



15 March 2017

**I Won’t Have Blood!
A Battle Between Belief and Duty?**

Professor Martin Elliott

**Introduction**

In this lecture, I am going to consider the belief held by some that they should not receive transfused blood. I shall explain the basis of that belief; the implications for such individuals who then suffer massive haemorrhage; and the implications for those who care for them. I shall also consider the relative safety of blood transfusion, and whether the challenge of believers has been harmful or beneficial to the wider community.

Blood is normally inside you, neatly and safely contained. When it appears outside the body it can cause anxiety, alarm and even fainting in onlookers. But you cannot live without it.

Blood is incredible, multifunctional stuff. It provides a fantastic courier system, carrying vital oxygen and nutrients to even the most remote parts of the body. Blood delivers cells and antibodies to fight infection wherever it breaks out, and transports waste products to recycling centres like the liver and kidneys. Blood carries platelets and proteins which can seal up holes in blood vessels and, by distributing heat, helps control body temperature. It is a vital *physical* life-force.

Blood accounts for about 8% of an adult’s body weight, and about 5 litres in volume. Cells, mostly red blood cells account for 45% of blood and the remaining 55% is called plasma which comprises 91% water, 7% proteins and 2% other solutes including waste products and circulating hormones. Blood is liquid in the blood vessels, but clots when exposed to air or foreign surfaces.

An unavoidable consequence of trauma and surgery is damage to tissue. Tissue bleeds, and although our reparative techniques have improved considerably over the centuries, sometimes that bleeding can be life-threatening, especially after massive trauma.

Most bleeding can be stopped using diathermy (electrocautery) or by tying ligatures around larger vessels. But if large vessel tears, or if a wide surface is bleeding then such techniques may be overwhelmed, and without additional treatment, the patient would simply exsanguinate. Bleeding (haemorrhage) in humans is classified into four groups depending how much blood is lost, with Class IV haemorrhage being the worst and equating to over 2 L of loss. About 40% of blood volume. There are certain types of surgery which, historically, have been known for the scale of the bleeding incurred. For example, major orthopaedic work, some neuro-surgery, cranio-facial surgery and my field of cardiothoracic surgery.

We have learnt that lost blood can be replaced. This can be with alternative fluids such as electrolyte solutions, synthetic colloids or with donor blood or its components. This is part of what the anaesthetist manages during major surgery, along with anaesthesia itself. Blood and its components have saved the lives of countless major trauma victims.

**History of Blood Transfusion**

Although blood-**letting** has been around since the time of Hippocrates, blood **transfusion** has only become commonplace in the last 100 years. Its history was beautifully reviewed by Giangrande in 20001. **Gresham College** forms part of that history. Richard Lower (1631-1691) had conducted experiments in Oxford2, transfusing blood from one dog to another. Samuel Pepys describes in his diary an evening spent at Gresham College on 14 November 1666 where he witnessed such an experiment1. This is what he wrote:

*“At the meeting of Gresham College tonight, there was a pretty experiment of the blood of one dog let out, till he died, into the body of another on one side while all his own ran out the other side. The first died upon the place, and the other very well and likely to do well. This did give occasion to many pretty wishes, as of the blood of a Quaker to be let into an Archbishop and such like; but may if it takes be of might us to man's health for the mending of bad blood by borrowing from a better body.”*

Jean-Baptist Denys (1643-1704), in the late 17th Century, transfused the blood of calves and lambs into humans not because of bleeding, but to treat mental illness, in line with the classic humoral theories of the time. But it was not until 1818 that human blood was used, by syringe, to treat casualties in the Franco-Prussian war. And James Blundell, a London obstetrician, reported human-to-human transfusion as a lifesaving procedure in the aptly named Lancet in 1828, all without any attempt at cross-matching.

It was not until 1900, that Karl Landsteiner (1868-1943) discovered the three major ABO blood groups. We must not forget Jan Janský, a Czech psychiatrist working in Prague at the turn of the century, who described four blood groups and called them Types I, II, III, and IV, terms still used today in the countries of the former USSR. Landsteiner received the Nobel Prize for Medicine in 1930, a just reward considering he was also involved in identifying the polio virus in 1909 and, with, Weiner, the Rhesus blood group in 1940. We have a lot to thank him for.

***Why blood groups matter***

*If transfused, you must be given ‘compatible’ blood. The four main blood types are A, B, AB, and O. If you’re type A, your red blood cells have proteins attached to them known as A antigens. Type B blood cells carry B antigens. Type AB blood has both A and B antigens, and type O blood has neither A nor B antigens.*

*Your immune system will produce antibodies against any blood antigens you don’t have in your own blood. That means people with type A blood create antibodies against B antigens. A person with type A blood receiving a transfusion of type B or AB blood would lead to an ABO incompatibility reaction. In an ABO incompatibility reaction, your immune system attacks the new blood cells and destroys them.*

*If you have type AB blood, you have both A and B antigens. This means you’re a universal recipient and you can receive any type of blood. However, you can only donate blood to other people who have type AB blood.*

*If you have type O blood, which has no antigens, you’re a universal donor. You can give your blood to anyone without triggering their immune system, but you can only receive type O blood.*

*ABO and Rh are the most common groups, but there are over 34 including the rare ones.*

In 1914, Richard Lewinsohn demonstrated that small quantities of sodium citrate acted as an effective anti-coagulant, facilitating transfusion and storage. Citrate-phosphate-dextrose (CPD) solution remains a widely-used anticoagulant to this day.

The casualties of the First World War gave surgeons opportunities of developing and improving the techniques of transfusion and in this they were helped by the readily available source of donors. Lightly wounded men were invited to act as donors, and rewarded with 14 days in “Blighty”. There were no blood banks to store blood; it was used ‘fresh’.

We have a librarian from South London to thank for the organisation of voluntary blood donation which has saved so many lives worldwide[[1]](#footnote-1). **Percy Lane Oliver** O.B.E. (1878-1944) worked at Camberwell library, and in October 1921, in his capacity as Hon. Sec. of the Camberwell Branch of the Red Cross, he received a telephone call from the nearby King’s College Hospital. They were in urgent need of a blood donor and sought his help. He and several colleagues went to the hospital, and from them Sister Linstead, a Red Cross worker, was chosen, becoming the first voluntary blood donor. The results of this exercise so impressed Oliver that, mainly with the help of his wife, he set about devising and organising a system for a panel of donor volunteers, whose health and blood details were checked by the Hospital and kept on record cards in his home, where there was continuous telephone cover. In the first year, there were four members of the panel and they had one call. Five years later there were 400 members and over 700 calls. To cope with the organisation and the paperwork it was also necessary to move to a larger house!

The first blood bank was opened in Cook County Hospital in Chicago in 1937, after Bernard Fantus (1874-1940) worked out that you could refrigerate anti-coagulated blood. Frederico-Duran Jordan from Barcelona did the same during the Spanish Civil War, and with Dr Janet Vaughn in London established a blood bank at the Hammersmith Hospital in 1938. Just in time, you might say, and the MRC established four such banks in London in anticipation of War.

The War Office itself established the Army Blood Supply Depot (ABSD) in Bristol in 1938. Churchill’s face predictably appeared on posters asking for blood donors. Whole blood proved difficult to transport and preserve under wartime conditions. A problem partly solved after Edwin Cohn, professor of physical Chemistry at Harvard, developed (1940) a method by which the component parts of whole blood could be fractionated into 5 parts, the fifth being largely albumin. Eighty-seven victims of the Pearl Harbour attack were treated in this way with only 4 reported adverse events. Further developments in fractionation have led to the effective management of, for example, haemophilia and advances in bone marrow transplantation and immune-therapy.

Blood donation is now managed in England by NHS Blood and Transplant. NHSBT collects **1.7 million units[[2]](#footnote-2) of blood from over 23,000 donation sessions in more than 3,000 venues**. Blood of all blood groups is needed, proportional to the distribution of those groups in the population. Groups A Rhesus +ve and O +ve are the most prevalent of the ABO blood groups[[3]](#footnote-3) at 30 to 36% of the population respectively, with AB-ve being the rarest at around 1%. Blood group O-ve is ‘the universal donor’ group, and occurs in 12% of the population. It is in the greatest demand as it can be given to almost anyone in a dire emergency. More than 6,000 blood donations are needed each day to meet an ever-increasing demand for blood and blood products. And to cope with the fact that red blood cells can only be stored for a maximum of 35 days, and platelets for a maximum of 7 days. Supplies constantly need topping up. **Sadly, last year only 3% of the population of England aged between 17 and 70 donated blood**. As a doctor, my primary duty is to the patient and to save life with minimal harm. Haemorrhage in humans is divided up into 4 categories, depending on the severity;

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **Class I** | **Class II** | **Class III** | **Class IV** |
| **Blood Loss (ml)** | <750 | 750-1000 | 1500-2000 | >2000 |
| **Blood Loss (%)** | <15% | 15-30% | 30-40% | >40% |
| **Pulse Rate (BPM)** | <100 | 100-120 | 120-140 | >140 |
| **Blood Pressure** | Normal | Low | Low | Low |
| **Respiratory Rate (breaths/min)** | 14-20 | 20-30 | 30-40 | >35 |
| **Urine Output (ml/h)** | >30 | 20-30 | 5-15 | minimal |
| **CNS Symptoms** | Normal | Anxious | Confused | Lethargic |

If bleeding occurs, and if I cannot stop it in any other way, the existence of blood for transfusion is a lifesaver, and using it to do so seems utterly logical. It is backed up by years of evidence. The more you lose, the greater the risk to life, and the more likely blood is to be necessary. Why then, if blood can save your life, would you choose not to have it? All my training had taught me that blood saves lives; lose too much and you will die. Replace it and you will live. I had seen it work multiple times after trauma and surgery.

**Why I care**

Yet during my training as a cardiac surgeon, one of my seniors operated on a patient who, for religious reasons, refused to have blood transfused. In those days, before the advent of intensive care specialists, junior surgeons, fresh from a day’s operating, looked after the patients on the ICU, and I had to care for this man who came out of the operating room already severely anaemic, having had his cardiopulmonary bypass pump primed with clear fluids rather than blood [haemodilution]. He bled more, at least in part because of low concentrations of clotting factors and platelets from the haemodilution, but **we were not allowed to give him blood or blood products**. All we could use were clear intravenous fluids, none of which could effectively transport oxygen from lungs to the tissues that needed it. His heart, in its weakened post-surgery state, had to beat faster to pump the smaller amount of oxygen around, and several organs began to suffer, notably his kidneys and liver, and we became more anxious that his brain might also be oxygen–deprived. Worse, he continued to bleed, as his clotting factors were further diluted and ideally, he would have needed even more blood.

His haemoglobin level became ever more critically low. His lungs deteriorated and he started to go into true renal failure. Those of us in the ICU were spending most of our time with him, making it a struggle to care for our other patients. His family were adamant that he should not have blood, and the consultant who had consented the patient for surgery was called at home and confirmed (from his bed) that was the case. **We were not allowed to give blood**.

Everyone working in the ICU was finding this situation difficult, unable to comprehend how someone could hold such strong beliefs that they would allow either themselves or their loved one to die. However, the family were secure in their belief, indeed they were disconcertingly calm; accepting blood was worse for them than refusing it. It meant, they led us to understand, ‘eternal damnation’. Not only were we uncomprehending, but also frustrated, angry and desperate. We **knew** we could make him better quickly; we had the skills, the tools and the resources; but we could not use them. **We were not allowed to give blood.**

Amazingly, that patient did not die, but he had to stay in the hospital for weeks; anaemic, prone to infection, and with very slow organ recovery. The costs to him, to his family, to the staff and financially to society were huge. His long stay in hospital prevented several others from having access to a bed, and hence treatment. Relationships with the family were sometimes difficult. Several members of staff resented the consultant for agreeing to the patient’s demands, essentially without wide consultation.

Of course, we were all glad to see the patient go home, and proud that he had made it. Others have not been so lucky.

**Jehovah’s Witnesses and Blood**

We need to understand the origins of the belief that you should not have a transfusion, a view held dominantly, and proselytised by, the Jehovah’s Witnesses.

The Jehovah’s Witness grew out of the Watch Tower Society founded around 1880 by Charles Taze Russell (1852-1916)3, 4. Born in Allegheny (now part of Pittsburgh), he had a mainstream Christian background, but for a while lost his faith and explored Eastern religions before beginning to associate with the Adventists, whose views were increasingly heard in the early 19th Century.

First and foremost, the Adventists believed in Christ’s second coming, which they expected to happen within their lifetime.  They believed it was possible to estimate the exact year that would happen by intensive bible study in search of complex numerical clues hidden within the text of, particularly, the books of Daniel and Revelation. It was a commonly held view in the 19th Century that these books predicted events in human history.

Adventists (whose several branches often disagreed amongst themselves) mostly believed that when Christ returned, he would gather up his followers into heaven, and the earth would be burned in order to purify it.  After this would come the **millennium;** a 1000-year period during which Satan would be bound and subsequently released for a short time.  Adventists were thus *pre-millennialists*; humanity is living before the 1000 years.

A great deal of bible study was devoted to identifying the date when Christ would return to earth, and an industry of Chronology was born, of which the most famous product was William Miller’s Prophecy Chart, with calculations based on dates and times from the scriptures.  Miller predicted that Christ would appear in 1853. He didn’t, and that year became known as ‘the great disappointment’. Since then multiple re-workings of the calculations have been undertaken, and new predictions (beyond the scope of this essay) evolved. Incidentally, Sir Isaac Newton, who was a theologian as well as a scientist, published “*Observations upon the Prophesies of Daniel and the Apocalypse of St John’* in 1773 as his own attempt to untangle the clues in the two books. An excellent discussion of Chronologies can be found in Chryssides’ 2016 book3. Despite failures of predictions, the beliefs of the Adventists have found fertile ground, and by 2010 there were **22,000,000 members** of the derivative churches.

Russell’s Watch Tower Society has also grown, and morphed into the Jehovah’s Witnesses in 1931 under his successor Joseph Franklin Rutherford (1869-1942). The idea of Bible Study on which it is based, and an absolute commitment to evangelism, by using the door-to-door techniques which are well known and which are now most visible outside Tube station, as fewer people are predictably at home. Jehovah’s Witnesses have also demonstrated a remarkable and recurring commitment to the use of new technology. They were the first to use (in 1914) multi-media presentation in the 8 hour, 4-part religious film The Photo Drama of Creation which cost $300,000 (about $7,250,000 in today’s money) to make. You can find a 3-h version of it on YouTube (<https://www.youtube.com/watch?v=N4g_ipuuJZk)>. It is a fascinating watch, not least because of the relentless oratorical delivery. They were amongst the first to use radio as an evangelical tool, establishing Radio WBBR on Staten Island in New York in 1922. It only closed in 1957. Today, they have a huge and impressive web presence at JW.org. In 2014, they launched JW Broadcasting (<https://tv.jw.org/#en/home)> a dedicated television platform. These techniques have proved quite effective, despite intermittent victimisation. **In 2016, there were 8,340,982 Jehovah’s Witnesses and 119,485 congregations in 240 countries** ([https://www.jw.org/en/jehovahs-witnesses/faq/how-many-jw-members/)](https://www.jw.org/en/jehovahs-witnesses/faq/how-many-jw-members/%29).

So why do Jehovah’s Witnesses believe that they should not receive blood? What is the origin of that belief? It is surprisingly recent. Reference to it first appeared in Watchtower articles in December 19445 and July 19456, perhaps related to the improved resuscitation techniques in the 2nd World War and the increase use of blood. The current statement on the Jehovah’s Witnesses website states that ‘the Bible commands that we not ingest blood. So, a Jehovah’s Witness should not accept whole blood or its primary constituents in any form, whether offered as food or as a transfusion’. The Biblical texts on which this belief is based are these:

[**Genesis 9:4**](https://www.jw.org/en/publications/bible/nwt/books/genesis/9/#v1009004)**. ‘***God allowed Noah and his family to add animal flesh to their diet after the Flood but commanded them not to eat the blood. God told Noah*: “Only flesh with its soul—**its blood—you must not eat.**”’

The website explains that *‘this command applies to all mankind from that time, because all are descendants of Noah.’*

[**Leviticus 17:14**](https://www.jw.org/en/publications/bible/nwt/books/leviticus/17/#v3017014)**.** “You **must not eat the blood** of any sort of flesh, because the soul of every sort of flesh is its blood. Anyone eating it will be cut off.”

*‘God viewed the soul, or life, as being in the blood and belonging to Him. Although this law was given only to the nation of Israel, it shows how seriously God viewed the law against eating blood.’*

[**Acts 15:20**](https://www.jw.org/en/publications/bible/nwt/books/acts/15/#v44015020)**.** “but to write them to abstain from things polluted by idols, from sexual immorality, from what is strangled, **and from blood**.”

*‘God gave Christians the same command that he had given Noah. History shows that early Christians refused to consume whole blood or even use it for medical reasons.’*

The beliefs are profoundly held and a core value. Any non-consensual transfusion is regarded as a ‘gross physical violation’7. Even pre-donation (in which one’s own blood is removed, stored and re-transfused when needed) is unacceptable. These beliefs have resulted in the deaths of believers. It is difficult to discover exactly how many, but attempts have been made to estimate the number, based on a combination of reported cases, incidence of surgery requiring transfusion and the number of active Jehovah’s witnesses. The most widely quoted estimate is about 9000 deaths per year, based on a 1993 paper looking at surgical outcomes in Jehovah’s witnesses8. My own view is that this is very likely to be an over-estimate, and for reasons which will become clear, the numbers should be declining.

**The Consequences for Jehovah’s Witnesses if they accept or are given blood**

Despite internal debate, external criticism and multiple law suits, the position of the JWs remains absolute. In 2000, church elders in New York were reported9 to have voted to allow members to accept blood transfusion in critical circumstances provided they repent afterwards. However, the position of the church was clarified immediately in a letter to The Times on 23rd June 2000 from the Jehovah’s Witnesses’ Public Affairs Coordinator. In that letter, it was stated;

*“If a baptised member of the faith wilfully accepts blood transfusion and has no regrets, he indicates by his own actions that he no longer wishes to be one of Jehovah’s Witnesses. The individual revokes his own membership by his own actions, rather than the congregation initiating the step”.*

That person may then be ‘**shunned’** by the community in which they live, and with whom they have built up an entire social life. This is also called ‘**disfellowshipping’**. Beingcut off from the community you have grown up with and shared so much must be very difficult to bear. You can find many stories on the Internet from people who explain this better than I can. Shunning sounds terrible, but it may be perceived as nothing if you believe that receiving blood will prevent you from entering a higher kingdom after death.

The inability to give blood clearly places constraints on the surgeon’s ability to care for the patient. We are used to acting under our duty of care to make the patient better and improve the quality and quantity of their life, but this clearly comes into conflict with the patient’s right to make decisions regarding their own healthcare. Their own autonomy.

**Maybe they have a point; how safe is blood transfusion?**

So far, I have presented a story which suggests that bleeding kills and blood saves. Both are truisms, but it is of course not that simple. I have already pointed out that transfusing incompatible blood can produce a transfusion reaction, but that is not the only potential complication. In England, an organisation with the acronym SHOT (Serious Hazards of Transfusion) collects all data (as SHOT reports) relating to adverse transfusion events and publishes an annual report in close collaboration with the MHRA (Medicines and Healthcare Products Regulatory Agency) and The Royal College of Pathologists. The full 2015 report can be found online10. In 2015, **2,213,239** issues of blood components (**1.6m issues of red cells**) were made from blood services in the UK. The number of SHOT reports was **15.4/10,000 issues** of components giving a total of **3,288** reports of which **78% were identified as process or human error,** involving under-transfusion, delayed transfusion, avoidable transfusion, handling and storage errors, immunoglobulin errors and, sadly, incorrect blood component transfused. There were common themes in the errors reported, and as Bolton-Maggs has pointed out10, 11, there is no substitute for ICE; Identification, Communication and Education when it comes to transfusion.

There have been deaths reportedly associated with transfusion. In 2015, there were 26 deaths amongst the 2.25 million issues (an overall risk of 1:99,010 components issues). Not all these were *certainly* due to transfusion. The incidence of serious harm[[4]](#footnote-4) was 1:15,1528 components issued.

Thus, whilst the incidence of transfusion-related adverse events and subsequent harm is very low in this country, blood transfusion is not completely safe, and should be utilised only when necessary to help mitigate those risks. Avoiding blood may be a good thing.

**What can we do to avoid using donor blood?**

For simplicity, I have chosen to discuss what we can do in any form of surgery, and divided our options into care **before**, **during** and **after** surgery. Here, I provide a summary of the key aspects of that care. I will consider cardiac surgery separately because it presents some additional challenges. There are some excellent reviews available7, 12 of the entire topic of how to help meet the needs of Jehovah’s Witnesses (including on the Jehovah’s Witnesses own website13, 14) each with a very extensive and informative set of references if you wish to read more.

**Before Surgery**

1. The most important consideration is to **try and avoid surgery** in the first place by considering and discussing alternatives. Is there a drug or other treatment which might help? Even if surgery is decided upon we must ask how invasive it should be7. Advances in endoscopic (minimal-access) surgery have been enormous, and if surgery can be done through this key-hole approach, the number of vessels cut and the potential for bleeding should be markedly reduced.
2. **Careful planning** is mandatory.
	1. It is necessary to know whether the patient has any personal or family history of bleeding or blood clotting issues. Even if trying to avoid using blood, it is wise to at least define the blood group of the patient. Drugs such as aspirin, non-steroidal agents such as ibuprofen and other drugs which can increase blood loss should be stopped if possible. Evidence of anaemia should be sought by appropriate blood tests, which should include looking for problems of iron storage (iron is needed to make haemoglobin which carries oxygen in red blood cells) and levels of vitamin B12 and folate, both necessary for blood cell production in the bone marrow.
	2. It is wise to do blood tests to exclude any abnormal blood clotting and to measure levels of coagulation factors, especially fibrinogen. We get specialist advice if necessary.
	3. Sometimes, it is wise to prepare a patient for surgery in a more ‘intensive’ way than is usual. Apart from the standard recommendations (quit smoking, lose weight, drink less, eat healthily), it may be possible to increase the blood haemoglobin levels by giving **erythropoietin (EPO)** for a few weeks before surgery. EPO can increase the production of red cells by bone marrow by a factor of seven. To be eligible for EPO, your haemoglobin must be below 13g/dL for a man and below 12g/dL for a woman, and there are some specific circumstances when its use is either contraindicated or constrained15-17. Patients may also need additional IV iron if their stores are low.
	4. The detailed planning of what to do during the surgery to avoid the use of blood must engage **all** those involved in care. Most importantly, this should include the whole surgical team, the anaesthetist, those in recovery or intensive care and the ward staff. This can add up to a lot of people; it takes time and commitment.
	5. Planning must describe all the stages of the procedure. The details of what is intended before, during and after surgery must be defined.
3. **Communication.** I have indicated that the team is a broad one. By far the best way of dealing with this is to hold a multi-disciplinary team (MDT) meeting, and this must include the surgeon, anaesthetist, the nurses and a haematologist. Everyone who might encounter the patient MUST be aware of the plan and that the patient wishes to avoid blood. The plan should be written and easily found. MDTs are expensive, and often heard to organise. But they may well be cheaper in the long term than managing a patient for whom no effective plan was made.

**During Surgery**

1. **‘Mechanical’ steps.**
	1. The most obvious way in which a surgeon can reduce bleeding is to do just that! Be gentle, be careful, be obsessional. We have moved on a long way since the days when surgery had to be done quickly to limit the period of anaesthesia. We can now take our time in most circumstances.
	2. Equipment has improved enormously, particularly sutures which are finer and have needles which are not wider than the suture. Stapling machines can be used for internal anastomoses. Lighting is more effective and surgeons can wear magnifying glasses for greater precision.
	3. We must diathermy (cauterise) any small vessels we cut and place ligatures around larger ones. Recent years have seen the introduction of the ‘harmonic scalpel’ which cuts and coagulates simultaneously using ultrasound vibrations at 50,500 Hz.
	4. Limb surgery can be done with tourniquet control, and major surgery can be managed in combination with the anaesthetist to reduce body temperature (hypothermia) and with it controlled lowering of the blood pressure (hypotension) to reduce bleeding18, 19.
	5. It is possible to collect blood from the operative field and return it to the patient. This is called **cell-salvage**20, 21, and uses a machine called a cell saver which automatically washes shed blood, centrifuges it and returns the washed red cells to a bag from which they can be re-transfused back into the patient.
	6. Simply reducing the amount of blood samples taken during and after procedures can make a big difference22. So too can simply accepting a degree of anaemia. Indeed recent evidence suggests that humans can tolerate remarkably low haemoglobin levels without harm, although 7g/dL may be a practicable lower limit23.
2. **Manipulating Clotting Mechanisms**
	1. Whilst Jehovah’s Witnesses resolutely decline the transfusion of whole blood and *primary* blood components (red cells, white cells, plasma and platelets) and the use of any sample of their blood for cross-matching, many of them will accept the infusion of coagulation factors.
	2. If blood clotting is a problem, and for whatever reason individual clotting factors are diluted, then it can be helpful to infuse clotting factors24, notably Factors VIIa, VIII and IX.
3. **Drugs**
	1. The clotting mechanism in humans is a complex process, beyond the scope of this lecture. However, the core principles are that a series of reactions follow activation, adhesion and aggregation of platelets at the site of damage. A cascade of reactions of circulating clotting factors result in the formation of fibrin strands which form a plug with the platelets. The fibrin is normally destroyed by fibrinolysis and if this happens excessively, bleeding can recur or accelerate. Drugs that interfere with this fibrinolytic pathway have an important, and now proven, role in reducing bleeding in complex surgery. The most widely used drug is t**ranaxemic acid**25-28, normally used intravenously, but it can also be used topically29. **Aprotinin** has also been used30, but has proved controversial in cardiac surgery because of unwanted side effects affecting brain and kidneys, and is now only used in limited circumstances.
	2. There are also other agents which can be applied to directly a bleeding or oozing site. The first of these is **fibrin glue** (e.g. Tisseel) which is composed of two components to mimic clotting. These components are (1) human fibrinogen and aprotinin and (2) human thrombin and calcium chloride. These are mixed at the table and sprayed or injected over the site of bleeding. The second haemostatic agent in common use is **oxidised cellulose**, which is a mesh which can stimulate clotting at the surface.
4. **Time**
	1. There is no substitute for taking your time, and dealing with each minor bleeding point. Important in all cases, but vital in patients who refuse blood.

**After Surgery**

When the patient returns to the ward, it is crucial to monitor for bleeding. This may take the form of simply measuring pulse and blood pressure, or watching what emerges in the drains if they have been inserted at surgery. If bleeding does occur, blood can be salvaged using a cell saver, or if very severe, the patient should go back to the operating room to stop it. As time goes by, and if the patient is anaemic, then red cell production can be stimulated with EPO, supplemented if necessary by additional iron and B12.

**Cardiac Surgery**

Cardiac surgery is different from most surgery because of the need to bypass the heart and lungs using a cardio-pulmonary bypass (CPB) or heart lung machine. I need to take a moment to remind you of a few relevant details of these machines.

The machine is connected to the circulation by pipes. Blood is drained from the patient to a reservoir, to which shed blood aspirated from the operative field can be added. The blood then passes through filters and a gas exchange device in which it can also be cooled or heated. The blood is then pumped back to the patient’s aorta on the arterial side of the circulation. The circuitry (piping, reservoir, oxygenator, filters etc.) of the heart-lung machine is **empty** when the machine is put together. It contains just air. If that were connected to the patient and the pumps started, air would be pumped into the patient and massive and fatal air embolism to the brain and other organs would result. Thus, the circuit must be **primed**. What it must be primed with depends on several factors; the starting blood cell concentration of the patient (haematocrit %), the ratio of the blood volume of the patient to that of the total pump, and the target haematocrit (%) one is aiming for once the two circuits are joined and the pump is running. The ratio between prime and patient has changed greatly in the last 60 years as equipment design has improved, but it remains an important variable.

If a heart-lung machine was primed with clear fluid (saline, dextrose or other medicinal fluids), then the combined blood cell % of the two circuits (patient and pump) will be reduced as the blood of the patient is diluted. This is called **haemodilution.** How much haemodilution can be tolerated has been the subject of much debate over the years and is beyond the scope of this lecture, but well reviewed for both adult and paediatric practice31, 32. For the greater amount of the history of open-heart surgery, pump-priming volumes have been large, and blood was required to be added to the priming fluid to prevent dangerous haemodilution. The blood we add to the bypass circuit comes in the main from blood donors, as it does for all other purposes.

There has been a gradual but remarkable evolution of practice over recent years leading to a significant reduction in the amount of blood used in cardiac surgery**.** I do not have time to cover all these advances in detail, but there are some important principles and specific developments. I mentioned earlier that the volume of the pump prime was an important issue in the predicted degree of haemodilution. Several design features contribute to that, not least the type and size of the oxygenator. An excellent brief history of oxygenators has been published by Lim33. From the enormous originals involving rotating discs or complex bubble systems evolved smaller, but still large, bubble oxygenators which were prevalent throughout the late 1960’s and 1970’s. By 1976, single use, plastic bubble oxygenators were the norm. They incorporated a reservoir and were usually bonded to a heat exchanger making cardiopulmonary bypass both reproducible and widely available, just in time for the massive expansion in coronary artery bypass operations which occurred at that time. Still, litres of fluid were required to prime the system.

 The next decade saw a crucial development; that of membrane oxygenation. Initially using flat semipermeable membranes with blood on one side and medical gases on the other, these evolved in to wonderful efficient micro-porous tubular membranes with a very small priming volume. This made possible the next important step; minimising the entire bypass circuit34.

Almost every other aspect of the CPB pump has got smaller over the years. The pump heads themselves, the piping diameters, the filters and so on. The pipes have been reduced in length, by bringing the pump heads much closer to the patient. And the quality of the surfaces has improved massively to increase biocompatibility. They are much smoother and have a reduced tendency for the clotting components of blood to coat the surfaces. Put simply, this means that more of the clotting mechanisms are preserved at the end of the procedure to minimise bleeding risk by leaving them available for the blood to do its real job. As the prime falls in volume, so does the need to add donor blood, and there has been a significant fall in the mount of blood cross matched in preparation for surgery.

During the 1980’s and 1990’s the age and size of babies on whom we could operate fell as equipment, knowledge and techniques improved. The procedures we could perform became increasingly complex, and many to longer to perform. It was discovered that the exposure of the patient’s blood to the artificial surface of the bypass machine initiated a complex inflammatory response which resulted in increased permeability of the child’s own capillaries, causing fluid to leak out of the blood vessels into the tissues. Low haematocrits were used on by pass (haemodilution) together with low temperatures (hypothermia) with the aim of protecting the brain. Babies looked like Michelin men when they came out of surgery, and their internal organs were stiff with fluid, reducing contractility of the heart and causing poor lung function. There was a vogue to replace the fluid lost to the tissues from the circulation. This often made matters worse, and increased organ dysfunction.

I became very interested in this problem at the time, and with a team of researchers in Newcastle and at Great Ormond Street we first worked out35 methods of measuring the amount of water accumulated in the body and studied different types of priming fluids. We then went on to show that water leaks out of the blood vessels into the tissues during surgery, and takes days to return to normal. The longer the bypass, the smaller the patient and the lower the bypass temperature, the more water accumulated. We developed a method filtering the CPB circuit at the end of the period of bypass which allowed us to recover fluid from the circuit, reversing the haemodilution induced at the beginning of CPB36, 37. Not only were we able rapidly (over 15 minutes) to increase the percentage of red blood cells in the patient’s blood, but we demonstrated38 improved contractility of the heart, a larger cardiac output and reduced resistance to the flow of blood in the lungs, all exactly what you would like to see after surgery. This technique was called modified ultrafiltration, and it is now in widespread use in adults and children worldwide39. It saves blood, reduces bleeding and improves the heart’s performance. I wish I had patented it!

It also meant that I could perform heart surgery in children without the use of donor blood, with relative safety. I was thus consulted by many Jehovah’s Witness families from around the UK, and started to ask myself if blood should be avoided for *everyone* and not just for Jehovah’s Witnesses. By adopting a multi-disciplinary, well planned and obsessional approach, taking advantage of all the techniques I have described, it is possible to undertake cardiac surgery without blood in a way that it was not just 25 years ago.

This creates the opportunity for constructive dialogue with patients who are Jehovah’s Witnesses. This dialogue has been greatly helped by the creation, within the Church, of Hospital Liaison Committees. These emerged after the formation in 1988 of Hospital Information Services by the Watch Tower Society, and they have maintained a watching brief on the ‘blood-saving’ literature, and a growing list of surgeons and physicians who are willing to undertake surgery on Jehovah’s witnesses. JW.org has an excellent series of links to the medical literature. I know that several members of those committees are here tonight, and can honestly say that they are incredibly well informed, very helpful and excellent arbitrators. Without them many relationships between doctor and patient, and hospital and family would have been destroyed. Working with the HLCs it is possible to create an agreed plan of action which minimises risk whilst meeting the tenets of their belief.

**The Law**

I started this lecture by suggesting that there was a conflict between the beliefs of Jehovah’s Witnesses and my duty as a doctor. As you may already have guessed, it is not as simple as that. The law, though, is clear. Lord Justice Mostyn beautifully described the relevant legal principles in a recent judgement40.

1. In principle, **every citizen who is of age and of sound mind has the right to harm or (since 1961) to kill himself.** This is an expression of the principle of the purpose of power found in the Declaration of the Rights of Man and of the Citizen (1793) and in John Stuart Mill’s essay *On Liberty* (1859) where he stated at pp14 - 15:

**“That the only purpose for which power can be rightfully exercised over any member of a civilised community, against his will, is to prevent harm to others. His own good, either physical or moral, is not a sufficient warrant . . . Over himself, over his body and mind, the individual is sovereign”[[5]](#footnote-5)**

1. Thus Judge LJ in *St George’s Healthcare NHS Trust v S* [1969] Fam 28, 43 stated:

**“Even when his or her own life depends on receiving medical treatment, an adult of sound mind is entitled to refuse it.”**

1. A very recent example is *Newcastle Upon-Tyne-Hospitals Foundation Trust v LM* [2014] EWHC 454 (COP). There a gravely ill 63-year-old female Jehovah's Witness urgently needed a blood transfusion but had told the doctors that she was adamant that she would not want treatment with any blood products. Jackson J declared that it was lawful for the doctors treating her to withhold blood transfusions or the administration of blood products notwithstanding that such treatments would reduce the likelihood of her dying and might prevent her death. He held at para 24:

**“There is no obligation on a patient with decision-making capacity to accept life-saving treatment, and doctors are neither entitled nor obliged to give it.”**

The clarity of the law has found equal expression in guidance form professional bodies including the General Medical Council ([http://www.gmc-uk.org/guidance/good\_medical\_practice/duties\_of\_a\_doctor.asp)](http://www.gmc-uk.org/guidance/good_medical_practice/duties_of_a_doctor.asp%29) , the and the Royal Colleges , in my case the Royal College of Surgeons7 which has summarised the relevant duties most simply.

* Surgeons are duty-bound to respect patients’ religious freedoms

Surgeons can feel uncomfortable refusing to treat patients because of restrictions stemming from a religious belief for fear of accusation of discrimination. The emotional impact on surgeons from this type of restriction on their practice must also be recognised, as the loss of a patient who they had the means and ability to save can be very distressing.

* Surgeons have the right to choose not to treat patients if they feel that the restrictions placed on them by the refusal of blood products are contrary to their values as a doctor.
* If a surgeon is not prepared to treat a patient who refuses blood they must refer them to a doctor who is suitably qualified and prepared to take on the patient knowing the circumstances of this refusal of blood.

This guidance is clear, but the emotional consequences for the accepting medical team which follow the observed demise of a patient can be considerable, and must be recognised.

**What about the Children of Jehovah’s Witnesses?**

It is quite hard to become a Jehovah’s Witness; baptism only occurs after a prolonged period of Bible study and training. As indicated on the JW.org website, whilst being raised ‘within’ the brotherhood, it is up to the individual to decide for themselves if they accept the teachings.

“*We raise our children “in the discipline and admonition of Jehovah,” just as the Bible commands. (*[*Ephesians 6:4*](https://www.jw.org/en/publications/bible/nwt/books/ephesians/6/#v49006004)*) However, as they grow, they must make a personal decision to learn, accept, and apply what the Bible teaches before they can qualify for baptism. (*[*Romans 12:2*](https://www.jw.org/en/publications/bible/nwt/books/romans/12/#v45012002)*) Ultimately, each person must make his own choice concerning worship.—*[*Romans 14:12;*](https://www.jw.org/en/publications/bible/nwt/books/romans/14/#v45014012)[*Galatians 6:5*](https://www.jw.org/en/publications/bible/nwt/books/galatians/6/#v48006005)*.”*

The UN Convention on the Rights of the Child defines a child as anyone under 18, unless “under the law applicable to the child, majority is attained earlier”[[6]](#footnote-6). The legal age of consent is 16 in England and Wales. Traditionally, the power to give or withhold consent for medical treatment for a child lies with those with parental responsibility41, and parental consent is legally necessary to perform any medical procedure on a child. Parents have the right to raise their children as they see fit and they have ‘religious freedom’. Both these arguments have been used by JW parents when defending *their* right to refuse blood on their child’s behalf. However, parents’ rights are qualified by a *duty* to ensure their children’s health, safety and wellbeing. A classic American judgement42 set out the core principle:-

*‘‘Parents may be free to become martyrs themselves. But it does not follow that they are free, in identical circumstances, to make martyrs of their children...’’*

I quote [with my own modifications] from Woolley41 :

*“In a child under 16, four main issues arise: (1) the child’s capacity to consent to treatment; (2) parental authority and its limitations; (3) whose view prevails when parents and children clash; and (4) the extent of the courts’ powers over adolescents. Gillick v West Norfolk (Gillick v West Norfolk AHA [1986] 1 AC 12 at 184G as per Lord Scarman) considered the first three issues, with the majority of the House of Lords holding that, if a child under 16 could demonstrate sufficient understanding and intelligence to understand fully the treatment proposed they could give their consent to treatment. If they failed this competency test, parental consent is required. Unfortunately, treatment refusal was not considered”. This has become known as Gillick competence, and logically one would have thought that competent children are competent not only to accept treatment, but also to refuse it. Several cases on, the situation is that in relation to minors, the Court can override the wishes of both the child and its parents, but that power should only be used if ‘the child’s welfare is threatened by a serious and imminent risk that the child will suffer grave and irreversible mental or physical harm’’. Courts have usually taken the view that when treatment refusal was religion based, there was concern about the child’s ‘freedom of choice’ in the context of their upbringing. Thus, while a child’s refusal should be considered, it is likely that the court will override the refusal ‘in the child’s best interests.”*

 *(BRB v JB [1968] 2 All ER 1023 at 1025D Lord Denning MR: ‘‘...the views of the child should be taken into consideration; but the child’s views are never decisive’’).*

It is my view (and my duty) that we should do all we can to respect the firmly held beliefs of the parents and their wishes for the children. We have learnt that **it is possible** to perform complex surgery without the use of blood, and the evolution of that learning has been in no small part due to pressure from Jehovah’s Witnesses to find other ways. Working with the Hospital Liaison Committees, detailed understandings relating to the care of individual children are being made throughout the world, usually on the basis that the medical team will do everything in its power to avoid the use of blood, and will only give it in either dire emergency. If there is time to consider, then we prefer to go to Court to allow those paid to make difficult decisions on society’s behalf to apply their considerable intellects to the problem, in an environment free of the emotion which is unavoidable in a hospital. Going to court is mercifully rare, and we are getting much better at minimising the need for blood in every patient, and not just Jehovah’s Witnesses.

**Concluding Remarks**

I led you to believe in the title of this talk that I perceived the relationship between those who refuse blood for religious reasons, and those who might want to give it for medical reasons as one of warfare. A battle. My own research, at one time, placed me in what could be regarded as the firing line in that battle, as I met more and more Jehovah’s Witnesses after I found a way of reducing blood requirements in cardiac surgery.

I hope I have convinced you tonight that it has proved not to be a battle but rather the development of mutual understanding. We have ended up in a similar place; it is a good idea to minimise the amount of blood that you give patients. The pressure from Witnesses has driven many workers worldwide to find alternative strategies for avoiding bleeding and treating it when it happens. These strategies have proved successful, and are now not limited to Jehovah’s Witnesses, for which wider society owes them a debt of gratitude.

But we are only in a *similar* place. For non-believers like me it remains very difficult to comprehend that life-saving and (on the whole) extremely safe treatment is refused for ideological reasons. Many of those outside the Church share this comprehension gap. As Woolley said in 200541, **“religion is a powerful persuading voice, but it is also an individual belief. A limited life experience cannot truly give one the opportunity to rationalise a belief that may eventually lead to death.”**

The **belief** is clear; absolute and profoundly held. My **duty** has been clarified over time, both by consensus and the courts. I must respect the beliefs of my patients and do everything in my power to abide by them. The Hospital Liaison Committees, well informed and caring as they are, facilitate these discussions, and agreement is usually reached. Resort to the courts is rare in England.

A competent person has the right to refuse treatment. If I cannot support their decisions, my duty is to refer them to someone who will carry out their wishes. I can leave the battlefield; the believer cannot. But they will feel secure in their belief that by refusing blood, they are going to be accepted into a better place.

Those of us left behind after trying to care for them are unlikely to be so certain.

©Professor Martin Elliott, 2017

**Special Thanks to**

Brian Brooks, Jehovah’s Witnesses Hospital Liaison Committee, N London

Wayne Sorsby, Jehovah’s Witnesses Hospital Information Services

David Malyon, Jehovah’s Witnesses Hospital Liaison Committee

Ri Liessner, Consultant Haematologist

Rachel Moss Senior Transfusion Practitioner

Alex Robertson Perfusionist

Jo Delahunty, Gresham Professor of Law

**References**

1. Giangrande PL. The history of blood transfusion. *Br J Haematol.* 2000;110:758-767.

2. Felts JH. Richard Lower: Anatomist and Physiologist. *Ann Intern Med.* 2000;132:420-423.

3. Chryssides GD. *Jehovah's Witnesses; continuity and change*. Farnham, England: Ashgate; 2016.

4. Cole M. *Jehovah's Witnesses*. London, England: George Allen & Unwin Ltd.; 1956.

5. Anonymous. The Stranger’s RIght Maintained. *The Watchtower*1944:355-364.

6. Anonymous. Immovable for the Right Worship. *The Watchtower*1945:195-204.

7. Caring for Patients who Refuse Blood. London: Royal College of Surgeons of England; 2016.

8. Kitchens CS. Are transfusions overrated? Surgical outcome of Jehovah's Witnesses. *Am J Med.* 1993;94:117-119.

9. Transfusion Row Rocks Jehovah’s Witnesses. *The Guardian*2000.

10. Bolton-Maggs PHB, Poles D, al e. The 2015 Annual SHOT Report. Manchester2016.

11. Hb Bolton-Maggs P. Blood transfusion safety: patients at risk from human errors. *Br J Hosp Med (Lond).* 2013;74:544-545.

12. Habler O. Focussed Update: Perioperative management of Jehovah’s Witness patients in relation to their refusal of allogeneic blood transfusion2016.

13. JW. Transfusion - Alternative Strategies - Simple, Safe, Effective)2015.

14. JW. Medical Information for Clinicians2016.

15. Munoz M, Gomez-Ramirez S, Kozek-Langenakar S. Pre-operative haematological assessment in patients scheduled for major surgery. *Anaesthesia.* 2016;71:19-28.

16. Kotze A, Carter LA, Scally AJ. Effect of a patient blood management programme on perioperative anaemia, transfusion rate and outcome after primary hip or knee arthroplasty: a quality improvement cycle. *BJA.* 2012;108:943-952.

17. Posluszny JA, Napolitano LM. How do we treat life-threatening anemia in a Jehovah’s Witness patient? *Transfusion.* 2014;54:3026-3034.

18. Morrison CA, Carrick MM, Norman MA, et al. Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial. *J Trauma.* 2011;70:652-663.

19. Paul JE, Ling JE, Lalonde C, Thabane L. Deliberate hypotension in orthopedic surgery reduces blood loss and transfusion requirements: a meta-analysis of randomized controlled trials. *Can J Anaesth.* 2007;54:799-810.

20. Ashworth A, Klein AA. Cell salvage as part of a blood conservation strategy in anaesthesia. *Br J Anaesth.* 2010;105:401-416.

21. Carless PA, Henry DA, Moxey AJ, O'Connell D, Brown T, DA. F. Cell salvage for minimising perioperative allogeneic blood transfusion. *Cochrane Database Systems Rev.* 2010;4:CD001888.

22. McEvoy MT, Shander A. Anemia, bleeding, and blood transfusion in the intensive care unit: causes, risks, costs, and new strategies. *Am J Crit Care.* 2013;22:eS1-eS14.

23. Carson JL, Patel MS. Red blood cell transfusion thresholds: can we go even lower? *Transfusion.* 2014;54:2593-2594.

24. Tanaka KA, Esper S, Bolliger D. Perioperative factor concentrate therapy. *BJA.* 2013;111:135-149.

25. Henry DA, PA C, AJ M. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev.* 2007;4:CD001886.

26. Ker K, P. E, Perel P. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ.* 2014;344:054.

27. Ker K, Prieto-Merrino D, Roberts I. Systematic review, meta-analysis and meta- regression of the effect of tranexamic acid on surgical blood loss. . *Br J Surg.* 2013;100:271-279.

28. Hunt BJ. The current place of tranexamic acid in the management of bleeding. *Anaesthesia.* 2015;70:46-49.

29. Ker K, Beecher D, Roberts I. Topical application of tranexamic acid for the reduction of

 bleeding (Review). *Cochrane Database Syst Rev.* 2013;7:CD010562.

30. Royston D. The current place of aprotinin in the management of bleeding. *Anaesthesia.* 2015;70:46-49.

31. Jonas RA, Elliott MJ. Cardiopulmonary Bypass in Neonates, Infants and Children. Oxford: Butterworth-Heinemann; 1994.

32. Cooper MM, Elliott MJ. Haemodilution. In: Jonas RA, Elliott MJ, eds. *Cardiopulmonary Bypass in Neonates, Infants and Children*. Oxford: Butterworth-Heinemann; 1994:82-99.

33. Lim MW. The History of Extracorporeal Oxygenators. *Anaesthesia.* 2006;61:984-995.

34. Elliott MJ. Minimizing the bypass circuit: a rational step in the development of paediatric perfusion. *Perfusion.* 1993;8:81-86.

35. Novak I, Davies PS, Elliott MJ. Noninvasive estimation of total body water in critically ill children after cardiac operations. Validation of a bioelectric impedance method. *J Thorac Cardiovasc Surg.* 1992;104:585-589.

36. Elliott MJ. Ultrafiltration and modified ultrafiltration in pediatric open heart operations. *Ann Thorac Surg.* 1993;56:1518-1522.

37. Naik SK, Knight A, Elliott MJ. A successful modification of ultrafiltration for cardiopulmonary bypass in children. *Perfusion.* 1991;6:41-50.

38. Davies MJ, Nguyen K, Gaynor JW, Elliott MJ. Modified ultrafiltration improves left ventricular systolic function in infants after cardiopulmonary bypass. *J Thorac Cardiovasc Surg.* 1998;115:361-369; discussion 369-370.

39. Timpa JG, O’Meara LC, Goldberg KG, et al. Implementation of a Multidisciplinary Bleeding and Transfusion Protocol Significantly Decreases Perioperative Blood Product Utilization and Improves Some Bleeding Outcomes. *J Extra Corpor Technol.* 2016;48:11-18.

40. Mostyn LJ. Judgment in “Nottinghamshire Healthcare NHS Trust and RC”. In: Court of Protection and High Court of Justice FD, ed. *[2014] EWHC 1317 (COP)*. London2014.

41. Woolley S. Children of Jehovah’s Witnesses and adolescent Jehovah’s Witnesses: what are their rights? *Arch Dis Child.* 2005;90:715-719.

42. Prince v Massachusetts*.* Vol 321 US 1581944.

1. <https://www.bbts.org.uk/downloads/03_article_written_by_tom_richards_in_1994.pdf/> [↑](#footnote-ref-1)
2. A unit of blood is about 470ml. [↑](#footnote-ref-2)
3. There are actually more than 30 different blood groups, but by far the most frequent are the ABO groups, and these drive most transfusion practice, [↑](#footnote-ref-3)
4. for definitions of serious harm see Bolton-Maggs [↑](#footnote-ref-4)
5. Although Mill baulked at the idea that liberty extended to suicide, arguing at p142, perhaps less convincingly, that “the principle of freedom cannot require that he should be free not to be free. It is not freedom, to be allowed to alienate his freedom.” *“On Liberty” is available on line via* [*www.gutenberg.org*](http://www.gutenberg.org) [↑](#footnote-ref-5)
6. 1. Office of the High Commissioner for Human Rights (1989) [UN Convention on the Rights of the Child](http://www.ohchr.org/EN/ProfessionalInterest/Pages/CRC.aspx). United Nations [↑](#footnote-ref-6)