INTRODUCTORY NOTES

This document was originally published in the Biomedical Scientist in 2005 though it is no longer accessible via the Institute of Biomedical Sciences (IBMS) website.

I gratefully acknowledge the IBMS and especially the author of this document Mr Anthony J. Harding, previous chair of the IBMS History Committee, for their agreement to allow me to reproduce a transcript of this informative document.

Whilst stated to be a 'brief' history it does in fact cover a wide range of relevant topics as an initial view of the contents lists will confirm. It was one of the first documents I read that credits the work of the Arabic scholar Ibn-al-Nafis describing the circulation of blood that pre-dates the published description by William Harvey. Whilst it documents the work of some of the early pioneers such as Richard Lower and James Blundell it continues this theme by also outlining the work of some of the later pioneer investigators, not only Landsteiner but also Levine, Wiener, Race and Sanger. It scholarly also includes the important effects that World War 1, the Spanish Civil War and World War 2 had on the development of anticoagulation, blood banking and plasma fractionation respectively.

A BRIEF HISTORY OF BLOOD TRANSFUSION

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A booklet to accompany an exhibition presented by the IBMS Historical Section Committee at the IBMS Biomedical Science Congress
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CONTENTS

EARLY HISTORY

There are numerous Biblical references to blood, which was considered as the very essence of life and synonymous with the same. Jehovah Witnesses quote *Leviticus*[1] on the forbidding of eating (taking) blood from another, as a key element of their stance against human blood transfusion.

One of the earliest accounts of the circulation of blood was by the Arabic scholar, mathematician and physician Ibn-al-Nafis[2] who, in 1260 A.D. described the 'minor circulation' of blood in the body. This was more than two hundred and fifty years before William Harvey described the continuous circulation of blood around the body, in 1616[3], which he published in 1628[4].

The advent of the understanding of human anatomy and the circulation of blood gave rise to experimentation in transfusion techniques involving animal to animal and animal to human procedures. This eventually resulted in human to human transfusion. In 1657 Dr (later Sir) Christopher Wren[5], now better known as the renowned architect, performed a series of experiments involving the injection of various fluids into the veins of animals, with mixed results. Subsequently in 1665, at a meeting of the Royal Society of London – of which he was a founder member – he demonstrated the transfusion of blood from one animal to another.

Jean-Baptiste Denis

Although Lower and King performed the first animal to human transfusion in England, the first ever transfusion was performed by the Frenchman, Jean-Baptiste Denis, five months earlier in June 1667[8] in Paris.

Amazingly, Denis had commented on the potential of transfusion not only to replace blood loss but also to treat disease. More importantly, he also considered that transfusions 'ought to be done with blood of the same species' – however he later rejected this policy, in favour of using animal blood, due to the perceived risk to the donor. The resultant fatal reactions recorded by Denis led to the transfusion of blood to humans being prohibited in France and subsequently in England. Transfusion fell into disrepute and neglect for 148 years.

The first successful blood transfusion in animals was performed by Richard Lower before members of the Royal Society of London in 1665[6]. Richard Lower and Edmund King performed the first animal to human transfusion in London in November 1667[7]. The recipient, Arthur Coga, was believed to have graduated from Cambridge University in 1660.

TRACTATUS
DE
CORDE.
ITEM
De Motu & Colore
SANGUINIS
ET
Chyli in eum Transitu.

AUTHORE
Richardo Lower, M.D.

LONDINI:
Typis *Jo. Redmayne* impensis *Jacobi Allestry* ad Insigne *Rosæ-Coronatæ* in Vico vulgò dicto *Duck-lane.* MDCLXIX.

Title page of 'Tractatus de Corde' (Treatment on the Heart) by Richard Lower

THE NINETEENTH CENTURY REVIVALISTS

James Blundell[9] graduated from Edinburgh in 1813 and became an obstetrician of note at Guys Hospital in London and is credited with reintroducing blood transfusion into medical practice. Blundell reported favourably on the benefit of transfusion in cases of post partum haemorrhage in 1828. He was clearly influenced by, and generously acknowledged, the earlier work of John Henry Leacock[10], also a graduate of Edinburgh, whose dissertation in 1816 had established the principle that donor and recipient must be of the same species.

Blundell accepted this principle and reported his results of injecting human blood using a syringe. He later devised an apparatus consisting of a funnel and pump for the collection of donor blood for indirect transfusion into the veins of a patient. This apparatus was known as Blundell's Impellor.

Blundell's Impellor Apparatus

James Blundell

The invention of the hypodermic syringe by Alexander Wood in 1853 provided an important aid to transfusionists and led to the development of new devices to carry out transfusions.

In 1864 Dr Roussel in France and Dr James Aveling in London both used india rubber tubes to carry out direct human to human transfusions. James Aveling's apparatus consisted of two silver tubes which were used to enter the donor and recipient blood vessels, and connected to a length of india rubber tubing, with a stop-cock at either end and a bulb in the middle. The bulb when squeezed acted as a pump to expedite the flow of blood

The main problem, which stood in the way of the development of blood transfusion, was the tendency for the blood to clot and to block the tubes or apparatus connected to the recipient. In 1873, Sir Thomas Smith of St. Bartholomew's Hospital, is reported as successfully transfusing blood from which the clot had been removed, i.e. defibrinated. Attempts by Dr James Braxton-Hicks at Guys Hospital in 1883-4 to overcome this problem using sodium phosphate mixed with the blood as an anticoagulant resulted in the deaths of the patients.

In the last decade of the nineteenth century there was considerable debate regarding the benefit of using blood rather than saline because of the clotting problems. George Washington Crile[11] carried out studies in 1898 to compare the efficacy of blood versus saline in maintaining blood pressure in shock. His conclusions kept alive the quest to find better and safer ways of transfusing blood, which did not became apparent until well into the second decade of the new century.

KARL LANDSTEINER AND THE IDENTIFICATION OF HUMAN BLOOD TYPES OR GROUPS

A great amount of work involving immune practice and reactions took place in the latter part of the 19th Century. Physiologists had shown that blood from another species could destroy the cells of transfused subjects. It was noted that a similar reaction, the agglutination of cells, could occur between the blood of individuals of the same species. Karl Landsteiner (1868 – 1943), through his elucidation of different blood groups in humans, demonstrated that this was a normal phenomenon. In 1901, Landsteiner[12] described three different human blood types, A, B and O. The following year, Alfred von Decastello and Adriano Sturli[13] defined a fourth type, AB.

Landsteiner suggested his findings might be applicable to blood transfusion practice. It is now astonishing that this idea was not adopted until more than a decade later. During this period other blood type designations were described in Czechoslovakia by Jansky[14] in 1907 and in the United States by Moss[15] in 1910, both were in use as much as Landsteiner's and still used three decades later.

Despite these advances, surgeons continued to perform transfusions without any preliminary 'cross-agglutination' testing. Direct transfusion, artery to vein, as described by Carrel[16] and Crile[17] were still the methods usually employed. Pre-transfusion testing did not become normal practice until indirect transfusion became popularised by the use of sodium citrate anticoagulation and collection of donor blood, which occurred after 1915.

The ABO Blood Group system originally designated by Landsteiner remains the principal donor- recipient matching criteria for human blood transfusion.

BLOOD GROUP CLASSIFICATIONS

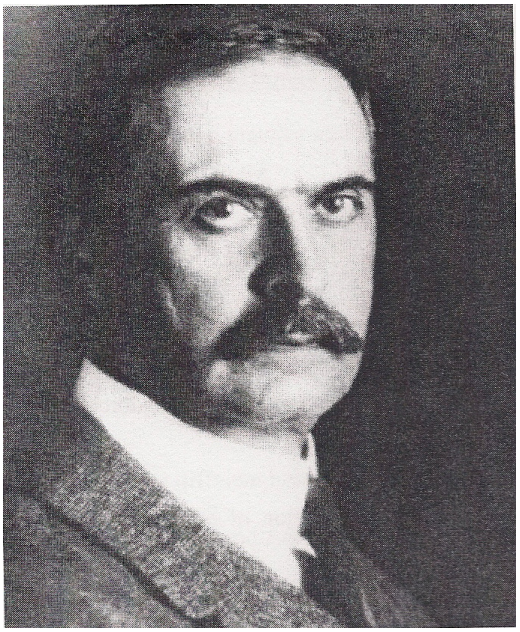
Landsteiner (1900)	Jansky (1907)	Moss (1910)	International (1927)
C	I	IV	O
A	II	II	A
B	III	III	B
-	IV	I	AB

Karl Landsteiner is without doubt, best known for his groundbreaking work on the ABO Blood Group System. His work on the identification and elucidation of other blood group systems is also without parallel.

In 1927, Landsteiner and Levine[18] proposed a new blood group system after the identification of two new genes which they called M and N. The system was later extended after Sanger and Race[19] identified the related S and s genes in 1947. Additionally in 1927, Landsteiner and Levine[20] discovered the Pp antigens of the P Blood Group System.

In 1940, Landsteiner (by now aged seventy-two) and Alexander Wiener described the first Rhesus blood group which initiated work on unravelling what is probably the most complex blood group system known.

Karl Landsteiner had many facets to his knowledge, one of the most important being his understanding of immunochemistry. His book entitled 'The Specificity of Serological Reactions' first published in 1936 is testament to his unique contribution to our understanding of antigen-antibody reactions and their importance in blood transfusion.



Karl Landsteiner

Philip Levine

A NEW ERA OF EFFECTIVE BLOOD TRANSFUSION

Throughout the 20th Century, milestones in the advancement of blood transfusion are synchronous with the onset of military conflict throughout the world.

The practice of blood transfusion advanced with the outbreak of the First World War, mainly due to the new knowledge of matching different blood groups and the use of an anticoagulant that facilitated indirect transfusion to take place. Prior to this time transfusion was only possible by using defibrinated blood, as described by Moss[21] in 1914, and by direct donor to patient techniques.

The Belgian, Adolph Hustin[22] in 1914, discovered that sodium citrate in tolerable quantities could anticoagulate blood for transfusion. Further work by Luis Agote[23] in Argentina and Richard Lewisohn[24] in U.S.A. in 1915 showed that sodium citrate would effectively anticoagulate blood at a concentration which could be transfused without harming the recipient. Until this time blood transfusion on the battlefield was only practical with a ready supply of donors close to the patients. Tank warfare changed the mobility of battle and required a stock of blood to be established; this enabled a supply to be available whenever and wherever needed.

The practice of blood transfusion was favoured by the American and the Canadian surgeons arriving at the Front to cope with the increasing number of casualties suffered in France and Belgium. The beneficial effect in combating blood loss in major trauma was soon recognised and adopted by British and French surgeons. As a result, the establishment of the first bank of stored blood is described by Oswald H. Robertson[25] in 1918. He stored blood for up to 21 days to treat haemorrhagic shock suffered in battlefield injuries.

Robertson also recognised the advantages of adding glucose to blood but it was twenty years later before his observation was fully appreciated in the development of large-scale blood storage during the Spanish Civil War between 1937 and 1939. The subsequent publication of the effectiveness of transfusion, by army surgeons, resulted in its introduction to civilian medical practice.

TRANSFUSION BETWEEN THE WARS – A PERIOD OF PROBLEMS AND CONFUSION

It is a strange facet of scientific discovery that rarely does it result in an early change of practice or a benefit to society. This is exemplified in transfusion practice between the World Wars.

The discovery of ABO blood groups by Landsteiner in 1900 and subsequent work by Jansky in 1909 and Moss in 1910 did not result in the adoption of a common blood group nomenclature until 1939. Confusion caused by blood donors having been grouped using the Jansky system when the Moss system was in widespread use, represented a potential for mismatched transfusion.

The availability of citrate treated, anticoagulated blood for indirect transfusion following the work of Hustin, Agote and Lewisohn, failed to persuade physicians and surgeons to relinquish direct person to person transfusion. A high incidence of febrile reactions, a lack of donor panels and the reluctance of the medical profession to change, were all contributory to the slow adoption of indirect transfusion techniques.

Ottenburg and Kaliski[26] in 1913 described the beneficial outcome of pre-transfusion compatibility testing or 'cross matching' in 128 patients at Mount Sinai Hospital in New York. Sadly this did not become a regular procedure world-wide, until many years later.

Lewisohn and Rosenthal[27] in 1933 showed that bacterial contamination and inadequately cleaned transfusion equipment were the causes of many transfusion reactions.

The common practice of only using group O 'universal donors' by hospitals and clinicians and performing cut down procedures for vene-section resulted in a rapid decline of available donors.

The reliability of blood group procedures was also in question due to the cost and availability of reliable antisera for blood group typing. The Burroughs Company was the only commercial source in the United Kingdom at that time. This resulted in attempts to produce 'home-made' antisera from staff and donor samples resulting in unreliable and potentially dangerous reagents being used when only 'tile grouping' techniques prevailed.

Differing views and practices prevailed until the imminent threat of war in 1939 despite the monumental work of Percy Lane Oliver[28] and Geoffrey Keynes[29] in establishing donor panels and the advocating of ethical standards of practice in respect of blood donors.

THE ONSET OF WORLD WAR II – TRANSFUSION ADVANCES

The Spanish Civil War (1937-39) gave rise to a fresh approach to blood transfusion, hastened by the threat of large numbers of civilian and military casualties. There was a major initiative to increase the number of blood donors and to establish large-scale blood banks to ensure adequate supplies.

One of the other outcomes of this period was the introduction by Jorda[30] of adding glucose to the citrate anticoagulant for blood collection, although Robertson had suggested this as early as 1918. This was found to improve the viability of transfused red cells and thus increase the benefit of transfusion.

In 1938, the Ministry of Defence established a committee in London to consider how blood transfusion support would be provided to military hospitals in the event of war. This led to the formation of the Army Blood Transfusion Service and the opening of the Army Blood Supply Depot (ABSD) in 1939; the first military transfusion service in the world.

Such was the demands at the outbreak of World War II that the ABSD processed more than 33,000 donations in its first year, six times more than the busiest

civilian service prior to the war. The ABSD went on to produce all dried products, crystalloids and grouping sera as well as all the equipment for collecting and administering blood.

THE RHESUS BLOOD GROUP SYSTEM – A NEW UNDERSTANDING OF OLD PROBLEMS

The discovery of the Rhesus blood groups by Landsteiner and Wiener[31] in 1940 and the related work done previously by Levine and Stetson[32] in 1939, was the most important and significant advancement in blood grouping and transfusion since the discovery of ABO groups, forty years before.

Landsteiner and Wiener reported the results of immunising guinea pigs and rabbits with the red cells of rhesus monkeys. The immune antibody produced was found to agglutinate the red cells of approximately 85% of random people tested. Earlier in 1939, Levine and Stetson were investigating intra-uterine death associated with severe anaemia. They reported a case where anaemia was due to antibody mediated cell destruction caused by the passage of maternal antibody into the foetal circulation. They clearly described a case of Haemolytic Disease of the Newborn (HDN). The antibody identified was not named.

Wiener and Peters[33] had recognised that the anti-Rhesus antibody could be a cause of haemolytic reactions to blood transfusion, establishing a key principle in transfusion and a landmark medical discovery.

In 1941 Levine, Katzin, Vogel and Burnham[34-36] described the aetiology of erythroblastosis foetalis or HDN, showing that incompatibility between mother and foetus to be the cause. They also found the causative antibody had the same specificity as the anti-Rhesus antibody described by Landsteiner and Wiener.

RACE AND SANGER – PIONEERS OF BLOOD GROUP SCIENCE

Robert Race and Ruth Sanger are undoubtedly the most well known names in blood group science in the post Second World War period up to 1980. Their contribution to the understanding of blood groups is probably only exceeded by the earlier work of Landsteiner.

Robert Race worked at the Galton Serum Laboratory before he and Arthur Mourant moved in 1946 to the Lister Institute of Preventive Medicine in London; Race becoming the director of the Medical Research Council Blood Group Research Unit and Mourant becoming director of the Blood Group Reference Laboratory. Their partnership and co-operation resulted in many significant contributions to the knowledge and practice of blood group science.

Robert Race was joined by Ruth Sanger in 1947, who became his wife. Together they wrote 'Blood Groups in Man'[37], first published in 1950 and subsequently translated into many languages and running to seven editions. This work became the standard reference book on the subject for several decades.

In their early work on the Rhesus blood group system, Race and Sanger, inspired and supported by Professor Ronald Fisher in the U.K. differed with Wiener in the USA - these differences reaching the point of acrimonious exchanges in the scientific press regarding the mode of genetic inheritance.

Robin Coombs working with Race and Mourant, developed the antiglobulin test, or 'Coombs Test', used for the detection of 'incomplete' antibodies. The test has become a standard technique in blood group serology and is described in three landmark publications.[38-40]

THE DEVELOPMENT OF PLASMA DRYING AND FRACTIONATION

The ability to preserve therapeutic antisera by drying in the late 1930's gave rise to the development of freeze-drying processes. Although this was originally not intended for human plasma, experimental batches were tested and proved safe, when transfused to human recipients.

Once again, the wartime situation in 1939 led to a demand for plasma supplies to treat military and civilian casualties. This accelerated the effort to find a large-scale process to satisfy the immediate requirements. There was a strong demand for dried plasma by the Army for use in the Tropics, where it could be stored effectively without deterioration.

In the United Kingdom (UK), the original freeze-drying plant in Cambridge was too small to meet the demands, even supported by a second unit built by the Wellcome Foundation at Beckenham. This prompted the Army Blood Transfusion Service (ABTS) to build its own plant. During the last two years of World War II over 250,000 400ml bottles of freeze dried plasma was produced. This was in addition to the supply of liquid plasma and serum which although still in use was becoming less acceptable due to changes and contaminants forming during storage.

At the same time as early efforts were being made to develop techniques for storage of plasma for transfusion, research was proceeding into separating and purifying plasma protein fractions. Much of the work in the UK was carried out at the Lister Institute during the early years of the war.

In 1944, Edwin Cohn[41] in the USA, published his classic work on the ethanol separation and purification of plasma proteins. However, much of the equipment and materials to carry out Cohn's procedure was not available in the UK and an alternative method had to be sought. Kekwick, Mackay and Record[42] in 1946, working at the Blood Products Research Unit in London, succeeded in producing fibrinogen and prothrombin from plasma separated by precipitation with ether. This pioneering work led to the production of other blood products and the foundation of the UK supply programme.

At the cessation of hostilities, the plasma processing equipment from the Army Blood Transfusion Service was moved to the Lister Institute in Chelsea. Further plants were installed at Elstree, which became the Blood Products Laboratory where it has continued to the present day.

THE DISCOVERY OF POLYTHENE AND INTRODUCTION OF PLASTIC TRANSFUSION SETS

The discovery of a new polymer, by a research team at Imperial Chemical Industries (ICI) in 1930, resulted in its rapid adaptation as a new electrical insulating material. The new material was light, flexible and waterproof, ICI named the substance, polythene.

The first reported clinical use of polythene in the UK, in 1948 was as a fine flexible catheter for neonatal use. In 1952, Walter[43] designed a polythene plastic blood collection bag with integral donor line and giving set. Walter's invention was soon recognised and the Fenwal Company was set up to mass produce the bags for use in American and Canadian hospitals. By 1960 they were in widespread use throughout North America.

Due to the adverse economic situation in the UK during this period and disagreement amongst directors of the regional transfusion centres, these bags were not introduced throughout the UK, until 1975.

Baxter Corporation (now owning Fenwal) in USA, Biotest in Germany, Terumo Corporation in Japan and Tuta in Australia further developed plastic transfusion sets

to enable more blood components and plasma fractions to be aseptically separated and stored for transfusion.

THE AGE OF AUTOMATION

In the ever developing world of biomedical science, many erstwhile manual laboratory techniques and procedures became automated. Technical progress by the equipment manufacturers and the advent of computer based technologies produced an avalanche of new machines available from 1975 onwards. The field of blood group serology and transfusion was one of the late corners to this changing world. Indeed it was believed by many of the experienced workers that no machine could take over the highly interpretative role of the skilled serologist. This was to prove wrong.

Reports as early as 1963, by Sturgeon, Cedergren & McQuiston[44] and Allen, Rosenfield & Adebahr[45], described the use of the Technicon Autoanalyzer for blood group antibody detection In their review of the subject in 1968, Marsh, Nichols & Jenkins[46] demonstrated that virtually all clinically significant blood group antibodies could be detected by automated means. The new technology was adopted by many transfusion centres for donor screening and larger hospital laboratories for antenatal screening. In addition to the provision for blood grouping and antibody screening an increasing requirement for microbiological screening of blood donations was becoming apparent. Originally only syphilis testing was deemed necessary, then Hepatitis B and subsequently CMV, HIV, Hepatitis C and now vCJD and malaria screening are standard on all blood donations. Without the technology, only an army of extra staff would be able to cope with the constant increase in testing to ensure the supply of safer blood products.

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