing the conditions of pooled plasma (e.g. the temperature or the acidity) so that proteins that are normally dissolved in the plasma become insoluble, forming large clumps, called precipitate. In Australia this is performed by CSL.
generation of test	A term used to describe improvements seen in diagnostic assays. In Australia, first generation tests for hepatitis C were introduced in 1990, second generation in 1991 and third generation in 1994. Tests for hepatitis C virus antibodies have become progressively more sensitive (i.e. fewer false negatives and less likely to miss real positive cases) and more specific (i.e. fewer false positives and better at excluding real negative cases) with time.
Haemophilia	An inherited clotting disorder where one essential clotting factor is either missing or not working properly. People with haemophilia bleed mostly internally into joints and muscles. The female acts as a carrier for the gene and the males are affected by the symptoms of the disease, thus needing clotting factors their entire life. There are two major types of haemophilia: Haemophilia A (Factor VIII missing) and Haemophilia B (Factor IX missing).
haemovigilance	Systems, which collect data in a central (usually government) agency on all adverse outcomes (infectious and non-infectious) from transfusion to investigate and determine the cause. These systems keep information about all forms of complications associated with blood transfusion.
HBsAg	Hepatitis B surface antigen, also referred to as “surface antigen” and formerly as “Australia antigen”, is a part of the hepatitis B virus. The discovery of HBsAg allowed the development of tests to screen blood donors for HBV. A positive HBsAg test indicates that an individual is infectious.
heat-treated plasma products	Treatment with heat at 60 degrees C for 72 hours to remove virus. Heat-treated products were first used in the early eighties. See also “super heat-treated (plasma products)”.

hepatitis	Hepatitis means inflammation of the liver. It can result from overuse of alcohol, reaction to certain medications or - infection by bacteria or viruses.
hepatitis A	A form of viral hepatitis mainly transmitted via contaminated food e.g. oysters or water. It usually causes a relatively acute illness with jaundice, and recovery is usual without chronic infection or a long-term carrier state.
hepatitis B	A type of viral hepatitis, spread by contact with infected blood or other body fluids (sometimes referred to as serum hepatitis). Mother-to-infant and sexually transmission is common. Screening of blood products for hepatitis B infection occurred for many years prior to the introduction of hepatitis C screening. Hepatitis B infection may be acute, and be followed by recovery, or may lead to chronic infection, where the virus is not eliminated from the body. In cases of chronic infection, the individual is at risk of liver damage such as cirrhosis and liver cancer.
hepatitis C	The viral agent responsible for the vast majority of what was previously referred to as non-A, non-B hepatitis (NANBH). Hepatitis C was first identified in 1988 but tests for detection of hepatitis C antibody became commercially available 2 years later. In February 1990, this test was adopted as a screening test for all Australian blood donors.
hepatitis B virus	Hepatitis B virus, the causative agent of hepatitis B.
hepatitis C virus	Hepatitis C virus, the causative agent of hepatitis C.
hepatitis virus	A virus that mainly infects the liver mainly and causes inflammation i.e. hepatitis.
hepatocellular carcinoma/hepatoma/ primary liver cancer	Cancer arising from the liver. Known causes of liver cancer include chronic infection with hepatitis B and hepatitis C.
immune response	The reaction of the immune system of the body to substances that are interpreted as "foreign" e.g. viruses and often resulting in the formation of an antibody ('humoral response"). However this is only one aspect of the immune response as the other important component of the immune response are the changes in the cells of the immune system ("cellular response").
incidence	The number of new cases of disease/condition occurring during a defined period in a defined population.
incubation period	The period of time between a person being exposed to an infectious agent e.g. a virus and the start of noticeable symptoms of the illness.
liver function test	A biochemical test of the blood to determine evidence of liver damage.
liver biopsy	The removal of a small amount of liver tissue, for diagnostic purposes, by the insertion of a fine needle.
Lookback	The process of tracing blood products released by a Blood Transfusion Service for normal use. The term is often associated with tracing blood units suspected to have been contaminated with an infectious agent.
low risk (of acquiring infection from transfusion currently)	For an understanding of the level of risk, compare with quoted figures of 1 in 1 million risk as the risk of being struck by lightning, whereas the risk of having a motor vehicle accident is of the order of 1 in 1000-2000.
non-A, non-B hepatitis (NANBH)	Hepatitis that is due to agents other than hepatitis A and hepatitis B viruses. Prior to the discovery of hepatitis C, this group would have included hepatitis C infection. It also includes hepatitis due to other viruses such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV).
markers	Proteins (or antibodies to them) from different parts of the virus used in assisting in the identification of the virus.
Morphologic (features)	Visible structural changes (such as observed under the microscope) when examining the features of a sample of tissue e.g. a liver biopsy (refer to other section in Glossary).
Notifiable Disease	Disease requiring notification to the State Health Department e.g. Hepatitis C infection by laboratories and acute hepatitis (which has symptoms) by clinicians. Notifications are forwarded to the *National Notifiable Diseases Surveillance System*, maintained by the Commonwealth Department of Health and Ageing, in anonymous aggregate format.

Nucleic Acid Test (NAT)	New technology that can directly detect the genetic material of viruses, such as HIV and hepatitis C, introduced in 2000 in Australia.
plasma	The liquid component of blood that remains following removal of formed elements (red cells, white cells and platelets). Plasma is the source of immunoglobulin, albumin and clotting factors.
plasma products	Protein components extracted from plasma in the manufacturing process by CSL for the production of albumin, clotting factors and gammaglobulin, used to treat a wide variety of diseases.
plasmapheresis	The collection procedure, which separates plasma from the other components of whole blood and returns the remaining components that have not been collected to the donor.
pooled plasma	The process by which large number of units of plasma are mixed prior to the extraction of specific proteins.
prevalence	The proportion of the defined population with a disease/condition (as detected by a particular method) at a given time.
Prothrombinex	A plasma product, which contains concentrated clotting factors (Factors II, IX and X) that can be used in the management of blood clotting disorders.
Prothrombinex - HT	A super heat-treated form of Prothrombinex.
reactive	Screening tests may come up reactive according to whether or not the level of the protein or antibody is above the defined cut-off level. But, strictly speaking, this generally is not regarded as a "positive" result unless the reactive result to the screening test has been at least verified by supplementary testing with Western Blot or NAT.
Recipient Triggered Lookback (RTLB)	A recipient is a person who has been transfused. A process, which occurs when patients, health authorities and others notify the ARCBS directly of a suspected case of transfusion-acquired hepatitis C in a recipient. The patient's history of transfusions is determined and the hospitals where the transfusions took place are notified, the records searched (where available) and the donation numbers involved are identified. Then the ARCBS looks through its records to identify the donor corresponding to the donation number, checks their hepatitis C status and if necessary recalls them for testing.
recombinant	A product made by genetic engineering techniques is generally safer (in terms of contamination) compared to the products derived from human plasma.
(RIBA) Recombinant immunoblot Analysis	Test for the presence of hepatitis C antibody. It is used as a supplemental test to verify that reactive screening tests are truly positive.
recovered plasma	Plasma derived from whole blood donations and not frozen under conditions suitable for manufacture of clotting factor concentrates.
"Red Cross"	Term used in the ARCBS submission to refer to the blood services managed by the Australian Red Cross Society prior to the formation of the ARCBS in 1996.
replacement donation	A situation where relatives or friends of the patient give blood to replace the units of blood that the patient has used.
replication	Production of a copy of itself.
Rh(D) Immunoglobulin	Also known as anti-D, a plasma product used for the prevention of a potentially fatal form of anaemia in newborn babies born to Rh negative mothers.
ribonucleic acid (RNA)	RNA is similar in structure to DNA. Most viruses are DNA viruses but there are also RNA viruses and hepatitis C is one of them.
sample/cut-off ratio	The ratio of the reading of the patient's sample, to the cut-off level.
screening tests	"Screening" tests are used to test populations not suspected of a particular disease (e.g. blood donors), as such, they are subjected to different and more rigorous licensing requirements compared to "diagnostic" tests as they are used on very large numbers of individuals usually.

sensitivity (of a test)	The rate at which a test is positive among those who have the condition. So the more sensitive a test, the fewer the false negatives i.e. the less likely it is to miss real positive cases, but the price paid is that many false positives may be included.
seroconversion	An immune response, usually occurring early in an infection, where the individual goes from having no antibody to the formation of an antibody to a specific infection.
serological tests	Serology tests are those that detect viral antigens (proteins) or antibodies formed by the body's immune system to the infectious agent in the individual's blood serum. The most commonly used tests for hepatitis C virus detect antibody to the virus.
serum	The fluid remaining after clotting of the blood.
"serum hepatitis"	Old name for hepatitis B, based on clinical observations, prior to the specific antibody test being available in the early 1970s.
specificity (of a test)	The rate at which a test result is non-reactive among those who do not have the condition. So the more specific a test, the fewer the false positives i.e. the better it is at excluding real negative cases, but the price paid for a test being too specific is that some real positives may be excluded.
self-sufficiency /sufficiency (in blood)	Means ability to achieve sufficiency through a national blood program without having to source products from other countries. A blood donation rate of 50 per 1,000 population (5%) is the general minimum donation rate required for a developed country to meet this objective.
source plasma	Plasma collected from a process called apheresis i.e. a collection procedure, which separates whole blood into its components and returns the remaining components that have not been collected to the donor.
super heat-treated (plasma products)	Treatment with heat at 80°C for 72 hours, a technique which was found to be more effective for virus inactivation than heating to 60°C for 72 hours. Introduced in 1990 for Factor VIII in Australia and in 1993 for Factor IX.
supplementary tests	See confirmatory tests.
surface antigen (HBsAg)	Usually refers to the hepatitis B virus outer coat protein.
surrogate test	Surrogate tests are used to try and detect evidence of virus infections where no specific test is available. They are an imperfect substitute for specific tests because they lack sensitivity and specificity (defined elsewhere in Glossary). The ones discussed in this submission are ALT and anti-HBc.
"transaminitis"	Elevation of liver enzymes due to non-viral factors eg. medication, tissue damage from bleeding etc, without other clinical evidence of liver inflammation.
von Willebrand's disease	A group of genetic bleeding disorders affecting both males and females in which, Factor VIII in the patient's blood can be deficient.
whole blood	This refers to the most common form of blood collected from a blood donor. The volume of each unit of whole blood collected is 450ml.
window period	Number of days during which the infection may be present but not detectable by the screening method in use.

ABBREVIATIONS

ACT	Australian Capital Territory
AIDS	Acquired ImmunoDeficiency Syndrome
AHF	Anti-haemophilic Factor, also known as Factor VIII
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B Core antibody also referred to as “anti-core”
Anti-HBs	Hepatitis B Surface Antibody
AST	Aspartase aminotransferase
BTS	Blood Transfusion Service(s)
CBTS	Canadian Blood Transfusion Service
CSL	Commonwealth Serum Laboratories and CSL Limited (as it later became)
DNA	Deoxyribonucleic Acid
DTLB	Donor Triggered Lookback
ELISA/EIA	Enzyme-Linked Immunosorbent Assay
FDA	(US) Food and Drug Administration
FLAG	Fractionation Liaison Advisory group
GP	General Practitioner(s)
HBsAg	Hepatitis B Surface Antigen, also referred to as “surface antigen”
HIV	Human Immunodeficiency Virus
IU	International Units
IDU/IVDU	Injection Drug User/Intravenous Drug User
NANBH	Non-A, Non-B Hepatitis
NAT	Nucleic Acid Test
NBA	National Blood Authority
NBTC	National Blood Transfusion Committee
NCHECR	National Council on Hepatitis C and Related Diseases
NHMRC	National Health and Medical Research Council
NIH	National Institutes of Health
NSW	New South Wales
PSC	(Canadian) Parliamentary Standing Committee
PTH	Post-transfusion hepatitis
REDS	Retroviral Epidemiology Donor Study
RIBA	Recombinant Immunoblot Analysis
RNA	Ribonucleic Acid
RTLB	Recipient Triggered Lookback
SA	South Australia
TGA	(Australian) Therapeutic Goods Administration
TTH	Transfusion-Transmitted Hepatitis
TTV	Transfusion-Transmitted Virus
vCJD	variant Creutzfeldt-Jakob Disease
WA	Western Australia
WHO	World Health Organisation

Index of Tables and Figures included in the submission

SECTION ONE

INTRODUCTION TO ARCBS

1.0 Introduction

The Australian Red Cross Blood Service (ARCBS) today is the sole collector and processor of blood from Australian volunteer donors. A not-for-profit community organisation, it is a critical part of the nation's health infrastructure. ARCBS distributes blood and blood products to patients in hospitals and pathology services, 24 hours a day, 365 days a year. It is able to do this only because of the support of generous Australian volunteer donors. Approximately 4% of the adult Australian population makes regular donations of blood. Without the support of this loyal volunteer base, the Nation would need to look elsewhere to support the provision of blood to Australians in need.

Thousands of blood donations are needed each week in Australia. Many different people need blood - from premature babies to the elderly, from people with life-threatening illnesses to accident victims. Medical products such as injections to prevent tetanus and hepatitis are also made from donated blood.

Every patient who receives a blood transfusion is in an emergency or a health-threatening situation. A patient who does not receive a transfusion in these situations could suffer a reduced quality of life, medical complications or death.

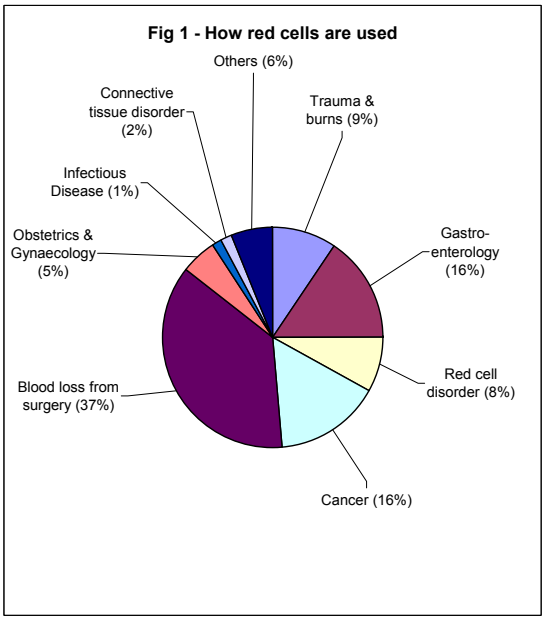
Out of the one million units of donations per year, over 700,000 fresh blood products are issued to approximately 100,000 Australian patients annually, and a further 100,000 patients benefit from plasma products every year. It is the generous gift of Australian blood donors who make these blood transfusions and products possible. Examples of the uses of one of the components of fresh blood i.e. red blood cells are given in Figure 1 (Cobain 2000).

1.1 Vision and mission

The mission of the ARCBS is to share life's best gift by the provision of quality blood products, tissues and related services for the benefit of the community.

1.2 The Present

Fig 1 - How red cells are used



The ARCBS is an operating division of the Australian Red Cross Society, a long established charity in Australia, referred to as the "*Red Cross*" in this submission. ARCBS operates according to the fundamental principles of the International Red Cross and Red Crescent Movement, namely:

- Humanity
- Impartiality
- Neutrality
- Independence
- Voluntary Service
- Unity
- Universality

These fundamental principles are central to the ARCBS vision and mission of providing quality blood products, tissues and related services to the Australian community. This is made possible by the goodwill and commitment of the approximately 500,000 dedicated unpaid blood donors, 2,000 loyal regular volunteers, and 2,200 specialised staff committed to a common aim of contributing to the nation's health and well being through donating and collecting blood for those who from time to time will find themselves in need of help.

The ARCBS does not work alone in the provision of blood and tissue products to the Australian community. A long established management and financial partnership engaging the Commonwealth, State, and Territory Governments and the Australian Red Cross Society has provided Australia with access to blood in both peace-time and war.

1.3 The Past

The Red Cross has been involved in the collection, processing, screening and distribution of blood and blood products since 1929, when the Red Cross established this service in Australia. The blood service developed across Australia on an individual State and Territory basis. The Red Cross Division in each State and Territory established and maintained a Blood Transfusion Service (BTS). This reflected the federal system of governance of Australia and the organisation and funding of public health services.

Each State or Territory BTS was responsible for the collection, processing, screening and distribution of blood and blood products in their respective geographic areas. Throughout the 1980s and 1990s, there were also other blood banks operating under the jurisdiction of State Departments of Health.

Decisions relating to national policy in relation to blood transfusion were coordinated at regular meetings of the National Blood Transfusion Committee (NBTC), the BTS Executive Sub-committee and the Fractionation Liaison Advisory Committee (FLAG). Members of the NBTC were leading haematologists, physicians and blood bankers, from around Australia. There were representatives of the Commonwealth Serum Laboratories (as it then was), the Commonwealth Health Department, and the Commonwealth.

Nancy's Story

Every three weeks 26-year-old Nancy receives a blood transfusion to help her live a normal life. Nancy has a congenital blood disorder known as Thalassaemia Major, a type of anaemia, and receives regular blood transfusions as the primary treatment for her condition.

Nancy's condition was diagnosed when she was three and half. After having her spleen removed when she was four, Nancy commenced regular transfusions at the age of nine, which continues to be part of her everyday life.

Department of Defence participating in the decisions made by these bodies. The NBTC acted as an advisory board to the operating divisions. Each State and Territory Division also had an advisory committee,(Appendix D) through which local medical authorities were able to engage in policy setting for blood practice and procedures.

All of these bodies deliberated on safety issues and policy and made appropriate recommendations on a regular basis. Each State and Territory division had autonomy, however, they worked closely with their respective State and Territory Health Departments, which were the primary source of funding. The NBTC approved policy, but it was up to individual divisions in each state and territory as to whether that policy was implemented.

In 1996 the NBTC ceased to exist with the formation of the ARCBS. *The Royal Charter* and *Supplemental Royal Charter of Incorporation and Rules of the Australian Red Cross Society* (January 1996) provided for a Board of Management, and Chief Executive Officer of a newly created operating division, the Australian Red Cross Blood Service (ARCBS). It was at this point that the State and Territory divisions of the Red Cross commenced the reorganisation of their blood services as a single national organisation known as the ARCBS.

James' Story

In September 2002, 17-year-old student James was diagnosed with an Osteogenic Sarcoma, a malignant bone tumour in his left leg. He immediately commenced 9 months of chemotherapy at Westmead Children's Hospital to help halt the growth of the tumour. However, the tumour began to grow even more aggressively, resulting in an above knee amputation in November.

James continued to receive chemotherapy every third week until May 2003. During the chemotherapy, he received transfusions of red cells. In January this year, James had a prosthesis fitted and his rehabilitation is going well with regular physiotherapy.

1.4 The Future

The National Blood Authority (NBA) was formed in July 2003 and the ARCBS is now accountable to this new body. ARCBS continues to change and adapt to the environment in which it operates, with a constant aim to provide a world-class network of services to the Australian community in relation to blood collection, screening, and distribution.

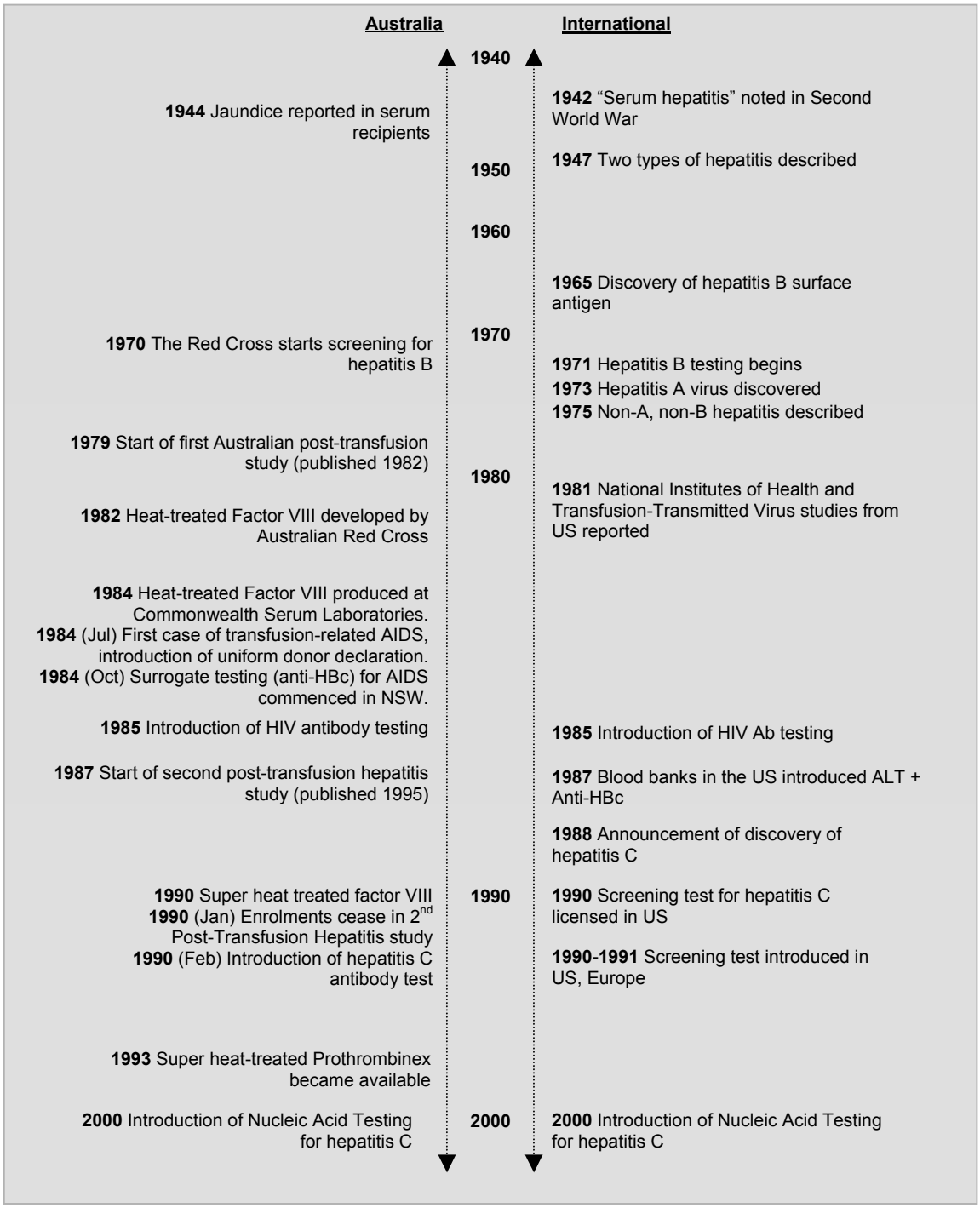
The ARCBS (and its previous entities as the Red Cross State or Territory Divisions prior to 1996) has been at the forefront internationally in the introduction of specific tests to increase the safety of the nation's blood supply (Refer to Tables 3 & 8).

The ARCBS has, and will continue to be, totally committed to the provision of a safe and adequate blood supply for the Australian community. The only constant in the international blood service is change, and as new blood-borne infectious agents emerge, there remains a need for constant vigilance and monitoring of national donor deferral and testing procedures.

ARCBS is committed to maintaining Australia's self-sufficiency of blood and blood products, quality and safety through initiatives such as strategic donor marketing and retention programs, adoption of proven cutting edge technology and further development of social and scientific research programs.

Responses to the terms of reference

Figure 2 – Timeline of history relating to post-transfusion hepatitis



SECTION TWO

a. The history of post-transfusion hepatitis in Australia, including when Non-A, Non-B hepatitis (hepatitis C) was first identified as a risk to the safety of blood supplies in Australia and internationally.

Post-transfusion hepatitis was first identified during the Second World War. Non-A, Non-B hepatitis was identified internationally, as a cause of post-transfusion hepatitis after the introduction of a screening test for hepatitis B in the early seventies. It took another two decades of intensive research to further characterise hepatitis C.

b. The understanding of hepatitis C by blood bankers, virologists, and liver specialists during the past 3 decades, including when hepatitis C was first identified as a virus transmissible though blood.

Hepatitis C was first identified in 1988. It was initially linked to post-transfusion hepatitis in 1989. Tests for hepatitis C antibody first became commercially available in February 1990 and were adopted by the Red Cross at that time, to screen Australian blood donors.

2.1 What is hepatitis?

Hepatitis means inflammation of the liver. It can result from:

- overuse of alcohol;
- reaction to certain medications e.g. anaesthesia;
- infection by bacteria and viruses (hence viral hepatitis).

There are many different types of viral hepatitis, the most common being:

- hepatitis A, transmitted by contaminated food e.g. oysters;
- hepatitis B, sexually transmissible and also passed by contact with infected blood, on shared injecting equipment, and in many third world countries transmitted mother-to-child during birth;
- hepatitis C, transmitted mainly through injecting drug use but, also by contact with infected blood, injecting equipment, tattoos and other means.

Other less common causes of transfusion-acquired viral hepatitis include cytomegalovirus (CMV), Epstein-Barr virus (EBV) and hepatitis D. The hepatitis D virus can only be transmitted in the presence of hepatitis B infection so any methods to screen out hepatitis B will effectively screen out hepatitis D virus. Hepatitis E behaves similarly to hepatitis A. Finally, the hepatitis G virus, identified in 1995, although transmissible via blood transfusions, is yet to be proven to cause hepatitis, with the balance of evidence suggesting that it prematurely designated a hepatitis virus (Refer to section 2.6).

Non-infectious hepatitis is acquired when liver cells react to chemicals that are consumed e.g. alcohol, or injected into the body such as anaesthetic medications. Infectious forms of hepatitis are acquired mainly via contaminated food or via blood exposures of some kind.

Initially, doctors relied on symptoms such as jaundice (i.e. yellowness of the eyes and skin) and brown urine to alert them to the fact that a patient may have hepatitis. However, this occurs only with severe inflammation of the liver. Blood tests known as liver function tests were introduced in the fifties including alanine transaminase (ALT) and aspartase transaminase (AST), to assist with diagnosis. Finally, the introduction of specific tests to

identify each particular virus, usually through specific antibodies formed in the blood of those infected, led to a more accurate indicator of the cause of the disease. Other tests depend on direct detection of a viral protein or genetic material.

2.2 Discovery of "serum hepatitis" during the Second World War

During the Second World War, major outbreaks of jaundice occurred after vaccination of military personnel and the authorities were alerted to the possibility of an infectious agent being transmitted through the vaccination serum. After the war clusters of cases were found to occur in patients receiving serum from the same batch and the disease was called "serum hepatitis" at that time. Later it became clear that hepatitis followed administration of whole blood as well as serum or plasma.

However, it was not until after the War, when methods to monitor liver function were developed, that the term "hepatitis" or inflammation of the liver came into use. The measurement of liver enzymes such as transaminases meant that there was an additional method to track the disease, other than relying purely on what was observable clinically, thus advancing knowledge of the disease. This led to the realisation that there might be more than one type of hepatitis:

i. Infectious hepatitis - transmitted by contaminated food ("faecal-oral" route) with a short incubation period and no carrier state (a carrier is an individual free of symptoms but infectious). In the seventies this type was renamed hepatitis A.

ii. Serum hepatitis - transmitted via serum, with a longer incubation period and a distinct carrier state. In the seventies this type was renamed hepatitis B.

2.3 Association of hepatitis with transfusion

Post-transfusion hepatitis was thought to be caused by the hepatitis B virus. In the US it was known that hepatitis was a significant problem. For example, post-transfusion hepatitis amongst patients undergoing heart surgery (which regularly necessitated blood transfusions) occurred at a rate as high as 33% (Alter 1994; Alter and Houghton 2000).

2.4 Discovery of hepatitis B

The discovery of a protein initially known as "Australia antigen", and later called the hepatitis B surface antigen (HBsAg referred to as "*surface antigen*") (Blumberg, Alter et al. 1965), led to the finding of an antibody which reacted with this particular protein. This antibody was subsequently used in developing a test to detect hepatitis B virus and internationally commercial tests for screening donors became available in the early seventies. It was later calculated that the rate of post transfusion hepatitis was reduced by around 20% in US by testing for hepatitis B. However, a larger reduction in risk occurred when only volunteer (unpaid) blood donors were used.

The NSW Blood Transfusion Service (BTS) was at the forefront of screening donations for hepatitis B ahead of many countries. An in-house surface antigen test was developed in 1970 in NSW and used throughout Australia to screen donors. This was eventually replaced by an improved commercial screening test in 1976. The NSW BTS also became a reference centre for hepatitis B screening, including patients referred by gastroenterologists and liver specialists.

2.5 Non-A, non-B hepatitis (NANBH) as a separate entity emerged in the mid-seventies

A specific test for hepatitis A virus was discovered in 1973 (Feinstone, Kapikian et al. 1973). Thus patients could now be tested for both hepatitis A and hepatitis B. It soon became apparent that post-transfusion hepatitis had not disappeared with the removal of donors with hepatitis B, nor were cases of post transfusion hepatitis associated with hepatitis A.

Despite a significant reduction of post-transfusion hepatitis, a number of cases continued to occur (Prince, Brotman et al. 1974). Closer examination of the cases indicated that many of them had a different clinical picture from hepatitis A or B. Experts therefore believed that there may be a third form of virus causing post-transfusion hepatitis. Thus a third form of hepatitis was described (Feinstone, Kapikian et. al 1975). It was initially called non-A, non-B hepatitis (NANBH) rather than hepatitis C because to do so would have implied the existence of a single agent. At that time the general thinking among the scientific community was that more than one infectious agent was involved and indeed there were many claims to have discovered markers for different viruses (Dienstag 1983; Alter 1994; Alter and Houghton 2000).

The diagnosis of NANBH in the seventies and eighties was based on symptoms e.g. jaundice, persistently elevated liver function tests and exclusion of other known diseases associated with hepatitis. Liver function tests (e.g. transaminases such as ALT or AST), however, can only detect or confirm the presence of inflammation, but do not differentiate between the different possible causes. It was important to exclude not only hepatitis A and B but also other causes of hepatitis, including other viruses for which diagnostic tests were available at the time, such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Non-infectious causes of raised liver enzymes also had to be excluded: obesity, overuse of alcohol, medication, occupational exposure to chemicals and hereditary and metabolic diseases.

Intensive efforts were made in attempts to detect the viral agent(s) throughout this period until finally Chiron Corporation announced in May 1988 (Ezzell 1988) the identification of a virus responsible for NANBH obtained by application of molecular biology techniques (Choo, Kuo et al. 1989). The association of this agent with post transfusion hepatitis (NANBH) was soon confirmed by others (Alter, Purcell et al. 1989; Van der Poel, Reesink et al. 1989; Van der Poel, Reesink et al. 1990b). The agent was then named hepatitis C virus and screening tests became available in 1990 (Tobler and Busch 1997; Alter and Houghton 2000).

2.6 Other viruses causing post-transfusion hepatitis

It was recognised in the seventies that cytomegalovirus (CMV) and Epstein-Barr virus (EBV) could cause post-transfusion hepatitis. Even after the identification of the hepatitis C virus, there were still cases of post-transfusion hepatitis where the causes remained unknown. These cases were sometimes referred to as non-A, non-B, non-C hepatitis. With the identification of hepatitis G (GBV-C) in 1995 and its presence in up to 1–2% (of Australian donors), scientists initially thought that this made the agent responsible for the residual cases; however studies have not found evidence that this agent causes clinical disease.

2.7 Awareness of risk of NANBH to the blood supply internationally

In the US, prior to 1970, the incidence of post-transfusion hepatitis was as high as 33%. Much of this was because of a high percentage of paid donors in the US (Koretz, Stone et al. 1985; Alter 1994; Alter and Houghton 2000). The incidence of post-transfusion hepatitis dropped to 7-10% (for recipients who only received blood from unpaid donors in the US), after screening for hepatitis B virus was introduced (Seeff and Dienstag 1988; Alter 1994). It

was postulated that the higher rate noted prior to 1970 was due to the higher volumes of transfusion per patient and the greater use of commercial blood sources. Harvey Alter made the observation in 1978 that since the introduction of mandatory hepatitis B screening for donor blood in the early seventies, more than 93% of cases of post-transfusion hepatitis were attributable to NANBH.

However, it took several large scale, long-term studies to ascertain the likelihood of acquiring NANBH from blood transfusions under a defined set of circumstances. What were needed were studies, which compared the new cases arising in the group under study (known as the incidence i.e. number of new cases arising each year) to a control group. Unfortunately, studies that capture a "snapshot" of the number of the NANBH cases present at any one time in a particular country give only an indication of *prevalence* and confuse the pre-existing with the new cases, since NANBH is a chronic disease. Thus, the principal sources of information belonging to the first category i.e. incidence studies will be the main ones cited in this submission.

There were two pivotal sets of US studies which started in the mid-seventies and were designed to define the incidence of post transfusion hepatitis in the US and evaluate what factors influenced its occurrence. The first, a multi-centre study from the Transfusion Transmitted Viruses (TTV) Study Group, showed an association with donor ALT levels (Aach, Szmuness et al. 1981). An independent study at National Institutes of Health (NIH) confirmed the findings (Alter, Purcell et al. 1981). In a further series of studies there was an association with the presence of "*anti-core*" in donors (detecting hepatitis B core antibody i.e. anti-HBc, a marker for past exposure to hepatitis B virus) (Stevens, Aach et al. 1984; Koziol, Holland et al. 1986). There were predictions made, in the US, that removing donors with higher levels of ALT and positive for anti-core might reduce the development of NANBH, by about a third, in recipients. The value of these studies was debated in the US for up to 6 years and it was recommended that randomised controlled prospective trials should be undertaken to determine whether or not the introduction of these tests (known as surrogate testing) would be shown to be efficacious (Refer to Term of Reference (e), Sections 4.4 and 4.5).

The early US studies showed that risk of NANBH was related to whether the blood donations were obtained from commercial agencies or community blood banks. Centres which used only volunteer blood had a much lower rate of post-transfusion hepatitis than those which relied partially or fully on paid donors (Aach, Szmuness et al. 1981). There was however, an unexplained 3.3% "background rate" of NANBH among the controls who had NOT received any blood transfusions noted in the TTV study (Stevens, Aach et al. 1984). This was likely to be due to hospital-acquired rather than transfusion-acquired hepatitis.

The applicability of outcomes noted in the US to other settings was hotly debated in the eighties (Refer to Term of Reference (e), Section 4.5.3). This was seen in the papers from the Council of Europe meetings in the mid-eighties. They strived to find a consensus. According to surveys conducted by the Council of Europe in the mid-eighties the incidence of NANBH in European countries varied from 2–16%. The Australian incidence of NANBH among recipients of blood from unpaid donors was 1.7% (Cossart, Kirsch et al. 1982). This was much lower than the US incidence of between 7–10% for blood from volunteer donors (Alter 1994) or the general European incidence. The countries with higher incidence included: Canada – 9.2% (Feinman, Berris et al. 1988), France – 13.8% (Courouce, Cabau et al. 1978), Italy – 13.8% (Tremolada, Chiappetta et al. 1983) Spain – 16% (Barrera, Bruguera et al. 1991) and Japan – 12% (Tateda, Kikuchi et al. 1979).

The risks discussed above apply to whole blood recipients and do not capture the extent of the risk to haemophilia patients who regularly received Factors VIII or IX, products made from

the pooled plasma of thousands of donors (Refer to Term of Reference (j), Section 7). It was widely known that there was a far greater risk of transmission of NANBH to haemophilia patients than to whole blood recipients because their risk was compounded by the dependence on pooling of donations, with subsequent exposure to thousands of donors. It became clear in the mid seventies that hepatitis was common in patients with haemophilia (Aledort, Levine et al. 1985) however it was generally thought to be a tolerable problem, because there were such significant benefits in using Factor VIII and Factor IX concentrates for management of the disease (Mannucci 2003).

In the seventies the known risk factors for NANBH, apart from transfusion with blood or blood products, included: injecting drug use and needle stick injury. There were also cases reported in renal dialysis patients and staff (Alter, Jett et al. 1990).

2.8 Australian awareness of post-transfusion hepatitis

In Australia, there was an awareness of the risks of hepatitis after transfusion from the Second World War onwards and Blood Transfusion Services (BTS) consistently warned doctors and hospitals about the risk. This is demonstrated by the resources provided to Australian healthcare providers, by the Red Cross in the seventies, eighties and nineties:

- Film entitled *Blood Components and their Uses* produced by the Red Cross and Commonwealth Serum Laboratories in the seventies, and updated in the eighties. This film included a description of risks associated with transfusions including hepatitis. This film was shown to medical students, nurses, medical technologists in training and potential donors.
- Information sheet to Resident Medical Officers was produced in 1975 and updated periodically. Special reference was made to the risk of transfusion-transmitted hepatitis and the need to provide details of patients presenting with symptoms of post-transfusion hepatitis to the BTS.
- Booklet *Notes for Nurses* produced in 1974 and updated periodically containing similar information to the one for medical officers.
- The book *A Guide to Blood Transfusion* (Archer and Parker 1982) was distributed to all NSW hospitals. The 1982 edition described NANBH as a risk of blood transfusion and the 1990 edition included additional information on the newly discovered hepatitis C.
- In the booklet *Blood Components and their use* the risk of hepatitis transmission by blood components was mentioned. This booklet was distributed widely by the donor recruitment staff to schools, businesses and factories. Copies were freely available to hospitals and distributed to staff at seminars.
- A *Circular of Information* was issued with blood components to hospitals and warned of the risk of hepatitis.

In 1982 Rickard et al. reported on a 4.5 year study of 243 Australian patients with haemophilia. They noted that many patients (63%) had markers of hepatitis B. During the study raised ALT levels were noted in 34% of the patients on at least one occasion. There were 66 episodes of presumed NANBH during the study for an overall incidence of 27.2% (Rickard, Batey et al. 1982).

The knowledge of NANBH around 1989 is summarised in an article by an eminent Australian gastroenterologist, Professor Geoff Farrell (Farrell 1989) and others, who described three different types of clinical patterns of NANBH:

1. *Epidemic type* – spread by contaminated food ("faecal-oral" route like hepatitis A) and occurring in India, South-East Asia and East Africa
2. *Sporadic type*
3. *Blood-borne type* of which there were two subtypes:
   - Short incubation period i.e. until symptoms were noted (3 days – 6 weeks) associated with receiving clotting factors i.e. Factors VIII and IX.
   - Long incubation period (6 – 12 weeks) acquired through blood transfusion or intravenous drug abuse and most likely to become chronic (10 – 20% cases).
   - In 1989, this subtype of NANBH was thought to account for at least 90% of the cases of post-transfusion hepatitis.

2.9 Research studies in Australia

Two important Australian post-transfusion hepatitis studies helped to characterise NANBH in the Australian setting. They were conducted in two different time periods: 1979 - 1980 (Cossart, Kirsch et al. 1982) and later 1987-1990 (Ismay, Thomas et al. 1995). The first study in Australia (Appendix E) followed 842 cardiac surgery patients prospectively for up to 24 weeks after their operation. The study showed that 18 patients became infected with hepatitis that was an extremely low rate (2%) by world standards. Out of the 18 cases identified, 3 cases were due to hepatitis B, one was due to cytomegalovirus (CMV), leaving 14 cases as NANBH which is equivalent to a NANBH post transfusion rate of 1.7% per patient. This means that NANBH constituted 78% of all the hepatitis cases in the study. It is possible that the three cases of hepatitis B were not due to blood transfusion as the donors were tested subsequently and found to be negative for hepatitis B.

The second study of the frequency of post-transfusion hepatitis in cardiac surgery patients (Appendix F) in the period 1987 - 1990 was of a similar design to the first except that a control non-transfused group was included and patients were followed for 52 weeks (Ismay, Thomas et al. 1995). Retrospectively, hepatitis C antibody tests (using first generation tests) were done and all blood products administered were tested for ALT, anti-core as well as a variety of other viral hepatitis tests. The results demonstrated that there were 8 cases of post-transfusion hepatitis (1.1% of the patients) and 7 of these 8 cases demonstrated the presence of hepatitis C antibody. Thus, in less than a decade the rate of post-transfusion hepatitis in Australia had considerably reduced (1.7% to 1.1%). Hepatitis C was shown to be the agent responsible for most of the post-transfusion hepatitis in this study and hepatitis C antibody tests detected about 85% of infective donations (Ismay, Thomas et al. 1995). The authors noted that the reduction in hepatitis might be attributable to other preventative measures, such as HIV testing and stricter donor selection and deferral procedures introduced in the wake of HIV/AIDS.

2.10 Evolution of understanding of long-term complications

During the seventies, literature at the time shows that the medical community did not have a full understanding of what became known as hepatitis C, in fact NANBH was considered by medical specialists (Alter, Purcell et al. 1978; Seeff and Dienstag 1988; Mannucci 2003) to be a relatively minor disease. NANBH was often referred to as "transaminitis" (elevation of liver enzymes due to non-viral factors eg. medication, tissue damage from bleeding etc). The ALT elevation during acute disease was not as high as was found with hepatitis B (Alter, Purcell et al. 1978). The majority of patients with post-transfusion hepatitis were usually asymptomatic and without any signs of jaundice, a hallmark of severe impairment of liver function.

Even in those patients in whom the disease appeared to follow a chronic course, it was not clear even in the eighties whether or not NANBH was the actual causative agent because no viral agent had been identified. It was suspected that other factors could be playing a role. By the mid-eighties, many international experts reported that on following up NANBH patients with liver function tests many patients continued to have periodically raised levels of ALT and AST in their blood, although the levels fluctuated and were at other times within the limits of the normal range. Some of the patients with elevated liver enzyme levels had a liver biopsy and were found to have evidence of ongoing inflammation. With follow-up over time, some were found to have developed more significant inflammation and even fibrosis.

In 1988 Leonard Seeff, a prominent gastroenterologist in Washington D.C. made the following observations (Seeff and Dienstag 1988):

- *"Three-quarters of the persons with acute NANBH are asymptomatic, as are a majority of those whose disease progresses and becomes chronic.*
- *Chronic hepatitis i.e. persistence of elevated aminotransferase activity for at least 6 months evolves in ~50% of persons with acute NANBH after transfusion.*
- *Morphologic* (refer to Glossary) *features or clinical complications of cirrhosis are observed in ~20% of patients with chronic NANB transfusion-associated hepatitis, or 1% of all transfused persons, within a decade after acute illness."*

Whilst it is clear that patients with NANBH do progress to chronic hepatitis and sometimes to more serious consequences the effects of this on mortality were not well understood. In 1992 in a study of 568 patients with transfusion associated NANBH, it was reported that, after an average 18 year follow-up, the group exhibited no increase in mortality over two control groups who had received transfusions but had no hepatitis (Seeff, Buskell-Bales et al. 1992).

The availability of a specific test for hepatitis C enabled a much greater understanding of the disease to be achieved in the last decade. The current knowledge according to the Australian National Council on AIDS, Hepatitis C and Related Diseases Hepatitis C Sub-Committee, in their *Hepatitis C Virus Projections Working Group: Estimates and Projections of the Hepatitis C Virus Epidemic in Australia 2002* (NCHECR 2002) published in August 2002 is as follows:

- 25% of people who develop hepatitis C virus antibodies clear the infection and are not at risk of any long term complications;
- of the 75% who do not clear the infection (i.e. have a chronic infection) about 7% progress to long term damage with cirrhosis of the liver by 20 years after infection;
- every year approximately 4% of those with cirrhosis may develop liver failure and 1% of the same group develop liver cancer.

2.11 Understanding the epidemiology of hepatitis C in Australia

Approximately 160,000 notifications of hepatitis C infection have been made in Australia between 1990 and 2000 (Dore, Law et al. 2003).

It has been estimated that 210,000 people are living with hepatitis C in Australia, with 80% having acquired their infection from injecting drug use.

Only a small proportion of people with hepatitis C in Australia have acquired it through blood transfusion, estimated to be about 5%. Risk factors other than injecting drug use include tattooing, occupational exposure in health workers and being born overseas in countries with a high prevalence of hepatitis C (Dore, Law et al. 2003).

2.12 Estimating hepatitis C risks associated with transfusion over the past three decades

With each subsequent generation of the test, the hepatitis C antibody test improved in accuracy and it is now able to dramatically reduce the risk of post-transfusion hepatitis C (Table 1). The introduction of improved tests for hepatitis C since 1990 has enabled better definition of the disease, better understanding of risk factors for transmission and of the long term complications. The improvement with each generation of the hepatitis C antibody tests meant more information became available on the cases that would have been missed previously i.e. *false negatives* and also those cases that were included because of the lower efficacy of the earlier tests i.e. *false positives* (refer to Glossary).

The risk of post-transfusion hepatitis C in Australia since the implementation of universal hepatitis C antibody testing in 1990 has declined almost a thousand-fold (Table 1). The reduction in the "window period" i.e. number of days during which the infection may be present but not detectable by the screening method in use, was an important advance. The risk of a donation from the 'window period' contaminating the blood going to Australian recipients (table 1) was estimated in several studies published recently (Whyte and Savoia 1997; Muller-Breitkreutz 2000; Seed, Cheng et al. 2002). These studies were based on retrospective analyses of large numbers of samples from Australian donors using, at least second generation, hepatitis C tests.

Table 1 – Declining risk of post-transfusion hepatitis C in Australia 1979 – 2002

Period	Residual risk of NANBH/Hepatitis C transmission by transfusion (risk per unit transfused^)	Hepatitis C screening
1979 – 1980	1:333	Unscreened – prior to specific test being available
1990 - 1991	1:3435	Hepatitis C antibody (first generation tests)
1994 - 1995	1:234,000*	Hepatitis C antibody (second generation tests)
1997	1:311,956*	Hepatitis C antibody (third generation tests)
2000 - 2002	1:3,112,000*	Hepatitis C antibody (third generation tests and NAT)

* Figure based on mathematical modeling

^ Risk expressed here as per unit, not per patient (as expressed in Cossart et al 1982 and Ismay et al, 1995 studies)

SECTION THREE

c. When the first cases of post-transfusion Hepatitis C were recorded in Australia

The first cases of post-transfusion hepatitis C were recorded by the State and Territory Red Cross Blood Transfusion Services in September 1989 when samples from the second Australian post-transfusion hepatitis study were analysed using unlicensed (research only) testing kits.

d. When Australian Red Cross and the plasma fractionator Commonwealth Serum Laboratories first became aware of infections from blood contaminated by hepatitis C, and the actions taken by those organisations in response to those infections.

Transfusion transmitted hepatitis C was first evident in September 1989 when samples from the second Australian post-transfusion hepatitis study were analysed using unlicensed (research only) testing kits. The responses of the ARCBS to this included universal hepatitis C antibody screening at the earliest possible time, the investigation of suspect donors and establishment of a Lookback process to identify those infected with hepatitis C.

3.1 Hepatitis C notifications in Australia

Between 1990–1995, hepatitis C became notifiable to the Public Health Units, which operate within the Department of Health of each State or Territory in Australia. Notifications are forwarded to the *National Notifiable Diseases Surveillance System*, maintained by the Commonwealth Department of Health and Ageing, in anonymous aggregate format. Laboratory notifications account for over 99% of notifications and the information collected is generally incomplete. For instance, under the *NSW Public Health Act*, only laboratories were required to notify diagnoses of hepatitis C whereas doctors and hospital managers are required to notify only diagnoses of acute hepatitis.

The majority of notifications do not provide enough information to differentiate between recently acquired (*incident* cases) compared with old (*prevalent*) cases of hepatitis C (refer to Glossary). Out of the 17,000 – 20,000 cases of hepatitis C notified per year between 1995–2000, it is been estimated that newly acquired cases constitute only approximately 100–450 cases per year (NCHECR 2002). The only data consistently available are age, sex, postcode and date of specimen collection.

ARCBS notifies the Public Health Unit in each State or Territory whenever a donor is identified by ARCBS as hepatitis C positive.

3.2 NANBH cases in Australia prior to availability of specific hepatitis C tests in February 1990

Prior to the availability of specific tests for hepatitis C, there would have been cases of non-A, non-B hepatitis (NANBH), which remained unreported, as the disease was usually associated with symptoms that could be mistaken for other medical conditions or there may have been no symptoms at all.

NANBH was in most states not specifically a notifiable disease in the seventies and eighties so the data collected by health authorities was incomplete. In the absence of consistent regulation at the time, reporting of NANBH cases was therefore very much dependent on the hospital or medical practitioner in charge of the patient notifying either the Epidemiology branch of the State or Territory Department of Health or the Blood Transfusion Service (BTS).

Notifications of "*hepatitis (unspecified)*" cases were one source of information, as shown in the summaries of notifiable diseases of the States and Territories in 1984 - 1988 (as recommended by the *National Health and Medical Research Council, Eighty-Sixth Session, October 1978).* These cases of unspecified hepatitis, which included all cases that could not be classified as either hepatitis A or B, were few by comparison to the many reports of hepatitis B in the period – Table 2. It is unclear what proportions were transfusion-associated. There did not appear to be any upward trend in the figures suggestive of increasing frequency.

Table 2: Notification of hepatitis (unspecified) in Australia 1984 - 1988

State	1984	1985	1986	1987	1988
ACT	-	-	2	1	2
NSW	74	68	74	43	15
NT	7	12	5	8	1
Qld	-	5	26	64	24
SA	15	2	23	15	11
TAS	(NN)	(NN)	(NN)	(NN)	(NN)
VIC	10	3	6	-	16
WA	28	32	(NN)	(NN)	(NN)
Total	**134**	**122**	**136**	**131**	**69**
As % of all notified hepatitis cases	5.7%	4.7%	3.8%	5.3%	2.9%
TOTAL = hepatitis A (infectious) + hepatitis B (serum) + hepatitis (unspecified cases)	2367	2615	3587	2451	2352

(NN) – not notifiable

There were very few notifications of cases of suspected post-transfusion NANBH to BTS between 1975 and 1990.

The two Australian post-transfusion studies provided the best evidence of post-transfusion NANBH cases during the eighties. Fourteen cardiac surgery patients in the first study had developed evidence of NANBH following blood transfusion (Cossart, Kirsch et al. 1982). In the second post-transfusion study (Ismay, Thomas et al. 1995) covering the years 1987 – 1990, there were 8 cases of post-transfusion hepatitis all attributable to NANBH, of which 7 cases were proven to be hepatitis C.

In December 1989, a letter was published in the *Medical Journal of Australia* (Gust, Nicholson et al. 1989) describing patients positive for hepatitis C antibody using the research test. These subjects included patients with haemophilia, renal dialysis patients, intravenous drug users and male homosexuals.

3.3 First donor blood screening with hepatitis C antibody assays in February 1990

In February 1990 the State and Territory Blood Transfusion Services (BTS) commenced the testing of all blood donations for hepatitis C antibody using the first generation assay (Refer Appendix B - Screening Methods) and it is significant that it was the second country in the world after Japan to do so (Table 3).

Table 3. Screening of blood donations for antibody to hepatitis C virus

Date	Country
Dec 1989	Japan
Feb 1990	Australia
Mar 1990	France (1 March): Luxemberg (new donors only, 1 March)
Apr 1990	Finland (1 April) - all donations: partially started 1 February
May 1990	USA (2 May): Austria: Amsterdam (other Netherlands centres later)
June 1990	Canada: Germany (by 1 July)
July 1990	Belgium (1 July)
Aug 1990	Switzerland (1 August)
Sept 1990	Luxembourg (all donors)
Oct 1990	Spain (all by 12 October, some started earlier)
1990 / 1991	Norway
Jan 1991	Sweden (legal requirement published 24 January to start as soon as possible)
Mar 1991	Portugal (mandatory, some earlier): Cyprus: Greece: Hungary: Iceland: Malta
June 1991	Netherlands
June 1991	Denmark
Aug 1991	Italy
Sept 1991	UK (1 September)
Sept/Oct 1991	Ireland
Aug 1992	New Zealand

At the time of introduction of the first available hepatitis C antibody tests there was uncertainty as to the specificity and sensitivity of the tests when they were applied to normal populations e.g. blood donors, rather than to people with disease. It was clear by the time second generation tests commenced, that approximately 70% of donors who were repeatedly reactive (see glossary) on screening by first generation hepatitis C antibody test (between February 1990 and June 1991) were in fact biological false positives i.e. they were not infected with hepatitis C. (Refer to Appendix B -Screening Methods)

A large number of donors who were reactive in the first eighteen months of screening were not actually infected with hepatitis C virus. Data on confirmed positive donors for this period (determined retrospectively) revealed a prevalence of 0.32% for Western Australia, 0.31% for NSW, 0.27% for Victoria and 0.25% for Queensland.

A limitation of the first generation test was its lack of sensitivity. This meant that all donors with hepatitis C could not be detected by the first generation test (it was approximately 80% effective). Second generation tests showed greater sensitivity and subsequent third generation tests, were even better (Refer to Appendix B - Screening Methods).

Those working with these early generation tests were frustrated by their inaccuracies. The development of new screening tests was a priority at the time in Australia and around the

world. Blood bankers in other jurisdictions faced similar frustrations. Until new generations of the test were brought out, blood bankers had to be satisfied with what was available. These advances naturally took some time to be developed and proven.

3.4 Actions by ARCBS following introduction of hepatitis C antibody test after February 1990

From the date of introduction of testing by the Australian Red Cross in February 1990 in Australia, no un-screened fresh products (red cells, platelets, frozen plasma and cryoprecipitate) were issued to hospitals.

In February 1990, Red Cross representatives proposed to their Health Departments that it might be desirable to make hepatitis C virus a notifiable disease so that appropriate statistics might be collected. Once hepatitis C became a notifiable disease, all confirmed positive donors were notified by the ARCBS to the relevant authority.

As explained above it was not clear, in 1990, which donors reacting to the new test were actually infectious and which were not infected at all. Nevertheless all fresh blood products made from donors who tested repeat reactive were discarded and not used for transfusion.

The fate of repeat reactive plasma during the period immediately after testing was introduced has been dealt with extensively by *The Report of the Expert Group on Hepatitis C and Plasma in 1990* (Barraclough, Angus et al. 2003).

Initially, donors whose blood repeatedly reacted to the hepatitis C antibody test on the first occasion the blood was tested and who had no obvious risk factor, were allowed to continue to donate blood, not for production of fresh products, but for the manufacture of plasma products, with the exception of Prothrombinex and Factor VII. Thus plasma labelled as hepatitis C reactive was sent to CSL on condition it was used in this manner only. The reason for this was that the plasma fractionation process was known to inactivate the NANBH agent in all plasma products except Prothrombinex and Factor VIII. This decision was based on best knowledge at the time.

As knowledge grew, the decision to fractionate reactive plasma was reconsidered, and after July 1990 the policy was changed. The practice of sending hepatitis C reactive plasma to CSL for fractionation ceased. Reactive plasma was dispatched to CSL, on the understanding that it would be set aside and used only for the possible future manufacture of a hepatitis C immunoglobulin (similar to hepatitis B immunoglobulin) either for treatment or prevention of hepatitis C, for which hepatitis C reactive plasma would be needed. This idea of manufacturing a special hepatitis C immunoglobulin was later abandoned.

There was no knowledge at the time about whether hepatitis C reactive plasma contained virus or only antibody (i.e. the donor had cleared virus from their system). Internationally, from FDA, there was concern that removing hepatitis C reactive plasma from the plasma pool (for the first time in 1990) would change the balance of antibody and virus in the plasma pool and may actually increase the risk of the plasma products transmitting hepatitis C. Again, scientific debate required time to evolve.

As concluded by *The Report of the Expert Advisory Group on Hepatitis C and Plasma in 1990* the decision-making in relation to this issue "*would, even in 2003, be regarded as complying with the highest contemporary international standards of safety*" (Barraclough, Angus et al. 2003).

3.5 Management of reactive donors

Following the introduction of the first generation hepatitis C antibody test for screening in Australia (February 1990), donors reactive on testing were asked to return for an in-depth interview including an analysis of risk factors. This was important as there was no supplementary or confirmatory test in that early period and it was suspected that a large proportion of those donors reacting in the assay would be false positives. A supplementary test did not become available until September 1990.

It soon became clear that there was a relationship between a donor having a risk factor (and therefore likely to be really infected with hepatitis C) and the ratio of the strength of the test result (using the sample/cut-off ratio – refer to Glossary). A low sample/cut-off ratio was generally associated with false positive results. This information enabled the donor deferral policy to be further developed during the first 6 months of testing.

It is important to understand that many hepatitis C antibody reactive donors were in fact not infected with the hepatitis C virus but simply caught up in the testing net i.e. they were "*biological false positives*". Automatic deferral (i.e. asking donors not to donate either temporarily or permanently), for everyone who was reactive with the new test, would have meant deferral of a large number of donors not infected with hepatitis C. Ninety percent of such donors could have been expected never to return, thus damaging the donor base and impacting on self-sufficiency. Instead, once confirmatory tests were available, a deferral policy was applied and true hepatitis C positive donors were permanently deferred from making further donations. Donations from these donors were never used for the manufacture of fresh blood components.

The first group of donors reactive with the hepatitis C antibody test were studied thoroughly by research teams including Red Cross personnel, epidemiologists and liver specialists. Interviews were conducted with the donors to discover any risk factors and the donors were referred to specialist liver clinics for further evaluation. As a result new information was made available to the Australian health community about the prevalence of hepatitis C antibodies in blood donors (Archer, Buring et al. 1992; Hyland, Kearns et al. 1992; Strasser, Watson et al. 1995) and the risk factors for hepatitis C (Kaldor, Archer et al. 1992) and the degree of liver disease and likely infectivity (McCaughan, McGuinness et al. 1992).

As knowledge grew, the donor selection guidelines were amended to be more effective in excluding donors who might have risk factors for hepatitis C virus. Donors who were confirmed positive were counselled and referred to their GP or to specialist clinics for advice. Information leaflets about hepatitis C were developed and promulgated for donors and the general community. The ARCBS also provided education to general practitioners and other areas of the health sector on hepatitis C.

3.6 First cases of transfusion-acquired hepatitis C in Australia

As explained above, Australia had undertaken its own post-transfusion NANBH study in 1987 partly funded by the Red Cross. The study was in progress and some hundreds of cardiac surgery patients had been enrolled in the study from hospitals in Sydney and Perth. Patients were being followed up after their surgery for 12 months with regular testing. By late 1988 only one patient in the study was suspected to have acquired NANBH. All the units transfused to that patient had been tested and found to be normal in the two kinds of surrogate test applied (ALT and anti-core – refer to Term of Reference (e) for further discussion on surrogate testing).

In 1988, it was made known throughout the transfusion world that Chiron Corporation had discovered a new hepatitis virus, which appeared to be the same as NANBH, and that a donor screening test was being developed for this virus (Ezzell 1988). The decision was made by the Red Cross to make all efforts to have the test made available within Australia as soon as possible. By late 1989, the first few test kits for hepatitis C antibody arrived in Australia, for use in research only, not for donor screening.

By 1989, there were eight suspected cases of post-transfusion hepatitis in the study. Applying the new research test kit to the eight cases revealed that seven of the eight were reactive, strongly suggesting that in fact those seven patients had contracted the newly described hepatitis C virus (Ismay, Thomas et al. 1995). The next step was to test samples from all the blood donations, which had previously been transfused to those eight patients. In each case there was a donor who tested reactive with the new test. Thus, these are the first documented cases of post-transfusion hepatitis due to hepatitis C in Australia and the date these tests were conducted was late 1989.

In the next few years other cases gradually came to light and the relevant BTS was informed by hospitals or health authorities of suspected cases.

3.7 Actions by ARCBS following confirmed cases

Suspected post-transfusion hepatitis C cases reported to the Red Cross were investigated by the ARCBS. Although the types of tests used have changed and improved in accuracy over the years, the approach adopted is similar.

Submissions were made to State or Territory governments to assist in supporting those potentially exposed to post transfusion Hepatitis C through the development of Lookback programs for hepatitis C as soon as it was evident that there were confirmed cases.

In December 1991, *The Working Party Reporting To the Communicable Diseases Standing Committee of the National Health and Medical Research Council (NHMRC)* reported that donor triggered Lookback for hepatitis C was “too expensive and inefficient to be conducted as routine”. The Standing Committee did, however, endorse recipient triggered Lookback for hepatitis C. The Australian Health Ministers Advisory Council, in October 1994, approved a hepatitis C Lookback Program endorsing both donor triggered and recipient triggered Lookback. The Lookback program is discussed in greater detail in the response to Term of Reference (m) and the process is described in Appendix G.

3.8 Window period transmission of hepatitis C virus through blood transfusion after 1990

As described above, NANBH was known to be a complication of transfusion for many years. There were many cases in Australia, as elsewhere, of NANBH (now known to be hepatitis C), which occurred as a result of transfusions from apparently healthy donors, which took place up to February 1990 when screening began. There have, however, also been cases of post-transfusion hepatitis C in Australia, which are attributable to transfusions, which occurred after 1990. The explanation for how these cases have occurred is that they are either window period transmissions or transmissions due to the fact that screening tests at the time (although state of the art) were unable to screen out all infectious donors.

As explained in the previous Section 2, the introduction of first generation hepatitis C antibody testing, whilst it was a major advance, did not detect all donors who were infectious. Some true hepatitis C positive donors were not detected by the first generation test. The

second generation test introduced in 1991 was an improvement and the third generation tests were even more sensitive and detected almost all positive donors. Thus a small number of patients acquired hepatitis C through transfusion in the early nineties because such tests were not 100% efficacious as described below.

Each test reduced the window period of infection. The window period is the number of days after an individual is infected during which infection may be present but not detectable by the screening method in use. By 1994, the window period for hepatitis C had been reduced from 82 days for second generation tests to 66 days for the third generation tests. However, even with third generation tests, a donor could not be identified as infectious until an average of 66 days after they acquired the infection. Because new infections occur regularly in the community from which donors are drawn, some donors therefore remained capable of transmitting infection in the period from 1990 to 2000. The number of cases however, was much lower when compared with the number in the decade before.

ARCBS is aware of 13 cases of post-transfusion hepatitis C, which occurred since 1995. These 13 recipients received blood products derived from seven donors screened with third generation tests, which were the most sensitive and efficacious tests available internationally at the time. The 13 recipients were identified through investigation instigated by the ARCBS of donors who were found to be positive for hepatitis C at a subsequent donation or where the donor has notified the blood service that they had become hepatitis C positive subsequent to their last donation. In the period 1995 to 2000 approximately seven million donations of blood were been made to ARCBS.

In June 2000 there was a quantum leap made in hepatitis C testing in Australia due to the introduction in Australia and internationally of Nucleic Acid Testing (NAT) for both HIV and hepatitis C. This new technology was very sensitive because it directly detected genetic material of viruses such as HIV and hepatitis C. This technology was introduced as an additional test to, not a replacement test for, the third generation hepatitis C antibody test. The introduction of NAT was made possible by specific government funding. In the three and a half years since the introduction of NAT there has not been a case of transfusion-transmission of hepatitis C in Australia.

This record accounts for the reason that the residual risk of acquiring hepatitis C in Australia from a single blood transfusion now stands at the very low figure of 1 in 3,112,000 (Table 1 in Section 2). However, transmission of hepatitis C through blood transfusion is still theoretically possible, although the risk is extremely small and hence, is expected to be a very rare event.

SECTION FOUR

e. The process leading to the decision by the Australian Red Cross not to implement testing (such as surrogate testing) for hepatitis C once it became available.

Surrogate tests, such as ALT and the anti-core test, are no substitute for a specific test as they lack sensitivity and specificity meaning that results could be inaccurate or inconclusive. The question of the value of surrogate testing was controversial and there was not international consensus on the appropriateness of its introduction. The Australian policy relating to the use of surrogate testing followed a review of international practice and was in accordance with advice of the Council of Europe, Committee of Experts on Blood Transfusion and Immunohematology. This highlighted the need for each country to establish the underlying prevalence rate of post-transfusion NANBH and to then determine the potential contribution of surrogate testing in their own population.

The Australian Red Cross was one of the earliest Blood Services in the world to adopt the first specific antibody screening test for hepatitis C for its blood supply in February 1990, second only to Japan.

4.1 Testing for hepatitis C

In answering this Term of Reference it is important to clarify that wording assumes that the Australian Red Cross (referred to as "*Red Cross"*) did not implement testing including surrogate testing for hepatitis C once it became available. This assumption is incorrect.

It is necessary in responding to Term of Reference (e) to clarify firstly the different tests involved and then differentiate between the two, specifically:

- specific testing for the presence of antibody for hepatitis C which was introduced by the Red Cross in February 1990 as soon as it became commercially available; and

- surrogate testing or non-specific testing (such as an ALT test), which was not introduced nationally by the Red Cross for what was then designated as non-A, non-B hepatitis (NANBH) in the seventies and eighties before the specific agent (hepatitis C virus) was identified.

4.2 Testing for antibody to hepatitis C virus

Antibody tests

Antibody tests are those that detect antibodies formed by the body's immune system to the infectious agent. The most commonly used tests for hepatitis C virus detect antibody to the virus. The function of antibodies formed in response to the hepatitis C virus is not known but they can be used in detection of the virus.

Development of hepatitis C antibody testing

Following the identification of the agent responsible for NANBH, hepatitis C, the first commercial antibody test became available in Australia in February 1990.

4.3 Surrogate testing for hepatitis C virus

Surrogate tests

Surrogate tests are used to try and detect donors likely to be infected with viruses in the absence of any specific test. Surrogate tests are no substitute for specific tests such as antibody tests. Because they lack sensitivity and specificity (refer to Glossary), it is difficult to determine with certainty their effectiveness in identifying blood donations that should be excluded, the number of donors that might be excluded unnecessarily and the type of explanation that might be given to donors whose blood is rejected.

In the absence of successful efforts to develop direct diagnostic screening methods for the NANBH agent in the eighties, two types of surrogate tests were proposed by some blood bankers to try and identify potentially infected donations. One such test was to measure the level of alanine aminotransferase (ALT) in a donor's blood. Levels significantly above normal might indicate liver inflammation, possibly caused by a hepatitis virus but there were other infectious agents and factors such as obesity and alcohol overuse that could have caused the elevated levels as well.

The second kind of test proposed was to measure the presence of a marker of infection with a virus that was not the one of concern but that had similar epidemiologic characteristics i.e. affected a similar group of individuals. Such a test detected the antibody to the hepatitis B core antigen (anti-HBc), which will be referred to as "*anti-core"* which denotes previous infection with hepatitis B virus.

Because of the imperfect nature of the two proposed tests, not surprisingly controversy arose in relation to their use in the eighties. Countries with comparable blood banking practices each experienced their own version of the debate over the use of surrogate tests to try and identify NANBH for which no specific test existed.

To understand the position adopted by Australia in relation to the surrogate tests, it is necessary to have reference to the two respectable schools of thought in the debate during the eighties and to then discuss the school of thought adopted by Australia.

However, it should be noted that the debate raged across most western industrialised nations and continued over a period of in excess of eight years. Reference to the debate is not intended to be exhaustive but rather a summary of the salient features of the debate leading to the position ultimately adopted by Australian blood bankers.

4.4 Summary of surrogate marker debate – arguments for introduction of the surrogate test

The catalyst for investigation of a surrogate test to identify donors potentially carrying the agent of NANBH arose in circumstances where there was no direct test available to detect NANBH carriers. The perception was that an efficacious surrogate test, when positive, might be indicative of the presence of the virus although not conclusive.

Advocates of the use of surrogate tests supported their introduction predominantly but not exclusively by reference to two studies conducted in the United States. ALT levels in the blood of US donors were tested to determine whether elevated levels might correlate with the risk of blood transfusion caused hepatitis in recipients. The two studies proceeded simultaneously and their seminal findings were reported on in 1981. The Transfusion-Transmitted Viruses (TTV) study reported an association between elevated transaminase

(ALT) in donors and the development of NANBH in the blood recipients. From their data, the TTV predicted that, by excluding donors with elevated ALT, 30%[1] of NANBH might be prevented, at a loss of 3.1% of the donor population (Aach, Szmuness et al. 1981). The National Institutes of Health (NIH) study found an almost identical outcome predicting donor exclusion based on elevated ALT might prevent 29% of transfusion associated hepatitis at the loss of approximately 1.5% of the donor population (Alter, Purcell et al. 1981).

In 1985 and 1986, the 1981 studies were reanalysed and showed an association between the hepatitis B marker, anti-core, in donors and the development of NANBH in the recipients. In the TTV study (Stevens, Aach et al. 1984), recipients of at least one unit of anti-core positive blood had a 19% frequency of NANBH compared to 7% amongst recipients of only anti-core negative blood.

In circumstances where there was no direct test for NANBH and the rate of NANBH in the US ranged from 7 - 27% (when including recipients of blood from both paid and unpaid donors), the American Association of Blood Banks (AABB) directed in February 1987 that units for routine transfusion in America be tested for ALT and anti-core by 1st June 1987. At the time of making the directive the AABB conceded problems associated with donor loss and increased expense generated by the introduction of such tests. In the NIH study (Koziol, Holland et al. 1986) recipients of anti-core positive blood had an 11.9% prevalence of transfusion associated hepatitis compared with 4.2% among recipients of only anti-core negative blood.

The FDA, the US authority responsible for blood banking safety standards, did not make surrogate testing mandatory subsequent to the AABB directive (Biswas 1989).

4.5 Summary of surrogate marker debate – arguments against introduction of the surrogate tests

It was argued that the measurement of ALT, although a test for one aspect of liver function, was not a specific test for NANBH. Between 1.5-7% of otherwise acceptable donors could have elevated levels of ALT for unknown reasons. Exercise, alcohol and use of many common medications could lead to elevated ALT levels. Males had higher levels than females and there were differences in normal ranges between various parts of the US. It was asserted that this lack of specificity could result in an intolerably high rate of unnecessary rejections. By reference to the two earlier studies at least 70% of donors excluded due to high levels of ALT were not implicated in the transmission of disease (because excluding those with elevated ALT would have removed 29-30% donations which could potentially have transmitted NANBH). In such circumstances the test would fail to detect seven out of ten carriers of NANBH whilst rejecting seven non-carriers for each three detected.

In circumstances where at least 70% of non-transmitting donors might be rejected arguments were advanced that this could seriously stress a nation's donor supply. It was asserted that studies on the effect of such reduction should be made available to ensure that severe blood shortages did not arise causing even more negative outcomes than might be prevented by introduction of the surrogate tests. Loss of healthy donors and the long-term effect of increased rejections on donor recruitment were expressed as a major concern on the part of the blood banking community outside the US who did not support the introduction of the surrogate tests.

[1] The TTV study exclusion at a donor ALT level of 45 IU/L would prevent approximately 40% of PTH/post-transfusion NANBH. However, this prediction is based on the crude rather than the corrected efficacy. After correction for number of units transfused (Alter, Purcell et al. 1981), and 'background rate' of hepatitis (Stevens, Aach et al. 1984), a better representation of the predicted efficacy is approximately 30%.

The Council of Europe's Committee of Experts on Blood Transfusion and Immunohematology, in May 1987 (Europe 1987), argued that the benefits derived from the introduction of the two tests would not be uniform throughout countries and that there was no guarantee that in any given country there would be a significant reduction in the transfusion of NANBH. This Committee surveyed their member countries on whether they were doing ALT or anti-core testing (anti-HBc) at the time, and the responses obtained was summarised:

Table 4 – Summary of results of Council of Europe member countries survey, May 1987 (Europe 1987)

Country	ALT	anti-HBc (anti-core)
Austria	No	Yes
Belgium	No	Limited testing
Cyprus	No	No
Denmark	No	No
France	No	No
Federal Republic of Germany	Yes	No
Greece	No	No
Iceland	No	No
Ireland	No	No
Italy	Yes	No
Luxembourg	Yes	No
Netherlands	No	No
Norway	No	No
Switzerland	No	No
United Kingdom	No	No
Finland	No	No
Canada	No	No
USA	Yes	(Phase in period of anti-core)

In such circumstances and where the introduction of non-specific tests could lead in some countries to severe depletion of blood donors which could compromise blood supplies, the Committee recommended in 1987 that individual countries would have to assess their own situation locally and decide on appropriate action to take. It was proposed that countries undertake their own studies to determine the suitability of the non-specific tests.

Concern was also expressed in the eighties as to the difficulty of establishing any standards for ALT testing. Given that the ALT level in donors varied by reference to geography, sex, size, health status, there was no clear cut consensus as to what ALT cut-off level (refer to Glossary) should be adopted above which blood would be discarded.

Difficulties were identified as inherent in dealing with donors found to have high ALT levels. Based on the figures canvassed in the US studies, it was probable that at least 70% of donors with raised ALT would be free of hepatitis (Refer to discussion in 4.5.1). However, they would have to be informed that their blood could not be used, that they might have a viral disease of unknown cause and that their long-term prognosis was unclear. This concern was noted to be of substantial significance where donors were volunteer, unpaid and repeat donors, bearing in mind that these donors are the safest donors in contrast to paid donors (refer to discussion in e/section 5).

It was known that ALT levels of an individual could fluctuate even where the individual was a carrier of the NANBH agent. Accordingly, a carrier might have a high ALT level (above the cut-off level) on one date and a lower ALT below the cut-off level on another date. This was a further factor considered in relation to the non-specificity of ALT testing and supported the concerns expressed about the poor specificity of the test and the cumulative loss of donations by permanent deferral of donors.

Although two US studies indicated a predictive value of certain surrogate tests, studies in other countries revealed no significant correlation (Aymard, Janot et al. 1986; Leikola 1987; Barbara 1995). These studies raised concern relating to the value of the US studies with countries using unpaid, volunteer donors with a lower risk of transmitting NANBH.

In circumstances where countries had a low incidence of NANBH it was argued that the impact of other risk reducing factors including antibody tests for human-immunodeficiency virus (HIV), measures to enhance donor self-exclusion and increased use of autologous blood utilisation would have further reduced the incidence and this would have to be taken into account in balancing the usefulness of the surrogate tests and the potential negative impact on the blood supply and the consequent lives lost from loss of donations and inability to meet demand.

4.6 Australia's response to surrogate testing

Review of debate

Australian blood bankers took all questions of safety extremely seriously and thoroughly reviewed and considered the 'surrogate marker debate' as it evolved in the United States, Europe and the United Kingdom.

International literature

The Red Cross subscribed to and/or received journals in which issues relevant to blood banking were canvassed and Australian expert blood bankers monitored and reviewed articles pertaining to the surrogate marker debate throughout the eighties.

Attendance at international forums

Delegates of the Red Cross attended numerous international forums prior to and throughout the peak of the debate in 1986/1987, including the International Society of Blood Transfusion and the Council of Europe meetings, to capture information relating to the surrogate marker debate for consideration by reference to the Australian donor population.

4.7 The Australian decision not to introduce surrogate testing as a national strategy

Having reviewed the arguments debated in the US and Europe relating to the surrogate tests as they were first reported, the Red Cross accepted the rationale and consequential recommendation of the Council of Europe, Committee of Experts on Blood Transfusion and Immunohematology of May 1987 that, countries should carry out their own prospective studies before introducing the debated surrogate tests to ensure a proper balance of risk factors including the potential for a reduction in the transmission of NANBH in the country concerned by use of the surrogate tests and the potential for depletion of a countries blood supply.

In adopting such a position, the Red Cross had reference to the following factors:

Cossart et al had reported in January 1982 a 1.7% rate of post-transfusion NANBH in cardiac surgery patients in Sydney (Cossart, Kirsch et al. 1982). This study revealed only one-quarter to one-fifth of the post-transfusion hepatitis rate of that of the US, suggesting a donor population in Australia quite different to that in the US.

By reference to the above, the Red Cross was concerned that imposition of surrogate marker testing might have less impact and engender a disproportionate donor loss in relation to efficacy. As had been noted by eminent blood bankers in the US, the surrogate tests might fail to detect seven out of ten carriers of NANBH while rejecting seven non-carriers for each three detected. It was considered that introduction of surrogate testing might lead to a rejection of at least 5% of voluntary blood donations (Victorian BTS data) at a time of serious shortage in the supply of platelets and Factor VIII (Refer to discussion of shortages in Term of Reference k/section eight). Further, limitation in the supply of red cells could lead to cancellation of elective surgery when blood of the required group was not available. In such circumstances, the Red Cross considered it paramount to weigh these factors by reference to the rate of NANBH and efficacy of the two surrogate tests in the Australian donating population through the introduction of a prospective study.

Leading proponents of surrogate testing in the US advised other countries to undertake a randomised prospective study on surrogate testing. According to Dr. Harvey Alter from the National Institutes of Health in Washington (Alter 1988b):

> "*…the major blood organisations in the United States have elected to adopt both the ALT tests and the anti-core test as routine donor screening measures for all blood donations. Although I am in agreement with this decision, I wish to stress again that these are predicted efficacies not proven efficacies, and that in countries that can do so, an effort should continue to be made to perform a controlled, prospective study to demonstrate whether such costly measures are truly indicated*."

The Australian donor population was considered to be much 'safer' than its US counterpart having regard to the use of much blood from paid donors in the US. The Red Cross was aware of views expressed in the blood banking community similar to the following:

> "*Prior to the advent of hepatitis serological assays, by far the most important hepatitis risk factor identified was the origin of donor blood. As early as the 1960s, investigators in America had noted that paid (commercial) blood was much more likely to be associated with subsequent hepatitis in the recipient than was blood that had been voluntarily donated (Kunin 1959; Allen and Sayman 1962). Even stronger support for this observation emerged from numerous studies conducted during the 1970s, including the prospective studies described above (Walsh, Purcell et al. 1970; Alter, Holland et al. 1972; Goldfield, Black et al. 1975; Seeff, Zimmerman et al. 1977; Aach, Lander et al. 1978; Seeff, Wright et al. 1978). In every study in which this was investigated, the frequency of hepatitis was found to be far greater in recipients of commercial donor blood than in recipients of volunteer donor blood. … Based on this accumulated evidence, it was declared mandatory in 1978 in the USA to label the origin of all donor blood, namely whether derived from a paid or from a volunteer donor. … … While payment per'se did not render a donor dangerous, the inducement of remuneration drew segments of the population that had hepatitis risks at least 10-fold higher than that of the general population.*" (Alter and Seeff 1998)

The US introduced surrogate testing in the context of a donor population with a high incidence of NANBH (7-27%) and a significant proportion of paid donors. The Australian Red Cross was aware of the risk of paid donors and ensured that its service remained reliant entirely on unpaid, voluntary donors.

It was considered that the Australian donor population may have changed since the first post-transfusion study (Cossart, Kirsch et al. 1982) in Australia having regard to the introduction of self-exclusion of individuals at high risk of HIV, intravenous drug users and persons generally at high risk for HIV transmission. Few cases of post-transfusion hepatitis were being reported to the Blood Transfusion Services (BTS) and a majority of these were hepatitis B (refer to Section 3).

It is relevant to note that this perception of a lower risk donor population subsequent to the introduction of HIV related precautions, was accepted by leading US blood bankers as a major influence on blood safety. It was estimated that self-exclusion based on explicit instructions to donors, direct donor questioning regarding high-risk behaviour and the promotion of donor programs (where the patient used their own blood minimising the amount of blood used during surgery) reduced the risk of transfusion-transmitted hepatitis by 40-60%. (Alter and Seeff 1998) The Red Cross had ensured that questions relating to high-risk sexual and injecting behaviour were introduced expeditiously in Australia (1983) initially to reduce the transmission of human immunodeficiency virus (HIV), and NANBH (hepatitis C) as a side benefit, through its volunteer donors.

In October 1984 the New South Wales BTS initiated a large study to measure the efficacy of the anti-core as a surrogate test for HIV infection. None of the anti-core positive donations tested subsequently at the Fairfield Hospital in Melbourne were found to be HIV antibody positive. The surrogate test did not establish a correlation between anti-core positive donations and the transmission of HIV. The study had demonstrated not only a potential loss of 2% of donations but that these donations would not have transmitted HIV. The results of this earlier study supported the concerns expressed by the Red Cross that in the absence of undertaking an Australian-based study of the efficacy of the surrogate tests and rate of NANBH in the Australian donor population, a disproportionate donor loss might arise.

The majority of donors with positive test results based on the US data would be unlikely to be carriers of NANBH. This would create difficulties in interpreting test results and problems with donor notification and permanent deferral. The Red Cross was aware that donors could suffer anxiety and stress with possible long-term consequences in circumstances where they were, in fact, more likely not to be infected with the virus. Further, it was noted that such donors would be unlikely to return to the donor panel in the event of the introduction of an antibody test confirming a negative status. In circumstances where Australia relied entirely on a voluntary, altruistic donor base (4-5% of the adult Australian population donating), issues such as donor fears were considered to be a relevant factor to take into account when determining whether to initiate a prospective study to fully understand the position in Australia, or to introduce surrogate tests based primarily on the US donor population.

The Red Cross was also aware of the technical difficulties arising in the selection of an appropriate ALT (cut-off) level for excluding blood for transfusion in the event that an ALT surrogate test was introduced.

4.8 The second Australian post-transfusion hepatitis study

Having thoroughly reviewed the surrogate testing data, the Red Cross accepted the position that the relevance and usefulness of both tests must be scrutinised within the Australian context to determine whether the advantages would outweigh the disadvantages. It was therefore proposed that an Australian-based study would be undertaken to determine the impact of the imposition of surrogate marker testing including whether they would engender a disproportionate donor loss in relation to their efficacy in reducing the transmission of NANBH.

In September 1987, the post-transfusion hepatitis study was commenced in New South Wales and Western Australia to examine the rate of NANBH in Australia and correlation with ALT and anti-core tests in donors. Although, Queensland introduced routine ALT testing, no other State or Territory introduced surrogate testing for NANBH.

The fact that the BTS in Queensland, having reviewed the same international data and arguments as the other services, reached a different conclusion from the remaining states is evidence of the highly controversial and inconclusive nature of the ‘surrogate marker debate’.

SECTION FIVE

f. The likelihood that hepatitis C infections could have been prevented by the earlier implementation of surrogate testing and donor deferral

Australian management and decision making about blood and its safety has been based on knowledge available at the time, and has been in line with the best international practice.

It is almost impossible, hypothetically, to quantify the potential benefit of surrogate testing or the impact on the blood supply of its introduction in Australia.

However, the decision relating to surrogate testing has recently been reviewed by the *Expert Advisory Group on Hepatitis C and Plasma in 1990* (Barraclough, Angus et al. 2003), who commented that it would be counterproductive to introduce surrogate testing in countries like Australia where the prevalence of post-transfusion hepatitis was low.

5.0 Introduction

In this section, the surrogate tests discussed are ALT testing and anti-HBc, referred to as "*anti-core*". In Australia, no State or Territory, (other than Queensland which introduced ALT testing), introduced surrogate testing for NANBH. It is difficult to speculate about the potential impact of surrogate testing after the fact; so a more useful discussion would be to consider the evidence from countries that did introduce surrogate testing for NANBH/hepatitis C and their retrospective view of the benefit. Additionally, it is important to look at countries that did not introduce surrogate testing and observe the incidence of NANBH during the same time period.

5.1 The Report if the *Expert Advisory Group on Hepatitis C and Plasma, in 1990*

In the *Report of the Expert Advisory Group on Hepatitis C and Plasma in 1990 (Barraclough, Angus et al. 2003)* the question of surrogate testing was examined and the comment was made because, surrogate tests were lacking in sensitivity and specificity (refer to Glossary).

> "*It was considered that it would be counterproductive to introduce surrogate tests in countries where the incidence of post-transfusion hepatitis was reported to be 1.6% (sic) in a study published in 1982*" (Cossart, Kirsch et al. 1982).
>
> "*It was also felt that the risk of transmitting non-A, non-B hepatitis … might have been further reduced by the intensive epidemiological screening of donors implemented to combat the risk of transmitting HIV*."
>
> "*The greatest potential benefit from using surrogate tests was in countries where the risk of transfusion transmitted hepatitis was highest, notably countries that used blood and blood products from paid donors. Thus, the United States introduced ALT and anti-HBc screening of donations in 1987*."

5.2 Retrospective doubts about the benefit of the introduction of ALT in the US

In *The Retroviral Epidemiology Donor Study (REDS*), a large multi-centre study in the US, the donations from first time donors who had been tested for surrogate markers were also subsequently tested with the second generation hepatitis C antibody test. It was noted that, of those who tested positive to a surrogate test, only 9% of those with an elevated ALT and 5.3% with anti-core also tested positive for hepatitis C antibody. Looked at in reverse, 91% of

US donors with an elevated ALT and 94.7% of those with anti-core were hepatitis C antibody negative (Busch 1998). This helped to explain why surrogate testing did not measure up to its predicted efficacy.

Furthermore, Donahue's multi-centre prospective study (Nelson, Ahmed et al. 1993; Alter 1994) in the US showed that the introduction of surrogate tests in 1986 - 1990 resulted in little difference in the proportion of multi-transfused patients who developed hepatitis C (table 5). Before surrogate testing, there was 4.49% and afterwards 4.43% of patients with evidence of hepatitis C. However, it was the introduction of a specific test in 1990 that resulted in a far greater magnitude of reduction of the proportion patients who developed hepatitis C (4.49% to 1.08%).

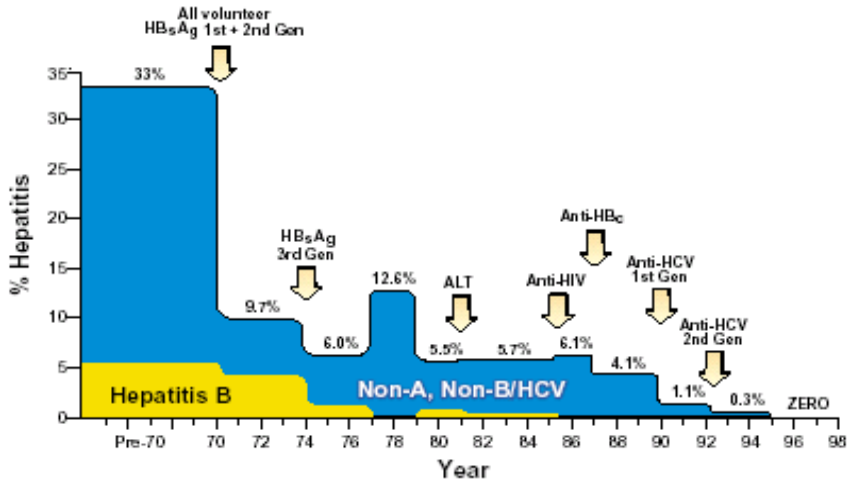
Table 5 – Efficacy of donor screening methods on reducing the risk of post-transfusion hepatitis C in the USA (Nelson, Ahmed et al. 1993)

Time period	Type of hepatitis C screening method used	Patients who developed hepatitis C antibody (%)
April 1985 – September 1986	Prior to Surrogate Tests	4.49%
October 1986 – April 1990	Surrogate Tests	4.43%
May 1990 – February 1991	Surrogate tests and Antibody to hepatitis C	1.08%

This was supported by Harvey Alter (Alter and Houghton 2000) who published a review on the key developments which affected the incidence of non-A, non-N hepatitis (NANBH) among transfusion recipients. These events are also represented diagrammatically in Figure 7 below. The most significant drop (from 33% to 9.7%) occurred with the exclusion of paid donors and introduction of hepatitis B surface antigen testing in 1970 and he estimated that 70% of this was attributable to the exclusion of paid donors.

Data for the next cluster of changes relating to surrogate markers were derived in the main from the National Institutes of Health post-transfusion hepatitis study. The combined effect of ALT testing (introduced at the NIH Blood Bank in January 1981) and implementation of anti-core as a surrogate test in 1987 was a drop in incidence of NANBH from 5.5% in 1981 to 4.1% (figure 7). This reduction was significantly less than that noted (from 4.1% to 1.1%) following the introduction of the first generation hepatitis C antibody test in 1990.

Figure 7 – Decreasing incidence of transfusion-associated hepatitis 1969-1998



Another eminent figure, Dr. Paul Holland, involved in the pivotal NIH studies, has said in retrospect that:

> *"Implementation of testing volunteer donations for an elevated ALT level at the National Institutes of Health in 1981 did not change the rate of post transfusion hepatitis seen there in ongoing prospective studies of cardiac surgery patients. The rate for the years 1981-1983 was no different than the rate found in the 3 years before testing units for an elevated ALT level."*

Further, in 1996 the American Association of Blood Banks (AABB), in their Technical Manual, although they required surrogate testing in 1987, arrived at the following conclusion (AABB 1996):

> "*… the impact of surrogate testing on the safety of transfusion has been difficult to evaluate. More stringent criteria for donor selection had recently been introduced in response to reports of AIDS in transfusion recipients.*"

5.3 The incidence of NANBH/hepatitis C declined due to other measures regardless of surrogate testing

A true randomised study on the potential value of surrogate testing was never carried out in the US. There was a greater reduction of post-transfusion NANBH, without the implementation of surrogate testing in Canada during the eighties, than what was predicted in the US. For instance, the incidence of post-transfusion NANBH in Canada fell from 9.2% in early eighties (Feinman, Berris et al. 1988) to 3.2% in the late eighties even without the implementation of surrogate testing (Table 6).

Many other studies from Australia and Europe showed a similar reduction in the incidence of NANBH without introducing surrogate testing. The reduction in the risk of post-transfusion hepatitis in the late eighties to the early nineties was documented in Finland, the Netherlands, Spain and Australia (Table 6). Without implementing surrogate tests there was an equal or greater fall in the rates of post-transfusion NANBH than the approximately 30% predicted by the pivotal US studies.

These studies cast doubt on the validity of the US Transfusion Transmitted Viruses (TTV) and National Institutes of Health (NIH) studies. In particular, they questioned whether the conclusions about surrogate testing made by the US studies were applicable to other countries.

Many experts believed that the reductions in risk of post-transfusion hepatitis in the late eighties was the side benefit of other preventative measures to reduce the risk of transfusion-transmitted HIV/AIDS. Swedish authors (Mattsson, Aberg et al. 1988) documented a two-thirds drop in the risk of NANBH in the eighties, which they directly attributed to "*restrictions for blood donations due to the human immunodeficiency virus*."

Table 6 – Reduction of rate of non-A, non-B hepatitis during the eighties in countries which did NOT implement surrogate testing (prospective studies)

Country	Reduction of incidence of NANBH / hepatitis C	
	From:	To:
Australia	1.7%	1.0%
	(Cossart, Kirsch et al. 1982)	(Ismay, Thomas et al. 1995)
Canada	9.2%	3.2%
	(Feinman, Berris et al. 1988)	(Blajchman, Bull et al. 1995)
Finland	4.6%	1.6%
	(Lagerstedt, Leikola et al. 1982)	(Ebeling, Naukkarinen et al. 1991)
Netherlands	3.4%	2.3%
	(Katchaki, Siem et al. 1981)	(Van der Poel, Reesink et al. 1989)
Spain	16%	9.6% - 11.7%
	(Barrera, Bruguera et al. 1991)	(Hoyos, Sarrion et al. 1989; Esteban, Gonzalez et al. 1990)

5.4 Anti-core testing

Little benefit of anti-core testing in Australia

Although the Cossart study (Cossart, Kirsch et al. 1982) had suggested that screening donors for anti-core (a marker of past hepatitis B infection) might be predicted to be beneficial in reducing NANBH/hepatitis C this was not confirmed in the second post-transfusion study in Australia (Ismay, Thomas et al. 1995). Ismay et al. showed that none of the 119 donations given to patients who subsequently developed hepatitis was positive for anti-core alone. Recipients of the 27 anti-core positive units transfused did not develop any indication of either hepatitis B or C. Thus, there was no correlation at all between donors being anti-core positive, and hepatitis C infection.

The finding made by Ismay et al was supported by studies from France (Aymard, Janot et al. 1986) and the Netherlands (Van der Poel, Reesink et al. 1989), which also failed to show any correlation between the use of anti-core as a surrogate test and prevention of NANBH. In the Aymard study, no case of NANBH developed among the recipients of anti-core positive blood and the four patients with NANBH received blood from anti-core negative donors. In the van der Poel study, there was no statistical difference in the exposure to anti-core blood between the two study groups i.e. those with post-transfusion NANBH and those without.

5.5 Other key factors responsible for reducing NANBH/hepatitis C in the eighties and nineties

Reduction of proportion of paid donors in US

> "*To this date there is no intervention that even approaches the impact of excluding paid donors*." (Alter 1987)
>
> "*… the frequency of hepatitis was found to be far greater in recipients of commercial donor blood than in recipients of volunteer donor blood. ... the inducement of remuneration drew segments of the population that had hepatitis risks at least 10-fold higher than that of the general population*." (Alter and Seeff 1998)
>
> "*Hepatitis occurs even among recipients of volunteer blood, but in recipients of paid-donor blood the frequency is 3-4 times higher*." (Seeff and Dienstag 1988)

The TTV study (Aach, Szmuness et al. 1981) showed a 2 – 5 fold increase in the incidence of NANBH among recipients when comparing the group who received blood collected from volunteers at community agencies compared to blood from paid donors at commercial agencies. The US Veterans Administration transfusion-associated hepatitis study (Seeff, Wright et al. 1978) also demonstrated very clearly how the percentage of blood transfusion recipients developing hepatitis is directly related to the source of donations. What is significant is that Australia maintained to this day a 100% volunteer non-remunerated blood donor system, unlike the US and many European countries.

Keeping the proportion of new donors low

With surrogate testing and deferral of those donors who tested positive, this would result in replacement of repeat donors with new ones, who actually present more of a risk of transfusion-transmitted infections. This effect has been confirmed in many studies.

A recent study of the incidence of hepatitis C in ARCBS donors found that the rate in new donors is twice that in repeat donors. This is comparable to the published literature from the US and UK where the incidence for hepatitis C in new donors was estimated to be 2.4 – 6.2 times greater in new compared to repeat donors (Dodd and Reesink 1995; Soldan, Barbara et al. 2003). Had Australia adopted surrogate testing, 5 – 7% (Farrell 1989) of the donors would have been deferred, only to be replaced by new donors. Since risk is directly correlated with incidence (Risk = Incidence Rate x Window Period) then increasing the proportion of new donors with higher incidence proportionately increases overall risk.

Significant beneficial impact from pre-existing donor selection measures

In 1995 Ismay and others in Australia concluded that the decline by 50% of the risk of post-transfusion hepatitis over the decade between the two Australian post-transfusion hepatitis studies could be attributed to effectiveness of donor selection and deferral (exclusion of homosexual men and injecting drug users) in the wake of HIV/AIDS, as well as reduction in the number of units of blood received by each recipient (Ismay, Thomas et al. 1995). Australia had been particularly active in introducing signed donor declaration forms as early as December 1984 when the State and Territory governments were asked by the Red Cross to assist in the implementation of these preventative measures. At the instigation of the Federal Minister for Health of the time, each State or Territory Health Minister was asked to introduce legislation requiring donor declarations and imposing penalties for false declarations, and this was enacted.

Types of screening tests used

In the nineties, most experts understood that the implementation of hepatitis C antibody testing alone really accounted for most of the decrease in the risk of post-transfusion hepatitis C worldwide. This was supported by the Donahue study (Donahue, Munoz et al. 1992) as shown by updated data from the Nelson study (Nelson, Ahmed et al. 1993) in table 5 above, and the ARCBS's own analysis (table 7). It is evident that the magnitude of reduction of the risk of post-transfusion hepatitis C is dependent on the window period (refer to Glossary) of the screening test used.

The most widely applied risk model estimating the risk of releasing infectious donation into the blood supply uses incidence rate (IR) i.e. the rate of new cases diagnosed per year, multiplied by window period (WP) i.e. number of days during which the infection may be present but not detectable by the screening method in use. Therefore risk = IR X WP (Refer to Appendix C for Critical appraisal of testing methods).

Assuming that in Australia the number of new cases arising per year remains similar, the risk will be reduced just by using a test with a shorter window period. For instance, the risk of releasing an infectious unit of blood can be reduced by approximately 90% by using a Nucleic Acid Testing (NAT) whose window period is 7 days to replace a third generation hepatitis C antibody test (WP 66 days).

Table 7 – Declining risk of post-transfusion hepatitis C in Australia between 1979 – 2002 compared to other countries (ARCBS data)

Year introduced	Risk of transfusion NANBH/Hepatitis C transmission in Australia as % units[2] transfused	Risk of transfusion NANBH/Hepatitis C transmission in US and Europe as % units transfused
1979 – 1980 Unscreened (for hepatitis C antibody)	1:333	1:100
1990 Hep C 1st gen test	1:3435	1:3,333
1994 – 1995 Hep C 2nd gen	1:234,000*	1:103,000 in US 1:223,000 in France
1997 Hep C 3rd gen	1:311,956*	1:120,000 in US 1:620,754 in 1997 EPFA study
2000 – 2002 Hep C 3rd gen + NAT	1:3,112,000*	1:2 million in US 1:2.5 million in Central Europe

*figure based on mathematical modeling

[2] Please note that the data is expressed as % UNITS transfused, a different figure from %PATIENTS transfused. For the 1979 – 1980 and 1987 - 1990 periods the figures for % patients transfused in Australia were 1.7% and 1% respectively.

Heat treatment of plasma products

Because surrogate testing was so inefficient in detecting infectious hepatitis C blood donations (ALT missed 85% and anti-core missed 95% of the hepatitis C positives according to the Australian study of Ismay et al, 1995) its introduction would have had a negligible effect on removing hepatitis C from the large plasma pools used for fractionation. Of far greater importance was the availability of products heat-treated (at 60° for 72 hours) in the mid eighties and the subsequent introduction of super heat treatment in the early nineties, which virtually eliminated any remaining risk of hepatitis C in clotting factors.

Conclusion

Australian management and decision making about blood and its safety has been reasonable, based on the knowledge available at the time and in line with the best international practice.

Australia has an excellent record in the timely introduction of new or improved blood screening tests. This is demonstrated in Table 8 in which the date of universal introduction of screening tests for infectious agents are compared in various developed countries.

Table 8 - Date of universal introduction of screening tests for infectious agents in Blood Services worldwide

Country	Hepatitis B (HBsAg)	HIV (antibody)	Hepatitis C (antibody)	HTLVI	NAT (hepatitis C virus)
Australia	July 1971	May 1985	Feb 1990	Jan 1993	June 2000
Canada	1972	Mar 1986	June 1990	1990	Oct 1999
England	1972	Oct 1985	Sept 1991	Sept 2002	Apr 1999
Finland	1970	Jan 1986	Apr 1990	Mar 1995	Sept 2000
France	Oct 1971	Aug 1985	Mar 1990	July 1991	July 2001
Japan	Jan 1972	Nov 1986	Dec 1989	Nov 1986	Oct 1999
Netherlands	1970's	May 1985	June 1991	Feb 1993	July 1999
New Zealand	1972	Sept 1985	Aug 1992	ND	Nov 2001
Scotland	Oct 1970	Oct 1985	Sept 1991	Nov 2002	Feb 2001
United States	1971	May 1985	May 1990	1994	1999*

ND= not done

*Under investigational new drug application

There was a measurable reduction of NANBH/hepatitis C in a number of countries which did not introduce surrogate testing, including Australia. This was thought to relate to the intensive epidemiological screening of donors to combat the risk of transmission of HIV.

In the US, where surrogate testing was introduced, the benefit of the introduction of ALT testing in relation to NANBH/hepatitis C was examined and was found to be hard to establish.

It is almost impossible, hypothetically, to quantify the potential benefit of surrogate testing, or the impact on the blood supply of its introduction in Australia.

SECTION SIX

g. The implications for Australia of the world's most extensive blood inquiry, Canada's Royal Commission (the Krever Report);

h. The implications for Australia for the recent criminal charges against the Canadian Red Cross for not implementing surrogate testing for hepatitis C in the eighties.

Primarily, the Krever inquiry was instigated to investigate the management of the Canadian Blood Supply with respect to HIV. In relation to HIV Krever made the following comments "The information known … was sufficient for public health officials, regulators and blood bankers in … Australia to take preventive action … it should have prompted a similar response in Canada." A minor focus of the Krever Inquiry was hepatitis C. In relation to hepatitis C, there are major differences between Canada and Australia. The key being that Australia had a much lower incidence rate of post-transfusion hepatitis C than Canada or the US.

Assumptions and/or inferences about the Red Cross cannot be drawn from the examination of a different system operating in another jurisdiction. The findings of the Krever Commission and the recent criminal charges against the Canadian Red Cross are not relevant in any way to the Australian situation.

6.1 The Krever Inquiry

By the early nineties several hundred Canadians infected with human immunodeficiency virus (HIV) developed Acquired Immunodeficiency Syndrome (AIDS). There was a growing recognition of the extent and gravity of the HIV contamination of the Canadian blood supply; questions were raised about how it had occurred, and concerns were expressed about the possibility of a similar contamination in the future. The sub-committee on health issues of the Canadian Parliamentary Standing Committee (PSC) on Health and Welfare, Social Affairs, Seniors and the Status of Women held hearings in Canada between November 1992 and April 1993 to determine the circumstances surrounding the contamination of blood, blood components and blood products by HIV and to reassure the Canadian public of the safety of the blood transfusion system.

In May 1993, the PSC submitted a report entitled "Tragedy and Challenge: Canadians' Blood System and HIV", that said that the Canadian blood system "did not respond to the HIV/AIDS challenge as quickly as it might have". The PSC was unable to determine the precise reasons for delay. In particular, it said that there were many unanswered questions with respect to two key elements. The first was the introduction of a test for HIV antibodies and means of screening blood donations for HIV. The second was the introduction of blood products that had been heat treated to inactivate HIV in order to reduce the risk of infection. The PSC reported that public confidence in the safety and efficiency of the blood system had been seriously shaken. It recommended that a comprehensive review of the Canadian blood system, in the form of a public inquiry be done, in part to fully clarify the tragic events of the eighties, in part to reaffirm public confidence in the system, and in part to ensure that the Canadian blood system will be able to deal with future challenges as well as the myriad requirements of day-to-day operations.

Justice Horace Krever (Krever) was appointed to undertake the Inquiry in October 1993. The terms of reference of the Inquiry were expanded to mandate Krever to review and report on the organisation, management, operation, financing and regulation of all activities of the blood system in Canada including the events surrounding contamination of the blood system in the early eighties.

6.2 HIV contamination of Canadian blood supply the major component of Krever Inquiry

The catalyst to the Krever Inquiry (Krever 1997) was the infection of the Canadian blood supply by HIV and much of the Inquiry deals with what Krever asserts was the tragic consequences of failure by the Canadian Blood Transfusion Service (CBTS) to act in accordance with practices adopted by Australia, the United States and other western blood transfusion services. It is relevant to note that, in proposing that charges be laid against Canadian officials, Justice Krever stated as follows:

> "*In evaluating the actions of the past, one must always be mindful of the danger of doing so with the benefit of hindsight. It would be unfair to criticise the conduct and decisions of persons and institutions about AIDS in the 1980s from the perspective of our knowledge in the 1990s. I have assessed the measures taken by the Red Cross to reduce the risk of transmission of AIDS through the blood supply not on the basis of today's knowledge, but rather, on the basis of the knowledge at that time that AIDS represented a significant, although unproven, risk to the blood supply. The information known in the period examined in this chapter was sufficient for public health officials, regulators, and blood bankers in the United States, Western Europe, and Australia, to take preventive action to restrict the blood supply from persons at high risk of contracting AIDS. It should have prompted a similar response in Canada.*" (emphasis added)

By way of example in relation to the above, Justice Krever commented in his report (Krever 1997) that:

> "*Australia was one of the first countries in the World to introduce nationwide comprehensive blood-screening tests. In November 1984, the Australian Prime Minister announced that the Commonwealth had asked the US Department of Health and Human Services to make available the HIV – antibody screening tests that were still under development. In January 1985, the Australian Minister for Health and senior officials visited London, San Francisco, Atlanta, Washington, New York to gain understanding of the AIDS testing kits. Meanwhile, in Australia, the National AIDS Reference Laboratory undertook its own evaluation of the test kits during January and February 1985. Routine screening of blood donors for the AIDS virus was fully implemented at all blood banks in May 1985.*"

In contrast, as Justice Krever noted, "*the delay in implementing HIV – antibody testing had tragic consequences in Canada*" (Krever 1997). It was not until March 1986 that all Canadian services had available HIV antibody testing.

> "*There is no reasonable explanation for the length of time it took the Canadian Red Cross to prepare pamphlets about AIDS, particularly when it is compared to the time it took other blood services throughout the World to prepare pamphlets or information sheets for donors. Blood collectors in the United States put pamphlets in place within days of being told to do so by the Department of Health and Human Services. European countries that had not already done so followed suit in the spring and early*

> *summer of 1983, soon after similar recommendations were made by the Council of Europe … The Red Cross development of a pamphlet was slow and bureaucratic … the pamphlet was finally distributed in the spring of 1984 for use at blood donation clinics, moreover, it contained an outmoded description of persons at risk of contracting AIDS. Its language was vague and confusing.*"

In contrast in Australia in May 1983 pamphlets were introduced about AIDS and by the end of 1984, donors were asked to sign declaration forms that they did not fall into high risk groups.

6.3 Differences in decision-making processes of the Canadian Blood Transfusion Service and the Red Cross

In circumstances where assertions of wrong doing have their genesis in the identification and analysis of facts relating to a specific blood system operating within identified jurisdictional boundaries, it would be wrong to make any assumptions or draw any inferences relating to a different system operating in another jurisdiction. The following commentary distinguishes the decision-making process leading to the CBTS decision relating to surrogate testing and the rationale of the Australian Red Cross for deciding to undertake a prospective study to determine whether or not to introduce surrogate tests.

Costs

A Canadian Blood Committee (*the Committee*) was created in the autumn of 1981 after a conference of Canadian Ministers of Health. As conceived, the Canadian Blood Committee was to have representatives from every Provincial and Territorial Government and the Federal Government. The Federal Government paid the salary of the members who were Federal Government employees. The Committee was tasked to direct the Canadian blood system in accordance with the principles established by the Ministers of Health for the therapeutic use of blood, blood products or their substitutes. It was required to recommend allocation of resources to meet costs of implementing blood policies and safety issues.

Krever reported that the Committee's attention soon became focused on issues of funding. With respect to surrogate testing for non-A, non-B hepatitis, Krever (Krever 1997) noted:

> "*Its interest from the outset was the direct cost of implementation of the surrogate tests. The committee's pre-occupation with costs was well known to the Red Cross, which reported to it that the cost of testing would be as high as $20M in the first year.*"

Costs were a factor but did not play a major role in decisions relating to the use of surrogate tests for NANBH in Australia. There is no evidence to suggest that the various State and Commonwealth Health Departments would not have funded their introduction had the Directors of the State or Territory Blood Transfusion Services (BTS) recommended their introduction. Costs did not dominate discussions relating to surrogate tests in Australia and did not form the basis upon which the decision was made to undertake a prospective study in Australia before deciding whether to introduce the surrogate tests.

Delays

Costs were also a major factor in the delay in Canada in introducing a multi-centre study to determine whether surrogate screening might be appropriate based on the epidemiology of the Canadian donating population. The decision to study the efficacy of surrogate tests rather than implement them was seen by the Committee according to Krever (Krever 1997) as the least expensive course of action in the short term.

> "*The Committee finally agreed to support a study financially because 'it made economic sense' and the 'two-year delay in finalising the research project had delayed implementation of surrogate testing, potentially saving $20M, with a potential for further savings until the results of the study became available*."

Funding for the Canadian multi-centre study was not approved until September 1989.

When the decision in Australia was made to undertake a prospective study to determine the rate of transfusion transmitted non-A, non-B hepatitis in Australia in accordance with the proposal of the Council of Europe's Expert Committee of Immunologists and Haematologists and the National Blood Transfusion Service, funding was immediately made available by the Red Cross and other parties and the project was initiated in September 1987. The delays experienced in Canada by reference to funding allocation problems were not similarly experienced in Australia.

Incidence of NANBH

Krever recognised in his report the need for information about the extent and nature of post-transfusion hepatitis and specifically post-transfusion non-A, non-B hepatitis (NANBH) in the decision-making process as to whether to implement surrogate testing. No reliable Canadian data was collected until a small study was undertaken by Dr. Feinman of the incidence of NANBH in Toronto. Results of the study demonstrated the incidence in Toronto of NANBH to be 9.2% (Feinman, Berris et al. 1988).

Krever accepted submissions that the incidence of the disease in the US, which had been estimated in various studies, could have served as a basis for estimating the Canadian incidence, but neither the CBTS nor the Laboratory Centre for Disease Control made use of such material. It was asserted that given the US data and the epidemiological similarities between NANBH, it would have been prudent to assume that the incidence of post-transfusion NANBH in Canada at least in urban areas was comparable to that associated with volunteer donors in the US, which was as high as 10% in certain regions. Indeed, Feinman's Toronto incidence study (9.2%) confirmed the similarity.

Krever (Krever 1997) concluded that:

> "*It became known in 1985 that the rate of post-transfusion Non-A, Non-B hepatitis in Toronto was similar to the rate in many US urban centres. When, during the 1980s, discussions took place among the CBTS, the Health Protection Branch, and the Canadian Blood Committee about whether surrogate tests for Non-A, Non-B hepatitis should be introduced in Canada, neither the CBTS nor the Health Protection Branch relied on the US data to recommend their introduction, although it was reasonable to believe the rate of post-transfusion hepatitis here was similar to that in the United States. Because of the proximity of the United States to Canada and the ease of mobility and migration between the two countries, significance should have been attached to the U.S. rate of transfusion-associated disease, and appropriate precautions should have been taken in Canada. In the absence of evidence that the rate was different in Canada, there was no sufficient reason to refrain from relying on the U.S. data and introducing the surrogate tests.*"

In contrast, the incidence of post-transfusion hepatitis in Australia was reported as 1.7% (quoted as 1.6% in the Krever Report) in a post transfusion hepatitis study in 1982 by Cossart (Cossart, Kirsch et al. 1982). No evidence suggested a rate in any way similar to the range noted in the US. In circumstances where the incidence of NANBH appeared to be considerably lower than that in the US/Canada, the Red Cross decided to undertake a

prospective study to determine the rate of NANBH to assist with its deliberations relating to the efficacy of the use of surrogate tests in Australia.

Comparison with other countries

Krever noted that in their submissions, the Government of Canada and the CBTS said that surrogate testing of blood donations for NANBH was not implemented in all western industrialised nations, and relied on this fact to support the reasonableness of the decision not to implement surrogate testing in Canada. Krever noted that it was correct that surrogate tests were controversial in parts of the world other than North America, and that it was decided not to implement them in most countries. Also, data from the ongoing NIH studies, showed no benefit from the introduction of ALT testing (Alter and Hoofnagle 1984).

Krever indicated that the United Kingdom was referred to as an example of an industrialised country that did not implement surrogate tests. However, he explained that the incidence of NANBH was much lower in the United Kingdom than in Canada and the US. One study found it to be 2.5% among cardiac patients who had received multiple units in transfusion. The low incidence and the need for a randomised study were given as reasons for not adopting surrogate testing.

Krever noted that in Australia, where surrogate testing was not conducted routinely, the incidence was reported to be 1.7% (quoted as 1.6% in Krever) in a study published in 1982 and suggested that in general, countries in which the incidence of post-transfusion NANBH was low were most likely to have decided not to implement surrogate tests routinely. Countries with a significant incidence were more likely to introduce at least one of the surrogate tests.

Loss of donors

When testing for hepatitis B was introduced, much of the blood supply in the US came from paid donors. The test confirmed what blood bankers in the US had known since the late fifties, that blood that was paid for was associated with a significantly increased risk of transmitting hepatitis. In a study conducted at the US National Institutes of Health, researchers estimated that, had blood from paid donors been excluded from the system before the introduction of the testing for hepatitis B surface antigen, post-transfusion hepatitis would have been reduced by about 70% (Alter and Houghton 2000).

In the early seventies the league of Red Cross Societies, had alerted the World Health Organisation to a transfusion-related health concern. Commercial fractionators were buying plasma from persons in developing countries irrespective of the state of their health. This practice posed a risk both to those paid for their plasma and to the recipients of blood products made from it. Preliminary enquiries by the World Health Organisation indicated that there was indeed “an extensive trade in human blood and its derivatives in many countries” and in May 1975 the organisation passed a resolution that, among other things, urging its member states “to promote the development of National Blood Services based on voluntarily non-remunerated donations”.

Canada whilst cognisant of the need to be self-reliant remained dependent on US fractionators for some blood products throughout the eighties. Blood for fractionation was collected from paid donors in the US. The ability of the CBTS to access fractionated product from the US was relevant to the impact that loss of donors might have on maintaining supply to patients with haemophilia in Canada.

In the eighties, there was a continuous and substantial demand for the provision of blood and blood products in Australia. This need was caused in part by the demand of doctors treating patients with haemophilia for Factor VIII (in the form of both concentrate and cryoprecipitate). This demand was continuing and substantial. From the mid seventies the objective of the blood transfusion services in Australia was the collection and maintenance of sufficient blood to produce up to 2 international units of Factor VIII (in the form of either cryoprecipitate or concentrate), per head of population. By way of example, as at March/April 1983, the Blood Transfusion Service (BTS) in New South Wales had only managed to produce sufficient quantities of Factor VIII to supply 1.2 international units per head of population, short of the recommended 2 international units, which has been defined as the target nationally and internationally. There was a distinct drop in plasma supplied to CSL in 1983/84 (Figure 4, Term of Reference k). The regular donor population at that time was assessed at 5% of the general population. There was therefore a constant and continuing endeavour to maintain and to increase donations.

Australia, unlike Canada, had no arrangement to enable it to source fractionated product from the US in circumstances where it experienced continual shortages throughout the eighties. Further, there would have been a reluctance to import product produced from paid donors such as American fractionated product. Consideration of loss of blood donors was therefore a fundamental issue for the Red Cross to take into account in introducing any surrogate test that might result in substantial donor losses. In this regard, the Red Cross noted the conclusions of the working group on surrogate tests for hepatitis C virus (comprising Professor Von Aken, Dr Gunson, Dr Habibi and Dr Leikola), established by the Council of Europe's Committee of Experts on Blood Transfusion and Immunohaematology (Europe 1987) and the European Health Committee (November 1987) whereby the working group concluded inter alia:

> "*The introduction of non-specific tests could lead in some countries to a severe depletion of blood donors which could compromise the blood supply and this is a factor which must be taken into account.*"

Review of debate

The Red Cross through its expert committees at both State and National level thoroughly reviewed the debate relating to surrogate tests as it evolved throughout the eighties. The committees included expert blood bankers, haematologists, scientists and medical practitioners. In contrast, Krever reported that the Committee responsible for the direction of the Canadian blood system was constituted as follows:

> "*All members of the Committee were employees of the Ministry or Departments of Health of their provinces, most coming from the division that established budgets for hospitals and ambulance services. Their experience was in accounting or financial management. Only a few had medical or scientific background.*"

6.4 Conclusion

The Krever Inquiry identified major systemic problems as contributing to the contamination of the blood supply in Canada with human immunodeficiency virus (HIV) and hepatitis C virus during the eighties. The systemic problems rely on factual information relating to Canada and conclusions drawn in relation to action taken by Canadian Health authorities can only relate to Canada. Insofar as it is possible to draw any inferences that might be relevant to other jurisdictions, it is necessary to identify the major systemic problems that Krever found to exist in Canada, which included the following:

(a) A dysfunctional relationship between the CBTS and Governments.
(b) Failure by the CBTS to improve the safety of blood where the measures necessary to do so entailed significant costs and such costs could only be obtained with the approval of the Committee of which the members were representatives of Provincial Governments.
(c) Lack of operational independence for the production of Factor VIII and Factor IX concentrates. When the CBTS concluded that heat-treated factor concentrate was safer than non-heat-treated concentrate, Connaught Laboratories Limited (providing fractionated product to CBTS) had not yet developed a means of manufacturing heat-treated concentrate.
(d) Divided control of the blood program where donor recruitment and information provided to donors was not subject to control by the CBTS blood program.
(e) Committee members and Boards of Governors with power relating to safety issues did not include medical experts or experts in blood banking.

It would be wrong to assume or infer that any of the identified systemic problems of the CBTS applied to the Australian Blood Transfusion Services in the eighties and indeed it would be submitted to the contrary. The Krever Inquiry should be seen in its proper context. It was an Inquiry relating only to the activities of the Canadian Health Services including Governments, commercial fractionators and the CBTS.

SECTION SEVEN

j. The high infection rate of hepatitis C in people suffering from haemophilia

Sadly, the high infection rates of people with haemophilia exposed to post transfusion hepatitis C in Australia, as in all other developed countries, is a result of a number of contributing factors:

- Lack of virus inactivation procedures for fresh frozen plasma and cryoprecipitate,
- the inability prior to the 1990s to effectively inactivate the NANBH agent (hepatitis C virus) in pooled plasma products,
- frequent long term use of certain blood products.

7.0 Introduction

Haemophilia A and B are genetic bleeding disorders which require injections of blood products (Factor VIII [eight] or IX [nine] respectively) for treatment.

Hepatitis C infection in haemophilia patients is related largely to the amount of Factor VIII, either in the form of cryoprecipitate or Factor VIII or IX concentrates infused. The amounts of Factor VIII or IX transfused per year are in turn proportional to the severity of haemophilia and the frequency of bleeding. For example treatment of bleeding into a joint may require the amount of Factor VIII in 15-30 blood donations. To cover removal of an appendix a patient may need the equivalent of 1000 donations.

The availability of cryoprecipitate made from individual plasma donations and the later availability of Factor VIII and IX concentrates made by the Commonwealth Serum Laboratories (CSL) led to major advances in the care of haemophilia patients and markedly improved their well-being and life expectancy. Not only could therapy at home be instituted, allowing earlier treatment and reduction in crippling joint deformities, but the necessity for frequent visits to hospitals were reduced. Surgery could be undertaken without the risk of uncontrollable bleeding. Furthermore, with the increasing availability of Factor VIII concentrates, preventative therapy was seen as a future possibility.

Unfortunately the pooling of thousands of donations of plasma to manufacture Factor VIII and IX concentrates, the absence of a specific test for hepatitis C prior to 1990, and the frequent and large doses of Factor VIII and IX needed to treat bleeding, all contributed to the risk of non-A non-B hepatitis (NANBH). It is now known that in the past there was a degree of inevitability in exposure to the agent of NANBH (hepatitis C), which has only been counteracted by specific hepatitis C antibody testing, processes to effectively inactivate viruses in concentrated plasma products, and the more recent availability of recombinant Factors VIII and IX products (genetically engineered products, not derived from human plasma). To explain this more fully it is necessary to detail the history of haemophilia treatment in past decades.

7.1 Background

The haemophilias are bleeding disorders and there are two types, haemophilia A and B. Haemophilia A is a sex-linked genetic disorder affecting males. It results in a missing plasma protein, Factor VIII, which is an important factor essential to the clotting of blood.

Haemophilia A is classified into three types according to severity - severe, moderate and mild - dependant on the percentage of Factor VIII in the blood (severe <1% of normal, moderate 1-4% and mild 5-25%). Female carriers of the haemophilia gene may also have reduced levels, and may require treatment in certain circumstances.

Haemophilia B is also a sex-linked genetic disorder affecting males, also referred to as Christmas disease, and the missing circulating protein is Factor IX, another important factor in the clotting cascade.

von Willebrand's disease is a group of genetic bleeding disorders affecting males and females in which among other clotting defects, Factor VIII in the blood can also be deficient in these disorders.

The major clinical features of haemophilia are recurrent spontaneous painful bleeding into tissues (haematomas) and joints. Bleeding into the urinary tract (haematuria) is also common. Head trauma and spontaneous bleeding into the brain (intracranial haemorrhage) is one of the most important challenges in the management of haemophilia. Surgery for patients with haemophilia is also problematic, and may require prolonged hospitalisation and treatment with Factor VIII.

7.2 History of treatment of haemophilia

The only specific treatment for the complications of haemophilia A and B until the mid-nineties were factors derived from blood, and patients with haemophilia A and B were almost totally reliant on State or Territory Blood Transfusion Services (BTS) for provision of these factors.

Treatment for haemophilia A has evolved over the years, from the use of plasma as the only specific therapy for haemophilia up until 1964. In 1964 a mechanism for concentration of Factor VIII by freeze thawing of plasma was developed - the product being known as cryoprecipitate. This allowed larger volumes of Factor VIII to be given for the treatment of haemophilia, and eventually led to the important development of home therapy, where cryoprecipitate could be stored at home and used early in the course of a bleeding episode.

From the late seventies, Factor VIII and IX concentrates were made in Australia by the CSL from large pools made from thousands of individual plasma donations. The availability of these concentrates revolutionised the treatment of haemophilia and allowed surgery to be carried out, particularly for the repair of chronically damaged joints.

Dr Joel Margolis commenced research at the NSW BTS in 1975 and developed an improved method for measuring the coagulation factor (Factor VIII), which is lacking in the blood of haemophilia A patients. From this he went on to devise improved methods for the extraction of Factor VIII from plasma. In particular, he was able to remove most of the fibrinogen. The CSL adopted the Margolis method for the preparation of Factor VIII concentrate on 3 March 1983. With fibrinogen removed, the Factor VIII concentrate could be pasteurised by heating at 60°C for 72 hours, thereby destroying some contaminating viruses e.g. hepatitis B virus and Human Immunodeficiency Virus (HIV) although this could not be proven until HIV testing was available. Heat treatment of the Margolis type Factor VIII concentrate commenced in October 1984.

Factor IX concentrates were not in short supply in the eighties. But this was not the case with Factor VIII concentrates, which experienced severe shortage throughout the eighties. In the 1982 paper by Rickard *et al* it was stated that the amount of Factor VIII available to treat the Australian haemophilia patients was about 25%, 50% and 75% of the amounts used respectively in West Germany, the US and the UK (Rickard, Batey et al. 1982).

The recommended production level for Factor VIII throughout the eighties to ensure adequate treatment of haemophilia A was 2 international units of Factor VIII per head of population. Despite ongoing efforts of the blood services in Australia to obtain sufficient plasma from volunteer donors and the activities by the CSL to increase the yield (amount of Factor VIII extracted from each litre of plasma), this level of 2 international units per head of population was not reached even as late as 1995 (Refer to Term of Reference k).

As with haemophilia A, initial treatment for haemophilia B in the past was with fresh frozen plasma, which provided limited amounts of Factor IX in an unconcentrated form. In the seventies, a Factor IX concentrate called Prothrombinex was developed by the CSL, but besides Factor IX (the required factor), it also contained Factor II (two) and Factor X (ten). Prothrombinex was the major form of therapy for haemophilia B until recent years. Prothrombinex was sometimes associated with a paradoxical abnormal clotting which restricted its use in surgery. More recently, a purer Factor IX concentrate (Monofix) has become available for the treatment of haemophilia B.

In a Swedish study (Larsson 1985), the median life expectancy of patients with severe haemophilia increased from 11.4 years prior to 1920, to approximately 25 years between 1921 and 1960, and to 56.8 years from 1961 to 1980. Unfortunately, the prognosis for patients with haemophilia A (particularly those who were dependent on plasma derived Factor VIII) has been drastically changed by the Acquired Immunodeficiency Syndrome (AIDS) epidemic, with a large number of patients with severe haemophilia treated prior to 1984 affected by HIV/AIDS.

This example of effects on patients with haemophilia, illustrates the risk/benefit dilemma inherent in the use of blood and blood products for treatment purposes. The reality is that there is always a risk in blood therapy and whilst the Australian Red Cross Blood Service (ARCBS) and all others in the health sector strive to keep the risk as low as possible, risk sometimes eventuates into a detrimental outcome.

7.3 Prevalence of hepatitis in haemophilia and von Willebrand's patients in Australia

Although hepatitis was recognised as a complication of the treatment of haemophilia in the seventies (Mannucci 2003) the disease was thought to be mild and it was difficult to distinguish transfusion–associated hepatitis from "transaminitis" (elevation of liver enzymes due to non-viral factors eg. medication, tissue damage from bleeding etc.) The first published report in Australia was that of Rickard *et al* in *The Lancet* in 1982 and entitled "Hepatitis and haemophilia therapy in Australia" (Rickard, Batey et al. 1982). This described 243 Australian haemophilia patients who had been studied retrospectively over 4.5 years to assess the effect of treatment products on liver function, and determine the frequency of hepatitis B markers in these patients. Cryoprecipitate was the major treatment product, and only small amount of Factor VIII and Factor IX concentrates had been used.

Markers of viral hepatitis were common in the patients studied.

Antibody to hepatitis B surface antigen was detected in 63% of patients (indicating prior infection, but recovery from, the hepatitis B virus), and there were 66 cases of NANBH during the study. Twenty-nine of these episodes persisted for longer than 6 months. Abnormal ALT and AST levels were found in 34% of patients, and in 8% of patients these abnormalities persisted for more than six months. Hepatitis was defined in this group as an elevation of serum ALT or AST levels above 100 units per Litre.

In their discussion, Rickard *et al* emphasised a greater risk of liver disease for patients with severe haemophilia than for those with milder haemophilia, and this appeared to be related to total annual dose. Those patients receiving large amounts (300 donations of cryoprecipitate plus some Factor VIII concentrate [23,000 Factor VIII international units]) per year had a significantly higher frequency of all forms of liver abnormality, and were more likely to have chronic NANBH than patients with mild or moderate disease. These figures for Factor VIII use are comparable to those for haemophilia home therapy in the United Kingdom quoted by Jones (Jones 1992).

The ARCBS only has limited information on the prevalence of hepatitis C in the haemophilia population. The Blood Transfusion Service (BTS) in Western Australia conducted a study (personal communication) on haemophilia patients in 1989. When hepatitis C antibody kits became available, the haemophilia patients were tested for hepatitis C antibody using a non-licensed research test in October 1989. Twenty-seven of 36 (75%) patients were repeatedly reactive using the test. Six of the 27 were subsequently tested on the first generation hepatitis C test, and 3 on the second generation hepatitis C (EIA) antibody test, and all of these were repeatedly reactive. A study at Fairfield Hospital for Communicable Diseases in Melbourne (Gust, Nicholson et al. 1989) showed that 89 of 146 (61%) of patients with haemophilia were positive using an early hepatitis C antibody diagnostic test.

A study (personal communication - J Lloyd) was also conducted by Royal Adelaide Hospital, South Australia. This showed that 70% of patients with haemophilia A and B were positive (Table 8), and the number of positives in haemophilia A increased with the severity of the disease, so that 24 out of 24 severe haemophilia patients were positive for hepatitis C (Table 9).

Table 9 - Review of patients attending the Haemophilia Centre, Royal Adelaide Hospital, November 2002

	No. of Patients	No. HCV* Positive	% HCV* Positive
haemophilia A	134	98	73%
haemophilia B	20	10	50%
von Williebrand's disease	89	23	26%
Total	243	131	54%

* hepatitis C virus antibody test

Table 10 - Review of patients with haemophilia A (above) by severity of disease

Severity of haemophilia	No. of Patients	No. HCV* Positive	% HCV Positive
Mild	72	44	61%
Moderate	38	30	79%
Severe	24	24	100%
Total	134	98	73%

* hepatitis C virus antibody test

7.4 Blood products developments in safety

The safety of Factor VIII concentrates was increased by the development of dry heat-treated Factor VIII concentrate (60°C for 72 hours) in 1984. This inactivated the HIV, but it subsequently became evident that it did not completely inactivate the non-A, non-B viruses. The first limited supplies of super heat-treated Factor VIII (80°C for 72 hours) became available in January 1990, and haemophilia A patients were advised to use this product in preference to the 60°C heated product as this had been demonstrated to inactivate the non-A, non-B virus (hepatitis C).

Prothrombinex concentrates were heat treated at 60°C for 72 hours from 1985 onward. Super heat-treated Factor IX concentrates (heating at 80°C for 72 hours, shown to inactivate hepatitis C virus) did not become available in Australia until 1993.

7.5 Conclusion

The rate of hepatitis C in patients suffering from haemophilia A or von Willebrand's disease is related largely to the amount of Factor VIII or Factor IX, either in the form of cryoprecipitate or Factor VIII concentrate infused. The amounts of Factor VIII transfused per year are in turn proportional to the severity of haemophilia and the frequency of bleeding. Similarly the rate of hepatitis C in Haemophilia B patients is related to the amounts of Factor IX infused per year.

The revolution in treatment made possible by the availability of cryoprecipitate and Factor VIII concentrates led to an improved quality of life and markedly improved life expectancy for haemophilia patients. Unfortunately, these improvements were in many cases impacted by the risk of transmission of HIV/AIDS and NANBH (hepatitis C).

The pooling of thousands of donations of plasma to manufacture Factor VIII and IX concentrates, the absence of a specific test for hepatitis C prior to 1990, and the frequent and large doses needed to treat haemorrhage all contributed to the risk of non-A non-B hepatitis. Because of these factors, exposure to the agent NANBH (hepatitis C) could not be avoided in the majority of haemophilia patients. This has been counteracted only by screening of the blood supply using sensitive and specific hepatitis C antibody tests and processes to effectively inactivate viruses in fractionated plasma products.

SECTION EIGHT

k. The extent to which Australia has been self-sufficient in blood stocks in the past three decades

Australia is one of the few countries in the world that has always been completely self sufficient in fresh blood stocks and almost completely self sufficient in plasma products (up until 1990) and this has been achieved with totally voluntary, non-remunerated donors. Each week 20,000 donations are needed to ensure the continued sufficiency of the service.

8.1 Self-sufficiency as a goal for all developed nations

Self-sufficiency in blood stocks has always been the goal of the health sector in Australia and was recently endorsed by the Commonwealth Review into the Blood and Plasma Sector (Stephen 2001). Australia has been very successful in meeting this goal, although the eighties presented a major challenge.

Sufficiency is having enough blood and blood products to meet demand. In developing countries the term primarily refers to fresh blood components generated from a blood donation including red cells, platelets, plasma but excluding manufactured plasma products. In developed countries such as Australia, the term can be taken to mean a sufficient supply of both fresh blood components and fractionated plasma products (e.g. albumin, clotting factors and immunoglobulins extracted from plasma in the manufacturing process).

Self-sufficiency in blood means being able to achieve sufficiency through a national blood program without having to source products from other countries. A blood donation rate of 50 per 1000 population is the general minimum donation rate required for a developed country to meet this objective.

The World Health Organisation (W.H.O. 1975) in 1975 urged member states to*:*

> *"promote the development of national blood services based on voluntary non-numerated donation of blood and enact effective legislation governing the operation of blood services and to take other actions necessary to protect and promote the health of blood donors and the recipients of blood and blood products".*

Although national self-sufficiency was not specially mentioned, both the discussion and the decisions implied that developed countries should be able to meet their needs without importing plasma.

More recently within the European Union, the policy of self sufficiency has been reinforced by Directive 89/831 (EEC 1989) which states:

> *"Member states shall take all necessary measures to promote self sufficiency in human blood and human plasma. For this purpose they shall encourage the voluntary unpaid donation of blood and plasma and shall take the necessary measures to develop the production and use of products derived from human blood or human plasma coming from voluntary unpaid donations".*

8.2 The problems with reliance on paid and replacement donors

Very few countries in the world are actually self sufficient with voluntary donors. For decades the US has had to pay for and import red cells from European centres in order to have enough blood for major East Coast centres like New York. In the US there is a dual system of blood and plasma collection. The payment of donors for blood donation by blood banks has finally been completely phased out in the US with the closure of the last commercial collection centre with paid donors in 2002. It was the very high rates of post-transfusion hepatitis in centres using paid donors, which led to the pressure to move to unpaid donors in the US. However, the plasma collection system in the US, which operates largely independent of blood banks, is still dependant on paid donors for approximately 80% of its annual collections.

In Europe many countries are self-sufficient for fresh blood components. However, in the UK and most large European countries, plasma products are available in an open market and hospitals purchase supplies from various sources, which could be manufactured anywhere. Europe relies very heavily on plasma products imported from the US paid donor plasma collection system.

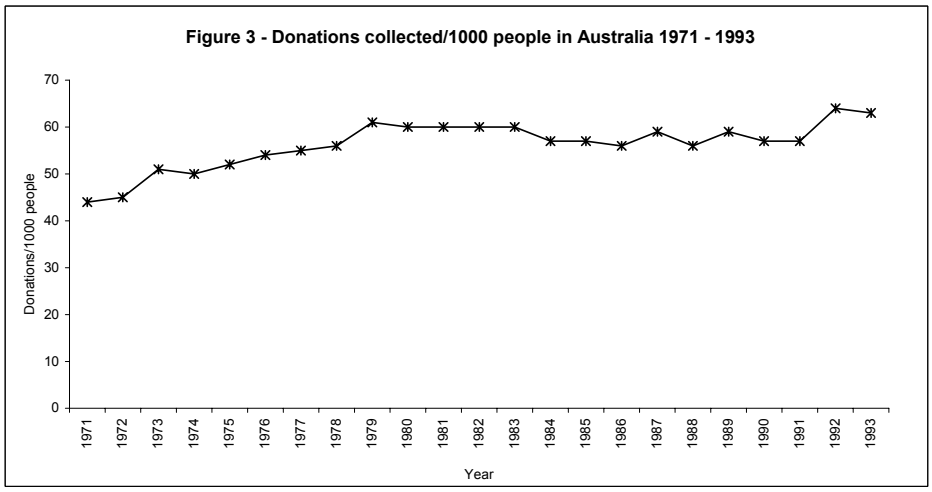
The UK has not collected any of its own plasma for several years due to theoretical risks associated with variant Creutzfeldt-Jakob Disease. It relies on importing and fractionating foreign (mainly US) plasma for its patients and thus in reality relies on paid plasma donors. In other European countries, which are nominally self-sufficient for fresh blood products, donors are essentially remunerated through the provision of very generous allowances for giving blood.

In most of the less developed countries of the world, donation rates are far below the level (of 50 per 1000 population) required to sustain a western style practice of medicine. In the absence of sufficient voluntary donors most Asian and African countries depend on the armed forces and on “replacement donation” (where relatives or friends of the patient give blood to replace the units of blood used by the patient). Replacement donors are known to have significantly higher risk profiles than non-remunerated voluntary donors. Consequently the complications of blood transfusion including infectious complications are generally many times higher in countries with these practices than they are in Australia.

8.3 Review of self-sufficiency in Australia

Records show a consistently high donation rate in Australia over a long period (Figure 3). This was despite the considerably more restrictive donation eligibility criteria, which were introduced to safeguard the quality of the supply since the mid-eighties. The introduction of more restrictions on donors each passing year would ultimately lead to fewer people in the community being able to give blood.

At times there has been great pressure on supply especially around traditional holiday periods, mid-winter and occasionally with events associated with major trauma. Despite the challenges of meeting increasing demand Australia never imported fresh blood and blood components (red cells, platelets, plasma etc.) except for a few infrequent occasions when an extremely rare blood type was not available in Australia. The goal of self-sufficiency in blood and blood products has always been a cornerstone of the safety of Australia’s blood supply.



By and large the demand for plasma products was also met with Australian-sourced product although there were a few specialised products (such as Factors VII and XI) required by just a few patients each year and which it was not practicable for CSL to produce. Shortages of intravenous immunoglobulin in the nineties have since been overcome with the agreement of Governments in future to support the plasma collection level necessary for self-sufficiency. Similarly shortages of Rh(D) Immunoglobulin, used for the prevention of a potentially fatal form of anaemia in newborn babies born to Rh(D) negative mothers, are being overcome by the expansion of the Australian Red Cross Blood Service program.

8.4 Issues with blood supplies in the eighties

In 1984 and 1985 the rate of donations (per thousand population) dropped for the first time from its previous level of 60 per 1000 population, which had been sustained between 1979–1983 to 57 per 1000 population (Figure 3). The lowest point was in 1988 when it dropped further to 56 per 1000 population. Another trough occurred in 1990/1991 when the level dipped to 57 per 1000 population, after rising to 59 per 1000 population in the intervening years. The most dramatic effect was seen in 1988 when for the first time ever, total blood collections fell by more than 16,000 from the previous year.

The advent of the human immunodeficiency virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) had a devastating effect on community confidence in the blood supply. In addition there were restrictions on donors to exclude those at risk (e.g. homosexual men and intravenous drug users). This meant that fewer people were able to give blood, leading to the most difficult period Australia had experienced to that time in maintaining adequacy of the blood supply.

The changes were due in no small part to new regulations making the blood supply safer. Information was provided to donors in 1983 about risk factors, warning them not to donate if they had risk factors for HIV/AIDS. Subsequently donors were asked to sign a confidential declaration that they did not fall into a risk category. Later private interviews were introduced. For example, a letter was sent out by a Red Cross Blood Transfusion Service (BTS), on 2 August 1984 to all blood donors as follows:

> *"In the light of present knowledge of AIDS we have no option but to ask the known 'at-risk' groups of people to refrain from giving blood. These groups are:*

1. *homosexual or bisexual persons*
2. *intravenous drug users (present or past)*
3. *sexual partners of the above*

If any of these applies to you PLEASE DO NOT GIVE BLOOD. If you would like further information or advice, please ask to see a medical officer."

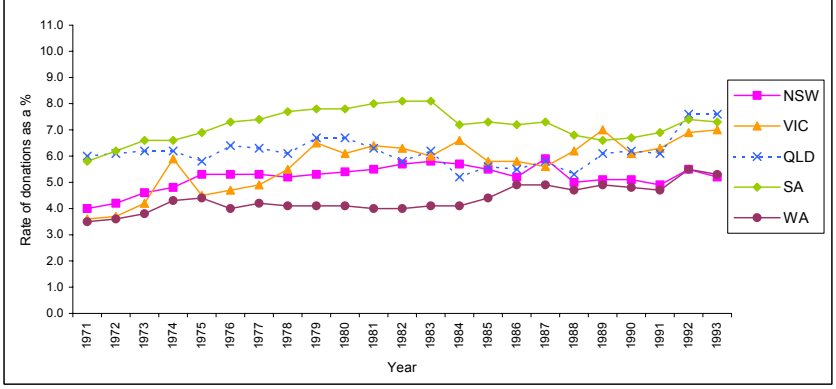
Australia was at the forefront of introducing these particular questions in the donor questionnaire as well as adopting the serological tests as soon as they became available. Australia was one of the first countries in the world to adopt screening of its blood supply with antibody to human immunodeficiency virus (HIV) test (Refer to Table 8). This was introduced to all Red Cross State or Territory BTS in May 1985 to ensure that all donations were screened for HIV antibody.

The *Sydney Morning Herald* commented on 11 April 1985 that there was a 6% drop in donations in the NSW blood bank since November 1984 due to "*a loss of Sydney's large homosexual donor community, the new high risk category*" and in the same article added that "*long waits while donors fill in new form and are being screened more rigorously lead to bad donor experience discouraging repeat visits. Legitimate donors were deferred due to fears of fines of up to $5,000 and/or 12 months jail*."

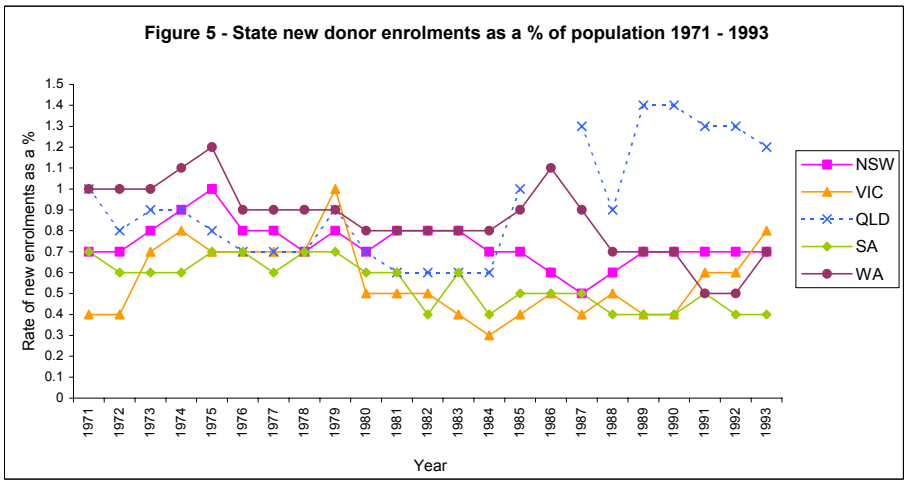
Nationwide, in tandem with the promotion of information on AIDS there was also a fear of AIDS associated with the Grim Reaper education campaign in 1987, where images of death mowing down a range of victims in a bowling alley. Although this campaign was widely criticised at that time, the TV ads did succeed in ensuring widespread discussion of AIDS. Wrong information also abounded in that period including an observation in the *South Australian News* on 27 June 1988: "*Reports show that two out of three Australians mistakenly believe that you can catch AIDS from donating blood*". This undoubtedly had an effect in deterring people from giving blood further adding to the tightening of the blood supply.

Attempts to compensate for the next period of dips in donations in 1986 and 1988 are exampled by the *Daily Telegraph* noting on 3 Jan 1987 that there was a mobile blood collection at Bondi Beach to increase supplies. The article stressed that blood donors are not at any risk of contracting AIDS. Another attempt to boost donations was the lowering of the age limit for donors from 18 to 16 on May 1987 for NSW. This was noted in the *Manly Daily* on 25 June 1988. Donations as % of the population in NSW dropped from the pre-AIDS level of around 5.5% to lows of 4.9% - 5.2% between 1986–1991 with 1987 being the only good year (Figure 4). In fact in 1989 the *Manly Daily* noted on 22 Feb 1989 "*Sydney needs 1000 blood donors per day, currently only receiving 750 – 800 per day*."

Figure 4 - Rate of donations collected as % of State population 1971 - 1993



Shortages experienced in the WA BTS were demonstrated by the *West Australian* starting on 20 June 1988 to publish a weekly chart of the amount of various blood groups required by the BTS. This tied in very well with the WA BTS data showing a drop in new donors (as a percentage of the population) for WA dropping from around 0.9% (1985 – 1987) to 0.7% in 1988, remaining at that level till 1990 and further dropping to 0.5% in 1991 (Figure 5).



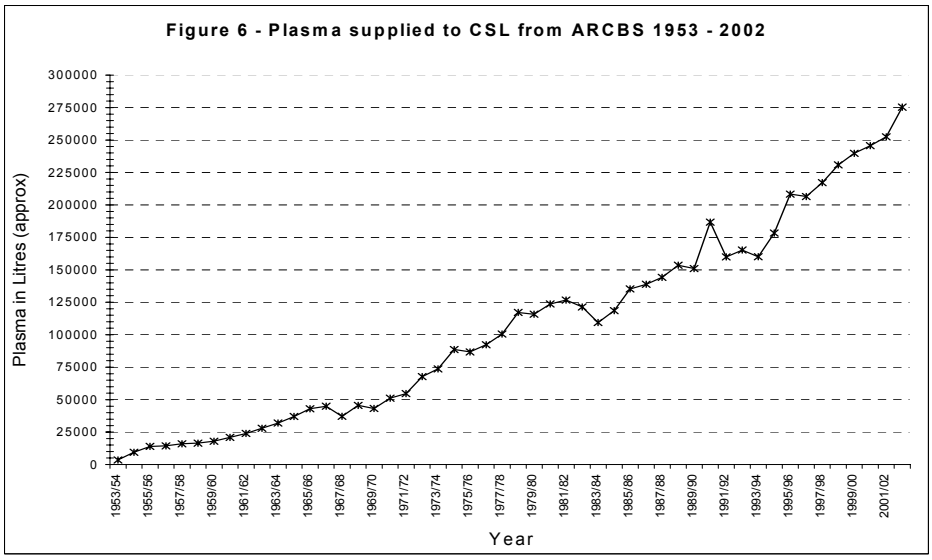
The *Courier Mail* in Brisbane reported in May 1988 that donations had fallen by 15% at the Queen Street Brisbane main donation centre. It could not be ruled out that fear of AIDS had contributed to the decline. Brisbane was experiencing difficulty in "meeting demand from Queensland hospitals".

Problems were experienced by the SA BTS too. *The Advertiser* noted on 13 July 1988 that mobile blood donation vans were utilised for door-to-door donor recruitment "*in a desperate attempt to increase a dwindling donor base*". In SA the new donors as a percentage of the SA population had dropped in 1984 from the pre-HIV level of around 0.6% to 0.4% in 1988 and remained at that low level till 1993 (Figure 5). The donation rate in SA also dropped in 1988 to below 70 per thousand and remained below 70 till 1992. Similar media stories from the other states demonstrate the great difficulties faced by the Blood Transfusion Services during the late eighties.

It was against the backdrop of such sufficiency of supply concerns that the risk/benefit decisions relating to surrogate testing had to be taken.

8.5 Plasma product shortages in the 80s

Red Cross supplies plasma from two sources to CSL for fractionation. Plasma comes from "recovered plasma" (i.e. separated from ordinary blood donation) as well as "*source plasma*" (plasma collected from a process called "*aphaeresis*"). There, the plasma is separated into different blood products. Any shortages in the blood supply would have been reflected in plasma product shortages as well. The supply of plasma to CSL fell to its lowest level in 1983/1984 (Figure 6) with 12,000 fewer litres sent to CSL for processing that year than in the previous year and it did not begin to recover until 1985/1986. Plasma supplies, which affected the production of plasma products, remained low all through the eighties. This translated into shortages for products such as Factor VIII and also albumin. Additional pressure on Factor VIII supplies was due to the loss of activity as a result of the introduction, as from 1983, of a heat treatment (a virus-killing step to protect against HIV) into the manufacturing process for Factor VIII.



An extract from the *Sydney Morning Herald* 19 Feb 1985 indicated the urgency of the situation in 1985:

> "*Supply of blood products used to make Factor VIII to treat haemophilia patients delayed due to new heat treatment used to kill the AIDS virus. Supply was so low that a young male haemophiliac who was in a critical position was given untreated Factor VIII to save his life*."

It was noted in April 1987 that, despite of the increase in plasmapheresis (refer to previous page on "aphaeresis") programs to collect more plasma that supplies of Factor VIII had not yet reached 1.4 international units per head of population, although a target level of 2.0 international units of Factor VIII per head of population had been set. In fact, there was evidence of critical shortages of Factor VIII concentrate supplies in all the states up to the early part of 1989. In the eighties plasma collections met the demand without the necessity to import plasma products. It was not until after 1995 however that the target of 2 international units per head of population was met.

Albumin was also in short supply right through the eighties. In this climate of constant challenge to sufficiency the Red Cross still had to ensure that adequacy of the blood supply. The introduction of surrogate tests resulting in a loss of at least 5% of donations (See Term of Reference e and f/sections 4 and 5) could have further jeopardised the ability of the Red Cross to meet the needs of Australian patients.

SECTION NINE

m. The number of Australians who have been infected with Hepatitis C through blood transfusion

The ARCBS has estimated, from its own sources, that there may be approximately 2,050 individuals living in Australia who could have been infected with post-transfusion hepatitis C. Additionally, it could be estimated that approximately 1,350 living patients with haemophilia may be infected. However due to the absence of a formal reporting system in Australia this may be an underestimate.

9.1 Background

Australia does not operate a register where all suspected cases of post-transfusion hepatitis might be found. Some countries have established haemovigilance systems, which collect data in a central agency on all adverse outcomes (infectious and non-infectious) from transfusion, investigate and determine the cause. These systems keep information about all forms of infection derived from blood transfusion in one central system. There is no national Australian haemovigilance system. However, there is currently a proposal for a haemovigilance scheme before the Commonwealth Government.

In the early 1990s, all State and Territory governments established hepatitis C as a notifiable disease, although the actual date of inception varied from 1990 to 1995. However, these local health authorities do not necessarily record or confirm the route of transmission of the disease. Therefore, State and Territory records are incomplete sources for information about post-transfusion hepatitis C.

9.2 Blood component recipients

The ARCBS itself has two means of learning about patients with suspected post-transfusion hepatitis C.

Blood donors who are identified by the ARCBS as positive for hepatitis C tests are informed of their test results and referred to their doctor. Many of the donors identified as hepatitis C reactive in the first few years of screening from 1990, turned out to be false positives. Donors that were true positives, and had been donating blood for many years, were mostly healthy and unaware that they were carriers of hepatitis C. It was not possible to determine at what time the donor might have acquired hepatitis C as the tests do not differentiate between old infections and newly acquired infections. The ARCBS examines the earlier donations made by the donor and investigates the outcome of any fresh blood components made from the blood. In cases where blood components were transfused, the ARCBS contacts the hospitals concerned and through them the recipients are recalled and tested for hepatitis C. This process of going back through records of previous donations is referred to as “Lookback” (refer to Appendix G). Through donor triggered Lookback approximately 1457 patients who contracted hepatitis C have been identified up to 31 October 2003. A large number of investigations are actively being pursued, mainly relating to donors who the ARCBS has problems finding. The process of donor triggered Lookback is ongoing within the ARCBS.

Another form of “Lookback” is undertaken by the ARCBS when patients, health authorities or others notify the ARCBS directly of a suspected case of transfusion-acquired hepatitis C (recipient triggered Lookback). Many cases are not notified to ARCBS because there is no

mandatory requirement for health authorities or medical practitioners to report suspected cases to the ARCBS. The patient's history of transfusions is determined and the hospitals where the transfusions took place are notified, the records searched (where available) and the donation numbers involved are identified. Then the ARCBS looks through its records to identify the donor corresponding to the donation number, checks their hepatitis C status and if necessary recalls them for testing. From this recipient-triggered Lookback process, 593 patients have been linked to positive donors up to 31 October, 2003. Thus, adding together donor triggered cases (1457) and recipient triggered cases (593), there is a total number of 2050 cases. Some of the patients are double counted, that is, they appear in both donor triggered and recipient triggered statistics. Due to the complexity, we have made no adjustment to this double counting. The biggest drawback with recipient triggered Lookback is that only some cases are referred to the ARCBS for confirmation. The extent of under-reporting is not known.

In many cases when a person is diagnosed with hepatitis C they are asked about possible risk factors. Many patients will have had a transfusion at some time in their life and their doctor may propose that this is the source of their infection. Transfusion may, however, not be their only risk factor. To be certain that hepatitis C was contracted through blood transfusion, especially where there are other risk factors, it is necessary to identify a hepatitis C positive blood donor whose blood product was transfused to the patient. Even though a hepatitis C donor is linked to the patient the donor may not have been hepatitis C positive at the time of donating that blood.

There are various limitations in the recipient triggered Lookback process. Many of the suspect transfusions happened a long time ago and the hospital transfusion department records are missing or incomplete and the ARCBS is reliant on other parties to conduct searches of records to which the ARCBS has no access. Many patient records are not found. Once implicated donations are found they can be linked to donors. Although the donor may be identified by the ARCBS it may not be possible to find the person as they might have changed addresses, moved overseas or have died in the meantime. In addition it may not be possible to link a positive donation to a definite recipient. Thus it can be expected that these figures are an underestimate.

The inefficiency of the Lookback process for HIV and hepatitis C has been described (Busch 1991) as has the fact that infections acquired after a transfusion may not have been transmitted by the transfusion (Holland 1996a) (Allander, Gruber et al. 1995).

9.3 Plasma Product Recipients

The patients identified through Lookback generally do not include those with haemophilia, who received plasma products such as Factor VIII and Factor IX unless they also received a suspect fresh blood component such as cryoprecipitate. As described in the response to Terms of Reference j (Section 7), the majority of haemophilia patients with hepatitis C acquired it in the period up to 1993 before the availability of super heat-treated plasma products (heated at 80° for 72 hours). Whilst the ARCBS has no direct link with these patients we have reviewed the literature and asked third parties who might be able to assist us in estimating how many patients with haemophilia now have hepatitis C.

The best rough estimate that can be made is that approximately 75% of Australia's approximately 1800 patients with haemophilia have hepatitis C. This could make the number living with hepatitis C approximately 1350. We understand the Haemophilia Foundation of Australia is conducting a survey of its members, which may produce a more reliable figure.

9.4 Modelling of Numbers

In response to these Terms of Reference, ARCBS can only draw on its own sources. An alternative method, employed by epidemiologists, of estimating the number of patients who have acquired hepatitis C though transfusion might be through modelling of population numbers. For example, it has been estimated that there were 210,000 notified cases of people living with hepatitis C antibodies at the end of 2001 in Australia (NCHECR 2002).

If it was known what proportion of patients living with hepatitis C have acquired the virus through transfusion, then it would be possible to model the number of people who acquired hepatitis C from transfusion. This proportion will change over time as transfusion has become less relevant as a route of transmission. For example, it has estimated that blood transfusion was a risk factor in only 4% of reported cases of acute hepatitis in a large US sample (Alter 1995). Another modelling exercise by a group from the UK puts an estimate for 'transfusion since 1980' as being the factor accounting for 4-7% of all hepatitis C virus infections in UK (Soldan, Barbara et al. 2003). Australian estimates vary but receiving a transfusion of blood products prior to 1990 has been reported as a risk factor in 5-10% of hepatitis C cases (Kaldor, Archer et al. 1992; Strasser, Watson et al. 1995; Dore, Law et al. 2003). Further epidemiological research in the Australian environment would be helpful in determining a more accurate figure for the number of post-transfusion hepatitis C cases in Australia.

9.5 Conclusion

The answer to this term of reference is therefore, at best, an estimate because there is likely to be under-reporting to ARCBS and there are also practical difficulties with historical tracing. Recognising the many limitations, ARCBS, from its own sources, has estimated that approximately 2,050 + 1,350 = 3,400 patients living in Australia today may have acquired hepatitis C through transfusion of blood or treatment with plasma products. This number may be an underestimation.

In addition, Australia does not have a national system in place such as a monitoring and reporting system for adverse reactions to transfusions (haemovigilance) that would enable a more accurate figure to be obtained.

ARCBS recommends due to the lack of an appropriate national information system for transfusion-transmitted infections, that a national government-sponsored haemovigilance system should be established. Further it recommends that support should be provided for epidemiological research into hepatitis C and its transmission to better understand all risk factors and to identify practices and actions to reduce transmission.

SECTION TEN

n. The impact that blood-transfused hepatitis C has had on its victims and their families

The ARCBS has worked with patients, donors, health professionals and organisations in assisting, counselling and offering referrals to blood transfusion recipients who have contracted hepatitis C. Through this experience, the ARCBS has learnt of the impact this disease can have on the person and their family. It is a responsibility of the health system as a whole to provide medical care and counselling to patients and their families.

10.1 Understanding the impact that blood-transfused hepatitis C has on an individual and their family

The ARCBS has worked with various health professionals and organisations in assisting and counselling blood transfusion recipients who have contracted hepatitis C. Through this experience, the organisation has learnt of the impact this disease can have on the individual and their family. It is committed to continuing to provide services for recipients in this way to try and minimise patient suffering and to working with the Australian, State and Territory Governments to improve options and remedies available to those in need.

The ARCBS extends its sympathy and understanding to each of the Australians who have acquired post-transfusion hepatitis C. It particularly extends its understanding to those who have or will develop symptoms and complications.

Through the Lookback process (Refer to Appendix G), the ARCBS is often in the front line of contact with blood transfusion recipients The ARCBS provides information and support to transfusion-acquired hepatitis C patients through its medical and counselling roles.

In the experience of the ARCBS there will be a variety of responses to being notified of this disease, as for anyone being notified of a chronic disease. This ranges from anger and resentment, to denial, grief and acceptance, depending on their particular circumstances and the stage of the process.

Blood recipients with hepatitis C have reported stigma and discrimination associated with the virus. Public ignorance and misinformation about the infection is often to blame. The ARCBS believes that patients with hepatitis C (whatever the route of transmission) should be free of stigmatisation and those greater efforts in public education about hepatitis C should be made.

While the ARCBS plays a role in providing information and education both directly to the patient and indirectly through General Practitioners and health departments, it is the responsibility of the health care system as a whole to provide in depth counselling and ongoing medical care and support to recipients and their families.

No country in the world can absolutely guarantee the safety of the blood supply. Blood transfusion benefits the community at large and we know that without receiving the unique gift of blood and its components many patients would be unable to have life saving treatments and operations. Patient safety and health is our top priority, and in accordance with our mission and guiding principles we remain ready and willing to continue to assist Australian patients within the scope of our service agreements with governments and the NBA.

SECTION ELEVEN

o. What services can be provided or remedies made available to improve outcomes for people adversely affected by transfused hepatitis C?

Personal, medical and social support and improved services could better the lives of those with transfusion-transmitted hepatitis C. Additionally, further research needs to be undertaken into the epidemiology of hepatitis C generally. ARCBS endorses the proposals of the Report of the *Expert Advisory Group on Hepatitis C and Plasma in 1990.*

11.1 Improving outcomes for people adversely affected by transfused hepatitis C

The Australian Red Cross Blood Service (ARCBS) endorses optimal personal, medical and social support and improved services for those with hepatitis C.

The recently released *Review of National Hepatitis C Strategy 1999-200 and 2003-2004* (Levy, Baum et al. 2002) is relevant to this Senate Committee inquiry. The review indicates that while Australia has had considerable success in tackling hepatitis C, there is a need for an invigorated and innovative approach to prevention of further cases and to counselling, treatment and care activities. The Australian government has reiterated its commitment to funding education, counselling and referral services and the ARCBS strongly supports this commitment. The ARCBS intends to fully cooperate with the newly formed Ministerial Advisory Committee on AIDS, Sexual Health and Hepatides, to work to improve the treatment and care options for people with transfusion acquired hepatitis C.

The ARCBS also recognises the significant and recent work of *The Report of the Expert Advisory Group on Hepatitis C and Plasma in 1990* (Barraclough, Angus et. al 2003) in its comprehensive review of policies and actions taken in relation to hepatitis C and plasma in Australia. In addition to its single recommendation for the establishment as soon as possible of the National Blood Authority, the Report proposes a number of matters for further consideration by the Minister. These include:

- *"That the Minister review progress of the implementation of the National Hepatitis C Strategy 1990-2000 and 2003-2004 with a view to full implementation as soon as possible;*
- *That the recommendation contained in the Report of the Working Party on the supply and Use of Factor VIII or IX in Australia 2002 be implemented as soon as possible;*
- *That there be expedited consideration of new anti-hepatitis C drugs so that Australian patients have timely access to treatment recommended by guidelines on international best practice;"*
- *That the Commonwealth support focused research into some aspects of hepatitis and in particular;*
    - *research to allow the level of medical and psychological disability to be quantified and monitored appropriately;*
    - *liver cancer research to monitor cancer rates and study ways to prevent the anticipated doubling of hepatitis C-related liver cancer in the next 10-20 years;*
    - *clinical research into the prevention of hepatitis C co-morbidity from factors such as alcohol, weight and diabetes."*

The ARCBS would add to this list of research topics epidemiological research topics, to quantitate more accurately the number of transfusion-acquired cases of hepatitis C in Australia, to establish more definitely the routes of transmission (as a significant number of incident cases have no identified risk factor) and to identify actions and practices to reduce transmission.

The implementation of the initiatives above will be of benefit to all people in Australia with hepatitis C, regardless of the means by which it has been acquired, whether through injecting drug use, tattooing or body piercing, blood transfusion (local or overseas), poorly delivered public health programs overseas (e.g. vaccination programs), occupational exposure in health workers, household contact, transmission through childbirth or through operations and other medical procedures undergone in the past.

People affected by the hepatitis C virus, including those with hepatitis C acquired from blood and blood products must receive optimal personal, medical and social support. Strategies to improve medical support have been discussed above and all Australian patients should be able to access the most effective treatment. Education, counseling and referral services for people with hepatitis C and their families all need increased resources and specifically tailored programs. Some patients with hepatitis C have reported stigmatisation: increased resources in public education are needed to combat such discrimination.

In terms of blood transfusion in Australia the ARCBS is committed to the safety and adequacy of the blood supply. Millions of Australians have benefited from blood and plasma products. In many instances, patients would have died without receiving these products. Blood is a biological material and it is never possible to say that there are no associated risks; accordingly, there is inherently a balance of risks and benefits involved in its use. The current very low risk of receiving a viral infection through blood and blood products in Australia has been documented in this submission. The choice of accepting this level of risk must be weighed against the possibly life-threatening consequences of not receiving a transfusion. ARCBS, clinicians and health authorities have a collective responsibility to understand levels of risk so that patients and the community at large can be adequately informed.

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APPENDIX A

Basic Information about Blood and its Components

Blood is made up of cellular and liquid components. The former consists of red cells, white cells and platelets and the latter is known as plasma, which constitutes slightly more than half the volume. A blood transfusion service may collect blood donations by donors either giving a unit of whole blood or having their plasma harvested through a process called *plasmapheresis*.

As whole blood donations cannot meet the demand for platelets and the specialised plasma products/derivatives, the gap is filled by collecting plasma and platelets by plasmapheresis. Plasma collected from plasmapheresis is called "*source plasma*" and the plasma separated from whole blood donations is called "*recovered plasma*". Most plasma is frozen to be further processed into specialised products by a process called *fractionation*.

In the 1980's donations of whole blood made up the vast majority of collections with plasmapheresis being done only for donors whose plasma had high levels of particular antibodies. When whole blood is donated it can either be left as whole blood and transfused or divided into two or more components. Making components achieve 2 important outcomes:

1. A single donation can benefit 2 or more patients
2. Patients only receive that part of whole blood that they need

The major blood components that can be made from whole blood are:

- Packed red blood cells (or packed cells)
- Platelet concentrates
- Fresh Frozen Plasma (FFP)
- Cryoprecipitate

Packed red blood cells make up greater than 99% of the packs of blood transfused in our hospitals today, virtually no whole blood is used.

Platelet concentrates contain large numbers of platelets, which are given to patients at risk of bleeding from low platelet levels, for example, patients with leukaemia or bone marrow failure.

Fresh Frozen Plasma (FFP) is the straw or yellow coloured part of the blood which contains most of the proteins, antibodies and clotting factors including Factors VIII (a clotting agent within blood which is deficient in Haemophilia A) and IX (a clotting agent within blood which is deficient in Haemophilia B). FFP can either be transfused directly to patients or it can be sent to CSL for further processing to make highly purified products such as albumin, antibody preparation and clotting factor concentrates (for example, factor VIII products).

Cryoprecipitate is made from Fresh Frozen Plasma and contains mostly factor VIII and another protein called fibrinogen that was present in the starting FFP. It enables relatively high concentrates of these proteins to be transfused in a small volume of plasma. It was the standard treatment for Haemophilia A prior to the development of factor VIII concentrates by fractionation.

Blood components have an expiry date
In the body normal red cells last 120 days but in packs they have a shelf life of around 42 days. Platelets have the shortest shelf life of 5 days. Plasma can be frozen and in this state can be stored under precise conditions for 12 months but once thawed, has to be used within hours.

Frequency of donating
Whole blood donors can donate every 10 – 12 weeks whereas plasma donors can donate every 2 weeks because they do not lose red cells, which take 5 – 7 weeks to be replaced.

Plasma products
In Australia, plasma obtained from aphaeresis donors and plasma separated from whole blood is sent to CSL for processing into many blood components that can be used to treat a range of illnesses.

Plasma processing provides many vital blood products such as:

Clotting factors
- Factor VIII concentrates used to treat patients who suffer from Haemophilia A. Anti-Haemophilic Factor (AHF), was the product made by CSL for this purpose until it was replaced by a higher purity product, Biostate in April 2003.
- Prothrombinex (PTX) a concentrate of factors II,VII,IX and X used to treat deficiencies of these factors and patients with Haemophilia B.
- MonoFIX a concentrate with a high level of Factor IX used in Haemophilia B.
- Thrombotrol, a specific concentrate of anti-thrombin III used to treat people with a deficiency of this protein and frequently used in pregnant women with this deficiency.

Immunoglobulins
- Specific Immunoglobulins that are used to protect patients against infectious diseases such as hepatitis B, chickenpox and tetanus.
- Normal Immunoglobulin, which is given intramuscularly particularly, as prophylaxis against hepatitis A especially for travellers.
- Rh (D) Immunoglobulin (Anti D) prevents people with Rh-negative blood making antibodies when exposed to Rh-positive blood by pregnancy or transfusion. This can avoid severe jaundice and a form of anaemia in babies born to Rh negative mothers
- Intravenous Immunoglobulin the current product of which is *Intragam* P and is used to treat a wide variety of disease including immune deficiency and autoimmune diseases.

Albumin Products
- Albumin is used to restore blood volume in the treatment of burns and severe shock and help in the treatment of liver and kidney problems. The product made by CSL is Albumex, which is available in four different preparations.

Production of clotting factors
A proportion of frozen plasma does not dissolve when thawed; this is called *cryoprecipitate* and is the starting material for the production of factor VIII concentrate. The cryoprecipitate also contains fibrinogen, von Willebrand factor (which is needed for factor VIII to function) and factor XIII so, before more sophisticated methods of processing were introduced, cryoprecipitate was used to treat patients with these deficiencies. Today plasma is processed into its various components for more effective use.

Coagulation factors like factor VIII, now called Biostate, are nowadays commonly freeze-dried during processing and packed into glass vials to be dissolved in sterile water for use. These factors are far more purified and highly concentrated than previously.

Risks associated with plasma products compared with whole blood
Large-scale fractionation involves the pooling of plasma from at least 1000 donors, sometimes up to 10,000 in Australia. This means that one infectious donation could contaminate all the material produced in that batch. This is why inactivation techniques such as heat treatment have been important steps in increasing the safety of these products.

APPENDIX B

Screening tests for hepatitis C

There are a number of different types of screening tests for hepatitis C virus, which have been developed over time.

Serology tests are those that detect viral antigens (proteins) or antibodies formed by the body's immune system to the infectious agent in the individual's blood serum. The most commonly used tests for hepatitis C virus detect antibodies to the virus (anti-hepatitis C virus). These antibodies formed by the body are not always protective since they do not necessarily eliminate the virus. The function of antibodies formed in response to the hepatitis C virus is not known but they can be used in detection of the virus.

Antibody tests
Currently all the third generation kits use a mixture of hepatitis C virus proteins (usually core, NS3, NS4 and/or NS5). Only the core protein is part of the structure of the viral particle, whereas all the others are non-structural proteins generated in the infected cell during periods when the virus is multiplying. These non-structural proteins were the first to be discovered (C-100 antigen) and the antibodies formed by the body in response to them were used for diagnostic purposes.

Other tests
While antibody tests have been available in the early 1990s and are the most widespread diagnostic and screening test for hepatitis C virus, tests for hepatitis C virus antigen are also becoming commercially available. These tests detect the viral core protein directly, and can be used to test directly for the presence of virus, rather than indirectly detect its presence through the formation of an antibody by the body.

The other type of hepatitis C virus test does not rely on demonstrating viral proteins, or the immune response (formation of antibody) to them. These are nucleic acid tests (NAT), which directly detect the genetic material of the virus (RNA) by special techniques used to amplify the detection, for instance PCR (polymerase chain reaction).

Screening, supplemental and other tests for hepatitis C virus
"Screening" tests are subjected to different and more rigorous licensing requirements compared to "diagnostic" tests as they are used on large numbers of tests usually. To assist in the confirmation of a debatable result there are two categories of tests used: supplemental tests are those that use the same protein/antigen whereas confirmatory tests usually employ a different protein/antigen.

What is the difference between "reactive" and "positive" results?
Screening tests may come up reactive according to whether or not the level of the protein or antibody is above the defined cut-off level. But, strictly speaking, this generally is not regarded as a "positive" result unless the reactive result to the screening test has been at least verified by supplemental testing with Western Blot or NAT (refer to section below).

What do False Negative and False Positive mean?
The more sensitive a test is, the fewer the false negatives - i.e. the less likely it is to miss real positive cases, but the price paid is that many false positives may be included. The more specific a test is, the more accurate it is.

False positive results with hepatitis C virus antibody tests
Hepatitis C virus antibody tests were originally developed to screen the blood supply and their usage was then extended to diagnostics. As screening tests, they are designed to pick up as many cases as possible ('sensitivity" - refer to Glossary) but they are prone to false-positive reactions. These false positive tests can arise for a number of reasons and there are a number of approaches to resolving this:

- The sample is retested using a test with proteins/antigens that are sufficiently different to avoid cross-reaction with non-specific antibodies. Since tests from different manufacturers may contain very similar proteins/antigens, the combination of screening and supplemental tests must be chosen carefully. Few samples that are reactive in two different tests eventually turn out to be false positives.

- A second approach to supplemental testing is to test for an antibody to each of the proteins/antigens individually. Several formats are available, the most common being a test similar to the Western Blot test used in HIV testing.

- In cases where doubt remains, detection of hepatitis C virus genetic material (NAT) in the blood sample increases the likelihood of detection, but a negative result is of little assistance. It should be noted that approximately 30 percent of blood donors who test positive with hepatitis C virus antibody are negative when tested by NAT (ARCBS data).

Hepatitis C virus NAT testing has also been introduced in blood bank screening to reduce the potential of a donor with early hepatitis C virus infection being missed by the screening tests, which detect only antibody, and therefore take more days to become reactive. For instance the addition of NAT reduced the window period from 82 days (for second generation hepatitis C antibody test alone) to 7 days.

False negative results with hepatitis C virus antibody tests
The most common reason for false negative test results lies in the timing of specimen collection. The slow and irregular antibody response to hepatitis C virus may not produce enough antibody to enable detection for 3 - 6 months. Repeating the test after an appropriate interval is worthwhile if clinical suspicion is strong, particularly in a situation where the person tested is at high risk of hepatitis C. This situation is of real concern on donor screening, since a recently infected individual generally has no symptoms and may also be antibody negative. The chance of a false negative result can be reduced by hepatitis C core antigen (protein) test or NAT testing.

What does "generation" of test mean?
Often first, second and third generation antibody tests for hepatitis C antibody are mentioned. In Australia first generation tests for hepatitis C were introduced in 1990, second generation in 1991 and third generation in 1994.

Tests for hepatitis C virus antibodies have become progressively more sensitive (i.e. fewer false negatives and less likely to miss real positive cases) and more specific (i.e. fewer false positives and better at excluding real negative cases) with time. There is also a reduction in the window period (i.e. number of days during which the infection may be present but not detectable by the screening method in use) with each successive generation of screening test e.g. 82 days for second generation to 66 days for third generation test.

APPENDIX C

Critical Appraisal of Testing Methods

The following is a review of the concepts that may contribute to a better appreciation of the complexity in understanding how risks have to be calculated against potential benefits.

- Virus characteristics
- Tests
- Donor population characteristics including prevalence and incidence
- Measuring the risk of blood recipients contracting hepatitis C
- Risk calculation using the Incidence/Window Period model
- Impact of replacing repeat donors with new donors
- Impact of paid vs unpaid/volunteer donors
- Donor selection and donor deferral
- Impact of number of units (of blood transfused) on the risk

Virus characteristics
If a virus were to produce lots of recognisable symptoms quickly (i.e. a short incubation period) in all the people infected (i.e. majority symptomatic), it would be relatively easy to diagnose without even resorting to tests. However most viruses are capable of infecting an individual and producing either no symptoms (asymptomatic) or very ill-defined ones such as tiredness and headaches commonly mistaken as indicative of many other illnesses. This causes difficulties for diagnosis, as in the case of hepatitis C, in the absence of universal screening of all individuals, because infected individuals have to present themselves for testing in the first instance. If the health care providers of these individuals were made aware of a particular risk in their history, then they may be alerted to the need for ordering the test even if the patients are unaware of the risk themselves. The likelihood of an infected person being tested is therefore very much dependent on the index of suspicion of the health care provider for that condition.

Tests
Once the individual is tested, then we enter the domain of the characteristics of the testing method used. For instance, the “WINDOW PERIOD” is defined as the number of days during which the infection may be present but not detectable by the screening method in use. All diagnostic tests, no matter how good they are, have an inbuilt period when the target (in this case hepatitis C) can escape detection, but it would be true to say that the window period has been significantly reduced with scientific advances e.g. for tests in current use:

- HIV antibody test – approx 22 days
- Hep C antibody test (3rd generation) - approx 66 days
- Hep B surface antigen (HBsAg) - approx 45 days.

Two important test characteristics are their sensitivity and specificity:

SENSITIVITY - the more *sensitive* a test, the fewer the false negatives i.e. the less likely it is to miss real positive cases, but the price paid is that many false positives may be included.

SPECIFICITY - the more *specific* a test, the fewer the false positives i.e. the better it is at excluding real negative cases, but the price paid for a test being too specific is that some real positives who did not quite make the criteria may be excluded.

Manufacturers of screening tests must carefully balance sensitivity and specificity. Generally those used in blood donor screening will be geared towards sensitivity to avoid false negative results.

Donor population characteristics
INCIDENCE is the number of NEW cases of disease/condition occurring during a defined period in a defined population whereas PREVALENCE relates to the proportion of the defined population with a disease/condition (as detected by a particular method) at a given time. Prevalence is derived by dividing the number of cases divided by the population at that point in time. In other words the incidence measures the rate of acquisition of new infection

whereas the prevalence measures the total number of infected people already in the population.

Measuring the risk of blood recipients contracting hepatitis C
One accurate method of determining the chance of a blood recipient being infected with hepatitis C is to test the blood for the agent before transfusion and then for the recipients to be tested after transfusion. One name for this method is "Recipient Follow-up Study". Examples of this type of study are the two Australian post-transfusion studies conducted in two time periods: 1979 – 1980 (Cossart 1982) and 1987 - 1990 (Ismay 1995). Both studies investigated the risk of post-transfusion non-A, non-B hepatitis/hepatitis C for Australian cardiac surgery patients who had received blood transfusions.

Because the current estimated risk of transfusion-transmitted hepatitis C in Australia is in the order of 1 in 3 million or below, the use of Recipient Follow-up studies to measure risk is no longer feasible. Therefore various mathematical models have been developed to estimate the risk of a potentially infectious donation being released into the blood supply. These models have been used extensively since the mid 1990s to estimate the risk at various time-points and, in particular, to compare the impact of introducing new tests for agents transmitted via blood transfusions. While it is not necessary to go into the details of the way these estimated risks are calculated, it is critical to our understanding of what factors contribute to the RISK of contamination by an infectious agent such as hepatitis C virus.

Risk calculation example using the incidence/window period mathematical model

- Window period (WP) i.e. number of days during which the infection may be present but not detectable by the screening method in use
- INCIDENCE RATE (IR) i.e. the rate of NEW cases diagnosed per year.

The most widely applied risk model uses IR multiplied by WP to estimate the risk of releasing infectious donation into the blood supply.
Risk = IR (incidence rate) X WP (window period)

One can therefore deduce that the risk is higher in a country where there a more new cases (high IR) arising per year. Similarly, the risk will be higher if the test used to screen has a comparatively longer WP. For hepatitis C, for instance, the WP for third generation antibody screening is approximately 66 days; however the WP for Nucleic Acid Testing (NAT) is approximately 7 days. Assuming a country is using antibody screening only then the risk of releasing an infectious unit of blood can be reduced by approximately 90% by introducing NAT since the WP is reduced from 66 to 7 days. This was the scenario in Australia when NAT was implemented for all blood donations in June 2000.

Impact of replacing repeat donors with new donors
The incidence rate in new donors has been estimated to be twice that in repeat ARCBS donors. This means that the risk is proportionately increased by increasing the proportion of new donors in the donor population.

This is important considering the rate at which repeat donors are deferred or excluded. By removing repeat donors and replacing them with new donors this would result in increasing the overall risk to recipients by replacing repeat donors with new donors who had double the risk for hepatitis C transmission.

Impact of paid vs unpaid/volunteer donors
Alter pointed out in 1985 that"… *to the present time, there is no direct or indirect test, no interceptive procedure, no single or combined approach which could have an impact on the reduction of post-transfusion hepatitis equal to that achieved by excluding the paid blood donor*." (Alter 1985).

Furthermore the degree of risk has been quantified by various international studies, which cited a 2–10 fold increase when comparing the incidence of Non-A Non-B hepatitis (NANBH) among recipients who received blood collected from volunteers with recipients who received blood from paid donors.

Donor selection and donor deferral
Donor selection is the process whereby a set of criteria are instituted mainly to try and reduce the likelihood of an at-risk donor inadvertently being admitted into the donor pool, thereby jeopardising the safety of the blood supply. Other general criteria are used to ensure the donor's health is not adversely affected by the donation of his/her blood. If a group of individuals, like injecting drug users, have been excluded for the prevention of HIV transmission, then obviously there will be a spin-off effect for the prevention of hepatitis C infection too.

Donor deferral is the action taken on the individual donor whereby they are rejected:

a) if they fail to qualify e.g. major illness in the past or carrier of hepatitis B;
b) if their screening tests are reactive and confirmed positive.

Donors can be deferred temporarily e.g. if they are found to be anaemic on that particular visit or permanently e.g. if they have a positive HIV antibody test. Once a donor is rejected this will obviously have an impact on the blood supply as their donation will have to be rejected with the consequences having an even greater impact if the donor is permanently deferred.

Impact of number of units (of blood transfused) on the risk
The risk from each unit of blood received is additive. For instance, if the risk for a single unit is 1 in 1 million, then receiving a second unit means the cumulative risk to the recipient is 2 in 1 million.

This was supported by the second Australian post-transfusion study. Ismay and others (1995) concluded that reduction in the number of units of blood given to each recipient (from an average of 6 to 4.6 units) contributed to the 50% decline of the risk of post-transfusion hepatitis over the decade between the two Australian post-transfusion hepatitis studies.

APPENDIX D

List of past Advisory Committees to the different Divisions of the Australian Red Cross Society Blood Transfusion Services (up to 1996)

National Level

- National Blood Transfusion Committee (NBTC).
- The Blood Transfusion Services Sub-Committee (reporting to the NBTC).
- Fractionation Liaison Advisory group
- Factor VIII and IX Sub-Committee

Queensland

- Queensland Blood Transfusion Service Committee

Western Australia

- The Western Australian Blood Transfusion Service Executive Committee

New South Wales

- The New South Wales Blood Transfusion Service Liaison Committee and the New South Wales Blood Transfusion Service Scientific Technical Advisory Committee.

Tasmania

- The Tasmanian Blood Transfusion Service Management Committee

South Australia

- The South Australian Blood Transfusion Service Committee

Australian Capital Territory

- The ACT Blood Transfusion Service Committee

Victoria

- The Victorian Blood Transfusion Service Committee
- The Victorian Blood Transfusion Service Management Sub-Committee

APPENDIX E

A key Australian study of post-transfusion hepatitis which is described in Term of Reference (a) and (b). It was conducted between 1979 and 1980.

Abstract

The Lancet, January 23, 1982; 208-13

Post-transfusion hepatitis in Australia [Report of the Australian Red Cross Study]
Y. E. Cossart, S. Kirsh, S. L. Ismay

Summary: Post-transfusion hepatitis developed in 2 % of 842 cardiac-surgery patients surveyed in Sydney (4 cases per 1000 units of transfused blood). 3 of the 18 cases were caused by hepatitis B virus even though all units of blood which contained hepatitis B surface antigen (HbsAg) had been rejected, 1 case was caused by cytomegalovirus, and there were 14 (78%) cases of non-A, non-B hepatitis. A significantly higher proportion of the units of blood given to the patients in whom non-A, non-B hepatitis developed contained antibodies against both hepatitis B core antigen and HbsAg than the units of blood given to the other patients. Rejection of blood with these markers of past exposure to hepatitis B may reduce the incidence of post-transfusion non-A, non-B hepatitis by up to half.

APPENDIX F

Another key Australian study of post-transfusion hepatitis which is described in Term of Reference (a) and (b). This study was conducted seven years later between 1987 and 1990.

Abstract

Medical Journal of Australia 1995; 163:74-7

Post-transfusion hepatitis revisited
Susan L Ismay, Sally Thomas, Annette Fellows, Anthony Keller, Kenneth G Kenrick, Gordon T Archer, Brenton R Wylie and Yvonne E Cossart.

Objective: To evaluate the risk of post-transfusion and postoperative non-A non-B hepatitis in Australia immediately before the introduction of screening for hepatitis C.

Design: Retrospective testing of blood samples from a prospective study of cardiac surgery patients. Samples were taken from transfusion recipients and non-transfused controls at regular intervals for 12 months after surgery during 1987-1989. For donor, recipient and control samples, alanine aminotransferase (ALT) levels were measured and tests for antibody to hepatitis B (anti-HBc, anti-HBs) and, when available, to hepatitis C (anti-HCV) were performed.

Setting: Cardiac surgery units.

Participants: Participants were included if they lived in the metropolitan area, and had not had a transfusion in the past year.

Main outcome measures: Post-transfusion hepatitis (two consecutive samples showing raised ALT levels, >90 IU/L with no other known cause); hepatitis C infection and carriage (antibody to hepatitis C).

Results: Post-transfusion hepatitis occurred in 1.1% of 736 recipients of blood not screened for hepatitis C (i.e. two cases per 1000 unscreened units given). No hepatitis occurred in 514 controls. Seven of the eight patients with post-transfusion hepatitis seroconverted to hepatitis C virus infection. Seven of the 26 anti-HCV-positive donations transmitted hepatitis C, six of these were positive by recombinant immunoblot assay (RIBA) (one by second generation testing only) and one was RIBA indeterminate. Nineteen were RIBA non-reactive; one transmitted hepatitis but the recipient did not develop anti-HCV, although hepatitis C RNA was detected in the donation. Serum ALT was raised in four of the six infective donations.

Conclusions: Hepatitis C virus infection accounted for almost all cases of non-A non-B post-transfusion hepatitis. First generation anti-HCV tests detected about 85% of infective donations. Surrogate testing of donations by ALT or anti-HBC offers no additional advantage.

APPENDIX G

Background information on the ARCBS Lookback Program

Each year in Australia close to one million blood donations are collected from approximately 500,000 donors. The scientific world is constantly faced with emerging diseases and, as blood is a living biological substance, managing the safety of the blood supply will always present a number of challenges including an element of risk.

Over the past years, very rarely, situations have occurred where infections have been transmitted to a recipient by a transfusion.

The Australian Red Cross Blood Service (ARCBS) is a humanitarian organisation and is committed to caring for anyone impacted with the utmost sensitivity and ensure they are referred to the appropriate medical and support services, including counselling.

Lookback is a rigorous process that has been in place for many years. Our Lookback program has dual systems to identify recipients who may have been exposed to an infection such as Hepatitis C via blood. The process works in two ways:

Donor triggered Lookback
The process of finding individuals who may have received potentially infected blood. If a blood donor is screened and found to be positive, prior recipients are traced by working sequentially backwards through the infected donor's prior donations and notifying recipients. These recipients are then tested to establish whether they are infected and referred to clinical and other services where appropriate.

Recipient triggered Lookback
The process of attempting to identify an infected donor when a recipient develops a transmissible disease. This involves the recall and testing of all blood donors whose blood was transfused to the recipient.

The Lookback process is a complex one and involves a number of key stakeholders. ARCBS must work together with these stakeholders (eg. hospitals for patient and transfusion records, tracing agencies) in order to ensure the process is successful.

Prior to establishment of ARCBS as a national organisation in 1996, each state and territory (which had primary responsibility for health matters) developed their own Lookback program involving government, the Red Cross Blood Transfusion Service (RCBTS) of the time and government agencies like hospitals and counselling services. The role of the RCBTS was / remains different in each state program.

ARCBS is attempting to harmonise the activity of all stakeholders involved with the Lookback process, and strongly supports the replacement of individual state and territory Lookback programs with a single Australian Lookback system. Legislation in some states and territories may need to be changed to achieve this goal.

Support services

The Lookback program includes the provision of information to recipients, donors and health care professionals. This information includes counselling services and support networks that are available to people with medically acquired infections free of charge, as well as opportunities for medical referral.

ARCBS encourages anyone who believes they may have been infected via a blood transfusion to contact their doctor or local Australian Red Cross Blood Service office.

APPENDIX H - Current donor questionnaire (see next 4 pages).

Australian Red Cross
BLOOD SERVICE

Sharing life's best gift

Blood Donor Questionnaire

Rh D negative mum, Frederique, received an Rh D injection prior to the birth of her son Luka. The injection was given to prevent her body from producing antibodies that may result in 'haemolytic disease of the newborn' in her next child. Rh D injections are made from special plasma donations.

"Thank you for taking the time to donate blood today."

Your gift of blood will help improve the quality of life of someone in need. This could be an accident victim, a person undergoing surgery, a recipient of a bone marrow transplant or someone suffering from a blood disease such as leukaemia.

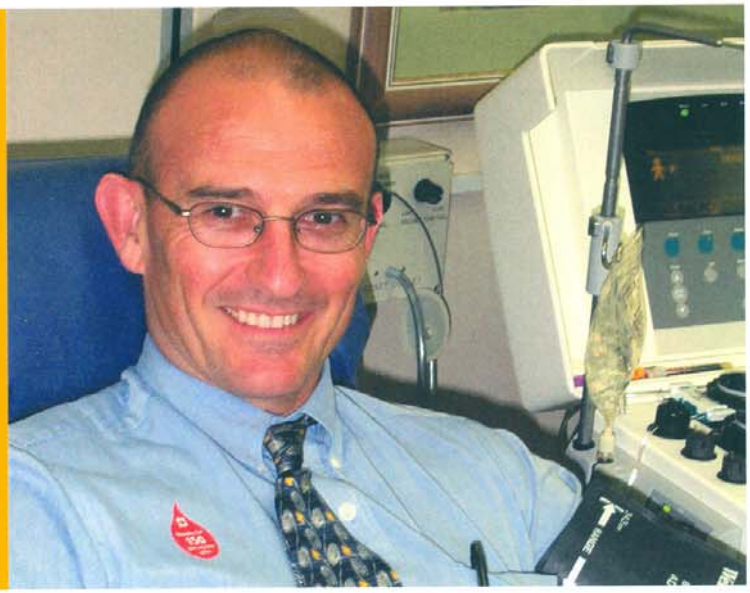
The Australian Red Cross Blood Service (ARCBS) is committed to providing safe blood and blood products for all those who need them. To maintain the very highest standard of safety, we ask you to answer a number of questions about your general health and your lifestyle activities. These questions help us determine if it is safe for you to give blood, and if so, how we can best use your blood donation.

Every question is important, your honesty in answering these questions is paramount for your safety and the safety of those who may receive your blood. We encourage you to discuss the questions with the staff member who interviews you.

In keeping with our Privacy Policy, all information you provide to us during the pre-donation interview is strictly confidential. All information will be gathered, kept and treated in accordance with the Federal Privacy Act and ARCBS Privacy Policy, and may only be released with consent or by obligation to comply with statutory notification or other legally enforceable requirements.

If you wish to see our Privacy Policy, please ask your interviewer for a copy. You can also obtain a Privacy Policy by calling **13 14 95** or online at **www.giveblood.redcross.org.au**

What happens when you donate blood?



Welcome to a special, select group of people who care.

Occasionally, a problem may arise during or after your donation. These problems are not common and we are telling you about them so that if they ever occur, you will know some simple and appropriate steps to take.

How to avoid bruising

Try to limit use of the arm from which the blood was taken for the first 15 minutes after donating.

If you develop a bruise that causes discomfort, a mild pain reliever (not aspirin) or an icepack may help.

Please phone us if a troublesome bruise occurs. Such bruises are not common and we want to hear about them as we may be able to give helpful advice.

Bleeding from the needle site

If this happens after a donation has been collected:

- Lift your arm above your shoulder and press on the bleeding site.
- Sit down and ask for a donor nurse.

You can avoid bleeding by:

- Limiting the use of the elbow for about 15 minutes.
- Being careful when using your arm to eat or drink and when putting on a jacket after donating.

Feeling faint

Fainting is due to a nerve reflex, which slows the pulse and lowers blood pressure for a short period.

If you feel dizzy, light-headed, or unwell and are still on the donor couch, tell a donor nurse immediately.

- Rest for around 30 minutes or until you feel well again.
- A drink of fluids is helpful.

If you feel faint after you have left the donor couch, sit or lie down as flat as possible rather than take the risk of falling.

If you have left the donor centre then follow the recommendations above or if you're driving, slow down and stop the car where it is safe to.

Reducing the chance of fainting

Make sure that you eat something in the 3 hours before donating and drink 4 glasses of water/juice prior to visiting the donor centre. In warm weather, be prepared by having plenty of liquid in the 24 hours before donation.

- Avoid strenuous exercise and drink plenty of liquid (preferably non-alcoholic) in the few hours after your donation.
- If you have a naturally low blood pressure and feel faint if you stand up suddenly, please tell us.
- Are you very anxious? Please tell us. We can help you feel at ease.

Rare events

Rarely a donation needle may come into contact with a nerve under the skin. This may be painful but is normally only momentary.

If you have any concerns, please speak to a member of the donor team, or if after leaving the venue you require medical attention, please contact a doctor, and notify your local blood service.

Very rarely, donors may develop a fast pulse or a sensation of tightness in the chest.

If this happens, tell a donor nurse immediately.

If you notice a problem after leaving the donor centre, contact a hospital or doctor so the problem can be assessed. Please contact us later and tell us what happened.

Keeping your blood healthy – iron stores

Whole blood donations contain iron, some of which is lost each time you donate. This is why we recommend a minimum of 10 weeks between donations to allow the iron to be replaced.

We measure your haemoglobin each time you donate and if it is too low, it is important that further tests of your iron levels are carried out.

As iron can be low and the haemoglobin test still acceptable, it is important that you have a well balanced diet containing sufficient iron to replace it.

Please wait and have some refreshments after giving blood.

If you become unwell within the next 5 days with a cough, cold, diarrhoea or other infection or become aware of any other reason why your blood should not be used for transfusion, then please call the Australian Red Cross Blood Service on **13 14 95.**

Section A

ALL donors to complete this section.

Please respond by placing a cross in the relevant box like this ☒

Today:

1. Are you feeling healthy and well? Yes ☐ No ☐ C0
2. Women only – Are you pregnant or breast-feeding or have you been pregnant in the past 9 months? Yes ☐ No ☐ C1

For safety reasons:

3. In the next 3 days, do you intend to participate in any activity which would place you or others at risk of injury if you were to become unwell after donating, such as:
   - Driving public transport Yes ☐ No ☐ C2
   - Operating heavy machinery Yes ☐ No ☐ C2
   - Underwater diving Yes ☐ No ☐ C2
   - Piloting a plane Yes ☐ No ☐ C2

In the last week have you:

4. Had any dental work, cleaning, fillings, or extractions? Yes ☐ No ☐ C3
5. Taken any aspirin, pain killers, or anti-inflammatory preparations? Yes ☐ No ☐ C5
6. Had any cuts, abrasions, sores, or rashes? Yes ☐ No ☐ C6
7. Had a gastric upset, diarrhoea, abdominal pain, or vomiting? Yes ☐ No ☐ C7

Since your last donation, have you:
OR if you are a new donor, have you in the last 12 months:

8. Been investigated or treated for any illness or had surgery? Yes ☐ No ☐ C9
9. Had chest pain/angina or an irregular heartbeat? Yes ☐ No ☐ D0
10. Taken tablets for acne or a skin condition? Yes ☐ No ☐ D1
11. Taken any other medication? Yes ☐ No ☐ D2
12. Worked in an abattoir? Yes ☐ No ☐ D3
13. Been overseas? Yes ☐ No ☐ D4
14. Had a sexually transmitted disease e.g. gonorrhoea, syphilis, or herpes? Yes ☐ No ☐ D5
15. Had any immunisations/vaccinations? Yes ☐ No ☐ D6
16. Had shingles or chickenpox? Yes ☐ No ☐ D7
17. **Do you know of anyone in your family who had or has:**
    - Creutzfeldt-Jakob Disease (CJD)? Yes ☐ No ☐ D8
    - Gerstmann-Straussler-Scheinker syndrome (GSS)? Yes ☐ No ☐ D8
    - Familial Fatal Insomnia (FFI)? Yes ☐ No ☐ D8
18. **Have you lived in, or visited** England, Scotland, Wales, Northern Ireland, the Channel Islands, or the Isle of Man for a cumulative (total) period of six months or more, between 1st January 1980 and 31st December 1996 inclusive? Yes ☐ No ☐ D9

Section B

Please complete ONLY if you are a new donor or have not attended for 2 years or more.

Have you:

1. Ever volunteered to donate blood before? Yes ☐ No ☐ NP
   If yes – where and when?
   _____
2. Ever been advised not to give blood? Yes ☐ No ☐ NP
3. Ever suffered from anaemia or any blood disorder? Yes ☐ No ☐ A4
4. Ever had a serious illness, operation or been admitted to hospital? Yes ☐ No ☐ A5
5. Had a neurosurgical procedure involving head, brain, or spinal cord between 1972 and 1989? Yes ☐ No ☐ A6
6. Ever received a transplant or graft (organ, cornea, dura mater, bone etc.)? Yes ☐ No ☐ A7
7. Received injections of human growth hormone for short stature or human pituitary hormone for infertility prior to 1986? Yes ☐ No ☐ A8
8. Ever suffered head injury, stroke, or epilepsy? Yes ☐ No ☐ A9
9. Ever had a heart or blood pressure problem, rheumatic fever or heart murmur, or chest pain? Yes ☐ No ☐ B0
10. Ever had a bowel disease, stomach or duodenal problems or ulcers? Yes ☐ No ☐ B1
11. Ever had kidney, liver, or lung problems including tuberculosis (TB)? Yes ☐ No ☐ B2
12. Ever had diabetes, a thyroid disorder, or an autoimmune disease e.g. rheumatoid arthritis or lupus? Yes ☐ No ☐ B3
13. Ever had cancer of any kind including melanoma? Yes ☐ No ☐ B4
14. Ever had malaria, Ross River fever, Q fever, leptospirosis, or Chagas' disease? Yes ☐ No ☐ B5
15. Ever had (yellow) jaundice or hepatitis? Yes ☐ No ☐ B6
16. Travelled or lived overseas in the last 3 years? Yes ☐ No ☐ B7
17. Ever spent more than 3 months in Central or South America? Yes ☐ No ☐ B8
18. Ever had treatment with the medication TIGASON (Etretinate) or NEOTIGASON (Acitretin)? Yes ☐ No ☐ B9

continued overleaf

Australian Red Cross
BLOOD SERVICE

Section C

Donor Declaration

There are some people who MUST NOT give blood as it may transmit infections to those who receive it. To determine if your blood or blood products will be safe to be given to people in need, we would like you to answer some questions. These questions are a vital part of our efforts to eliminate any diseases from the blood supply.

All donations of blood are tested for the presence of hepatitis B and C, HIV 1 and 2 (the AIDS virus), HTLV I and II and syphilis. If your blood test proves positive for any of these conditions, or for any reason the test shows a significantly abnormal result, you will be informed.

All of the questions are important to answer. Answer each question on the form as honestly as you can and to the best of your knowledge. There are penalties including fines and imprisonment for anyone providing false or misleading information.

To the best of your knowledge have you:

1. Had an illness with swollen glands and a rash, with or without a fever in the last 6 months? Yes ☐ No ☐ E1
2. Ever thought you could be infected with HIV or have AIDS? Yes ☐ No ☐ E2
3. Ever "used drugs" by injection or been injected, even once, with drugs not prescribed by a doctor or dentist? Yes ☐ No ☐ E3
4. Ever had treatment with clotting factors such as Factor VIII or Factor IX? Yes ☐ No ☐ E4
5. Ever had a test, which showed you had hepatitis B, hepatitis C, HIV, or HTLV? Yes ☐ No ☐ E5
6. In the last 12 months engaged in sexual activity with someone you might think would answer "yes" to any of questions (1-5)? Yes ☐ No ☐ E6
7. Since your last donation or in the last 12 months had sexual activity with a new partner who currently lives or has previously lived overseas? Yes ☐ No ☐ E7

Within the previous 12 months have you:

8. Had male to male sex? Yes ☐ No ☐ E9
9. Had sexual activity with a male who you think might be bisexual? Yes ☐ No ☐ F0
10. Been a male or female sex worker (e.g. received payment for sex in money, gifts or drugs)? Yes ☐ No ☐ F1
11. Engaged in sexual activity with a male or female sex worker? Yes ☐ No ☐ F2
12. Been injured with a used needle (needlestick)? Yes ☐ No ☐ F3
13. Had a blood/body fluid splash to eyes, mouth, nose, or to broken skin? Yes ☐ No ☐ F4
14. Had a tattoo (including cosmetic tattooing), skin piercing, electrolysis, or acupuncture? Yes ☐ No ☐ F5
15. Been imprisoned in a prison or lock-up? Yes ☐ No ☐ F6
16. Had a blood transfusion? Yes ☐ No ☐ F7
17. Had (yellow) jaundice or hepatitis or been in contact with someone who has? Yes ☐ No ☐ F8

This declaration is to be signed in the presence of a Blood Service staff member. (Please read the following statements.)

Thank you for answering these questions. If you are uncertain about any of your answers, please discuss them with your interviewer.

We would like you to sign this declaration in the presence of your interviewer (a Blood Service staff member) to show that you have understood the information on this form and have answered the questions in the declaration to the best of your knowledge.

Your donation is a gift to the Blood Service to be used to treat patients, or in some circumstances, for teaching, research, quality assurance or the making of essential diagnostic reagents.

You may be asked by the Blood Service to undergo further tests. A part of your donation may be stored for future testing and research. Approval from the appropriate Human Research Ethics Committee must be obtained before any research is undertaken on blood samples.

Should you become unwell in the 5 days following a donation with a cough, cold, diarrhoea or other infection or become aware of any other reason why your blood should not be used for transfusion, please call us on 13 14 95.

Declaration:

I agree to have blood taken from me under the above conditions. I have been advised that there are some possible risks associated with donating blood and that I must follow the instructions of the Blood Service staff to minimise these risks.

Donor (Please Print)

Surname _____

Given Name _____ Date of Birth _____

Signature

Please sign in the presence of the interviewer

Witness (Please Print)

Surname _____

Given Name _____

Signature _____

Interview Date _____ Supp Questions _____

Donor Identity Verified Yes ☐ No ☐ Donor Weight _____

Donation Number:

Even if you are unable to give blood today, we thank you for coming and appreciate your willingness to be a blood donor.