Blood Transfusion in History

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1430
2009

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Introduction

For thousands of years, the human body was a mystery to the world of science. Indeed, cultures across the globe employed various forms of observation, experience, ritual, intuition, and other methods to combat illness; such efforts met with varying degrees of success. Yet, profound exploration of human physiology remained elusive. Nowhere was this more apparent than in the understanding of blood ... what it is; what it does; where it flows; how it is created; and many other questions went unanswered. For many, one issue was clear: blood transfusion was a sound medical procedure.

The practice of blood transfusion, that is the transference of blood from the circulation of one individual to that of another for practical therapeutic purposes, is of relatively recent origin. Although it only became a practical possibility during and shortly after the Second World War, the concept of 'transfusion' has a longer history.

The transfusion time line highlights many of the discoveries, inventions, observations, and practices, which, since ancient times, have led to remarkable progress and resulted in the effective treatments that are now taken for granted. The 20th Century has witnessed the most progress in the enumerable transfusion practices, activities and safety.

The practicality of transfusion has, to some degree, paralleled and in some instances been the consequence of, developments in other sciences. The idea though of the theoretical beneficial effects of blood transfusion has been recognized for over three centuries. This older history is based on the traditional idea of blood as being the 'living-force' of the body.

Man must have recognized that loss of blood was frequently associated with weakness and death. This was manifested by Greeks and Romans committing suicide by 'opening a vein' (involving cutting their wrists). Blood was recognized as having numerous mysterious properties, including initially that of carrying both the mental and physical characters of its owner. Early attempts at replacing lost blood involved the drinking of blood by the patient. By choice, this was from a young, healthy, fit person or animal. The legend of the vampire originates from this concept. This somewhat mystical fascination with the properties of blood is to some degree still with us today[1].

[1] In my study I'll follow the next arrangement:
WS: Means Web Site. For Example, WS3: Web Site Number 3
Without WS, the number refers to Comments and Notes.

Chapter One

Blood in History

I- Blood in Myths, Beliefs and Religions:

Due to its importance to life, blood is associated with a large number of beliefs. One of the most basic is the use of blood as a symbol for family relationships; to be "related by blood" is to be related by ancestry or descendance, rather than marriage. This bears closely to bloodlines, and sayings such as "blood is thicker than water" and "bad blood", as well as "Blood brother". Blood is given particular emphasis in the Jewish and Christian religions because Leviticus[WS11] 17:11 says "the life of a creature is in the blood". This phrase is part of the Levitical law forbidding the drinking of blood, due to its practice in idol worship by surrounding societies. Mythic references to blood can sometimes be connected to the living-giving nature of blood, seen in such events as childbirth, as contrasted with the blood of injury or death.

1- Indigenous Australians:

In many indigenous Australian Aboriginal peoples' traditions, ochre (particularly red) and blood, both high in iron content were applied to the bodies of dancers for ritual. As the Robert Lawlor (1939-Now) states[WS11]:

> "In many Aboriginal rituals and ceremonies, red ochre is rubbed all over the naked bodies of the dancers. In secret, sacred male ceremonies, blood extracted from the veins of the participant's arms is exchanged and rubbed on their bodies. Red ochre is used in similar ways in less secret ceremonies. Blood is also used to fasten the feathers of birds onto people's bodies. Bird feathers contain a protein that is highly magnetically sensitive."

The anthropologist and historian Robert Lawlor comments that blood employed in this fashion is held by these peoples to attune the dancers to the invisible energetic realm of the Dreamtime.

2- Indo-European Paganism:

Among the Germanic tribes (such as the Anglo-Saxons and the Norsemen), blood was used during their sacrifices; the Blots[WS11]. The blood was considered to have the power of its originator and after the butchering, the blood was sprinkled on the walls, on the statues of the gods and on the participants themselves. This act of sprinkling blood was called bleodsian in Old English and the terminology was borrowed by the

Roman Catholic Church becoming to bless and blessing. The Hittite word for blood, ishar was a cognate to words for "oath" and "bond". The Ancient Greeks believed that the blood of the Gods, ichor, was a mineral that was poisonous to mortals.

3- Judaism:

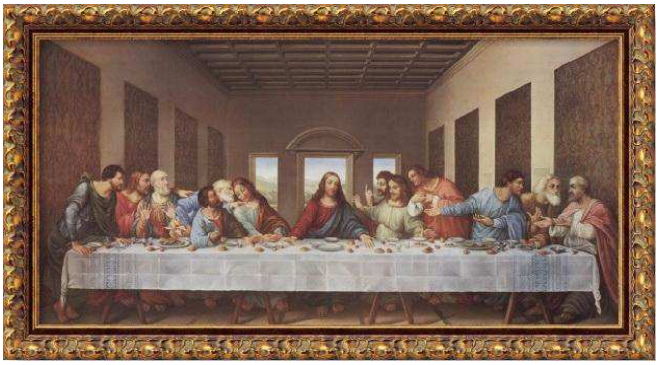
In Judaism, blood cannot be consumed even in the smallest quantity (Leviticus 3:17 and elsewhere); this is reflected in Jewish dietary laws (Kashrus). Blood is purged from meat by salting and soaking in water.

Other rituals involving blood are the covering of the blood of fowl and game after slaughtering (Leviticus 17:13); the reason given by the Torah is: "Because the life of every animal is in his blood" (ibid 17:14).

4- Christianity:

Christians believed that life of living being is located in his blood. *"...the life of the flesh is in the blood..." (Leviticus 17:11)*[1].

Some Christian churches, including Roman Catholicism, Eastern Orthodoxy, and Anglicanism teach that, when consecrated, the Eucharistic[WS17] wine actually becomes the blood of Jesus (symbolism). Thus in the consecrated wine, Jesus becomes spiritually and physically present. This teaching is rooted in the Last Supper as written in the four gospels of the Bible, in which Jesus stated to his disciples that the bread which they ate was his body, and the wine was his blood. "This cup is the new testament in my blood, which is shed for you." (Luke 22:20)[WS11].



The Last Supper by Leonardo da Vinci Painted in Milan[WS5]

Various forms of Protestantism, especially those of a Wesleyan or Presbyterian lineage, teach that the wine is no more than a symbol of the blood of Christ, who is spiritually but not physically present. Lutheran theology teaches that the body and blood is present together "in, with, and under" the bread and wine of the Eucharistic feast.

Christ's blood is also seen as the means for atonement for sins for Christians. *"...take drink...this is my blood, which is shed for you*, for the *remission of sins..."* (Matthew 26)[2].

At the Council of Jerusalem, the apostles prohibited Christians from consuming blood, probably because this was a command given to Noah "Only flesh with the life thereof, which is the blood thereof, shall ye not

eat." (Genesis 9:4). This command continued to be observed by the Eastern Orthodox.

5- Islam:

Consumption of food containing blood is forbidden by Islamic dietary laws. This is derived from the statement in the Qur'an, sura Al-Maida (5:3)[WS11]: "Forbidden to you (for food) are: dead meat, blood, the flesh of swine, and that on which hath been invoked the name of other than Allah."

6- Jehovah's Witnesses:

Due to Bible-based beliefs, Jehovah's Witnesses[WS24] do not eat blood or accept transfusions of whole blood or its four major components namely, red blood cells, white blood cells, platelets, and whole plasma. Members are instructed to personally decide whether or not to accept fractions, and medical procedures that involve their own blood.

7- Chinese and Japanese Culture:

In Chinese culture[WS11], it is often said that if a man's nose produces a small flow of blood, this signifies that he is experiencing sexual desire. This often appears in Chinese-language and Hong Kong films as well as in Japanese culture parodied in anime. Characters, mostly males, will often be shown with a nosebleed if they have just seen someone nude or in little clothing, or if they have had an erotic thought or fantasy.

8- Blood Libel:

Various religious and other groups have been falsely accused of using human blood in rituals; such accusations are known as blood libel[WS12]. The most common form of this is blood libel against Jews. Although there is no ritual involving human blood in Jewish law or custom, fabrications of this nature (often involving the murder of children) were widely used during the Middle Ages to justify Anti-Semitic persecution and some have persisted into the 21st century.

9- Vampire Legends:

Vampires[WS45] are mythological beings which live forever by drinking the blood of the living. Stories of creatures of this kind are known all over the world. Most of these myths in Western culture originate from Eastern European and Balkan folklore.

10- Blood in Art:

Blood is one of the body fluids that has been used in art. In particular, the performances of Viennese Actionist Hermann Nitsch[WS11], Franko B, Lennie Lee, Ron Athey, Yang Zhichao and Kira O' Reilly

along with the photography of Andres Serrano have incorporated blood as a prominent visual element. Marc Quinn has made sculptures using frozen blood, including a cast of his own head made using his own blood.

11- Blood in Films:

Blood is commonly associated with gore in motion pictures. Films with bloody scenes tend to receive a high rating by film licensing bodies, ranging from PG-13 to NC-17[WS61], depending on its depiction and its prominence[29]. Blood in video games has led to video game censorship.

II- Blood in Medicine:

1- Egypt:

Egyptians[3] bathed in blood for their health. It is believed that the ancient kings of Egypt apparently bathed in blood, believing such baths to " resuscitate the sick and rejuvenate the old and incapacitated" [4], as well as, believing it to be a cure for elephantiasis! The Egyptians also used bleeding to treat patients. A tomb illustration in Memphis-Egypt, belongs to 2500 BC depicts a patient being bled from the foot and neck.

2- China:

In 1000 BC[5] the Chinese believed that the soul was contained in the blood.

3- Classical Greek medicine:

In classical Greek medicine, blood was associated with air, springtime, and with a merry and gluttonous (sanguine) personality. It was also believed to be produced exclusively by the liver. In Hippocratic medicine, blood was considered to be one of the four humors, together with phlegm, yellow bile and black bile, and their imbalance causes disease.

4- Roman Empire:

In classical times the Romans and Greeks, as well as bathing in blood, have reportedly drank it. **Taurobolium**[6] mentioned the practice of bathing in blood as it cascaded from a sacrificial bull, was practiced by the Romans. '**Pliny the Elder**'[7], wrote in the 1st Century AD, describing how spectators rushed into the arena to drink the blood of dying gladiators. These people did this because they felt that such blood was especially beneficial since the athletes were strong and brave, qualities that they believed were present within, and therefore transmissible by, the blood of the person concerned. The situation apparently became so bad that by AD193, a decree was issued by **Septimus Severus** prohibiting

this practice. Pliny the Elder also wrote: *"…. a man's blood rubbed upon* himself will relieve him of pain" and that the drinking of blood *".... as if* out of a loving cup" was a cure for epilepsy. About the same time, the writer Galen advised that the drinking of the blood of a weasel, or of a dog, was a cure for rabies.

5- Viking Tribes:

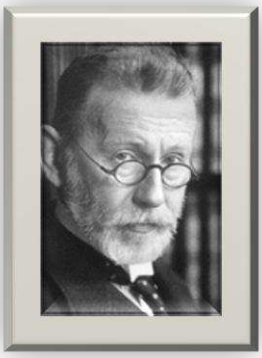
Ancient Norwegians reportedly drank the blood of seals and whales as a remedy for epilepsy and scurvy[WS11].

6- Modern Era:

The first person to describe red blood cells was probably the young Dutch biologist **Jan Swammerdam** (1637–1680)[8], who had used an early microscope in 1658 to study the blood of a frog. Unaware of this work, a Dutch doctor **Anton van Leeuwenhoek** (1632-1723)[WS8] provided another microscopic description in 1674.

It was the German anatomist **Max Schultze** (1825-1874)[9] who first offered a description of the platelet in his newly-founded journal "Archiv für mikroscopische Anatomie". He describes "spherules" much smaller than red blood cells that are occasionally clumped and may participate in collections of fibrous material.

Giulio Bizzozero (1846-1901), building on Schultze's findings, used "living circulation" to study blood cells of amphibians microscopically in vivo. One of his findings was the fact that platelets clump at the site of blood vessel injury, which precedes the formation of a blood clot. This observation confirmed the role of platelets in coagulation.



Paul Ehrlich (1854-1915)[WS34]

In 1878, the German-born physician **Paul Ehrlich** (1854-1915) formulated dyes for staining cells and transformed the field of hematology. He invented a simple technique for preparing blood films using one of his stains. One of Ehrlich's more significant achievements in regard to blood staining was the ability to clearly view white blood cells. Although white blood cells had been discovered about a century before Ehrlich made his discovery, scientists had little information about the cells. Using his unique staining techniques, Ehrlich was able to identify the two main types of white blood cells, lymphocytes and granulocytes. He was awarded Nobel Prize for his work with blood staining.

In 1959, English doctor **Max Perutz** discovered the structure of Hemoglobin[WS50].

Chapter Two

A History of the Discovery of the Circulatory system

The discovery of the circulation of the blood didn't belong to a single man, or indeed to a single era. There were three principal errors which masked the great fact of the circulation. The first was, the arteries contained only air not blood; the second was, the septum between ventricles of the heart was perforated; and the third was, the veins carried the blood to the extremities instead of bringing it from them. Let's see with whom these errors originated and who destroyed them.

The earliest known writings on the circulatory system are found in the **Ebers Papyrus** (16th century BC)[WS16], an ancient Egyptian medical papyrus containing over 700 prescriptions and remedies, both physical and spiritual. In the papyrus, it acknowledges the connection of the heart to the arteries. The Egyptians thought air came in through the mouth and into the lungs and heart. From the heart, the air traveled to every member through the arteries. Although this concept of the circulatory system is greatly flawed, it represents one of the earliest accounts of scientific thought.

Ebers Papyrus (1552 BC)[WS66]

The knowledge of circulation of vital fluids through the body was known to **Sushruta** (6th century BCE)[WS42]. He also seems to have possessed knowledge of the arteries, described as 'channels' in his medical treatise Sushruta Samhita. The valves of the heart were discovered by a physician of the Hippocratic School around the 4th century BC. However their function was not properly understood then. Because blood pools in the veins after death, arteries look empty. 350 BC, Greek philosopher Aristotle believes that the heart is the central organ of the body and therefore the seat of the soul. He conducts dissections of many different animals and describes their anatomical

structures. Based on his observations, Aristotle presumes the heart is a three-chambered organ, even in humans.

Ancient anatomists included **Herophilos** (335-280 BC)[WS20] and **Erasistratus** (304-250 BC)[WS17] assumed they were filled with air not blood and that they were for transport of air.

Greek physician Herophilos distinguished veins from arteries but thought that the pulse was a property of arteries themselves. Greek anatomist Erasistratus observed that arteries that were cut during life bleed. He ascribed the fact to the phenomenon that air escaping from an artery is replaced with blood that entered by very small vessels between veins and arteries. Thus, he apparently postulated capillaries but with reversed flow of blood.

Galen (129-217)

The 2nd century AD, Greek physician, **Galen** (129-217 AD)[WS63], knew that blood vessels carried blood not air; thus, he solved the first error. He identified venous (dark red) and arterial (brighter and thinner) blood, each with distinct and separate functions. Growth and energy were derived from venous blood created in the liver from chyle, while arterial blood gave vitality by containing air and originated in the heart. He mistakenly assumed that air caused pulse. Blood flowed from both creating organs to all parts of the body where it was consumed and there was no return of blood to the heart or liver. The heart did not pump blood around, the heart's motion sucked blood in during diastole. He still believed that the septum between ventricles of the heart was perforated and the veins carried the blood to the extremities instead of bringing it from them. These two errors were destined to pass from him to the moderns.

Galen[WS16] believed that the arterial blood was created by venous blood passing from the left ventricle to the right by passing through 'pores' in the interventricular septum, air passed from the lungs via the pulmonary artery to the left side of the heart. As the arterial blood was created 'sooty' vapors were created and passed to the lungs also via the pulmonary artery to be exhaled.

In 1242, the Arabian physician, **Ibn al-Nafis** (1210-1288)[WS64], became the first person to accurately describe the process of blood circulation in the human body, particularly pulmonary circulation, for which he is considered the father of circulatory physiology. In 1924 an Egyptian physician Dr. Muhyi al-Din Altawi, discovered a script No. 62243, titled "Commentary on Anatomy in Avicenna's Canon" in the Prussian State Library in Berlin, in which Ibn al-Nafis Stated[10]:

Ibn al-Nafis (1210-1288)[WS64]

> "...the blood from the right chamber of the heart must arrive at the left chamber but there is no direct pathway between them. The thick septum of the heart is not perforated and does not have visible pores as some people thought or invisible pores as Galen thought. The blood from the right chamber must flow through the vena arteriosa (pulmonary artery) to the lungs, spread through its substances, be mingled there with air, pass through the arteria venosa (pulmonary vein) to reach the left chamber of the heart and there form the vital spirit..."

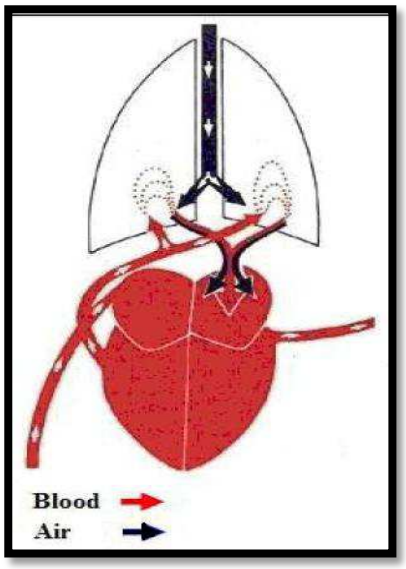
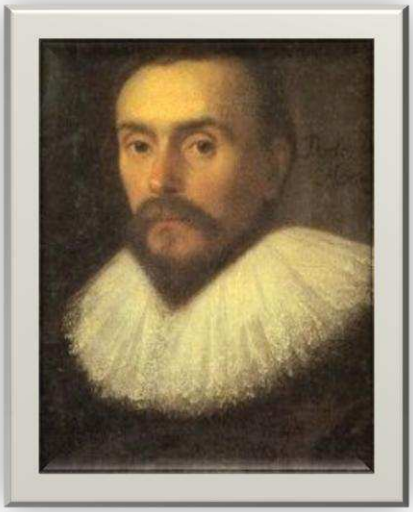


Illustration of the Minor Circulation of the Blood According to Ibn al-Nafis[11]

Ibn al-Nafis solved the second mistake; he found the real way which blood uses to pass from the right side to the left side of the circulation. It was through lungs, not through the assumed perforation of the heart.

Contemporary drawings of this process have survived. In 1552, Spanish physician **Michael Servetus** (1511-1553)[WS32] described the same, and the Italian physician **Realdo Colombo** (1516-1559)[WS37] after six years proved the concept, but it remained largely unknown in Europe.



William Harvey (1578-1657)[WS65]

Andrea Cesalpino (1519-1603)[12] used the term ‘circulation’ and believed that the veins and arteries were connected by a fine vascular network.

Finally, the English physician **William Harvey** (1578-1657)[WS65], a pupil of **Hieronymous Fabricius ab Acquapendente** (1533-1619), who[13] had earlier described the valves of the veins without recognizing their function, performed a sequence of experiments and announced in 1628 the discovery of the human circulatory system as his own and published an influential book "Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus" about it. This book of one hundred pages is considered by many as a master piece and its exposition slowly convinced the medical world. He discovered the real function of cardiac and venous valves. Besides, He concluded that arterial pulsation is only due to blood. Nevertheless, he never discovered the capillary system. He also contributed to the discovery of the circulation in fetus.

The Italian physician **Marcello Malpighi** (1628-1694)[WS30] completed Harvey’s work and discovered the capillary system connecting arteries and veins.

Gaspare Aselli, or **Asellio** (1581-1626)[14] an Italian physician, was noted for the discovery of the lacteal vessels of the lymphatic system in 1622. The Ancients knew nothing of the lymphatic vessels.

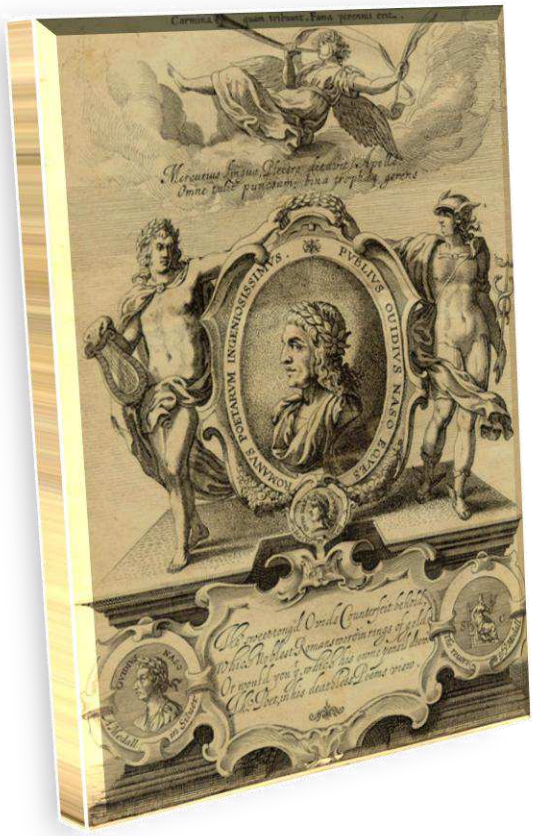
Chapter Three

Blood Transfusion from A to Z

I- Blood Transfusion in The Ancient and Medieval Eras:

There are many early documented references to the use of blood, for what can be at best described as ‘medicinal’ purposes.

One of the first of these relating to a ‘transfusion’ is contained in the seventh book of the epic poem **Metamorphoses**, which was written by the Roman poet **Ovid (Ovidius)**[WS31], the narrative poem, composed in fifteen books that describes the creation and history of the world. Ovidius wrote in 43BC in the seventh book named Medea, Cephalus and Procris, describing how (the witch) Medea rejuvenated Jason's aged father Aeson as follows[15]:



Cover of the English edition of Ovid's Metamorphosis[WS31]

> "Medea took her unsheathed knife and cut the old man's throat letting all of his blood out of him. She filled his ancient veins with a rich elixir Received through his lips and wound, his beard and hair no longer white with age, turned quickly to their natural vigor, dark and lustrous; his wasted form renewed, appeared in all the vigor of bright youth".

Medea's remarkable success was achieved with an elixir brewed in a bronze cauldron containing the following ingredients[16]:

> *"....* *root*-herbs, seeds and flowers, strong juices and pebbles from the farthest shores of oceans east and west; hoar-frost taken at the full of the moon, a hoot owl's wings and flesh, a werewolf's entrails, a fillet of a snake, the liver of a stag and the eggs and head of a crow which had been alive for nine centuries."

Medea's practice as a ‘transfusionist’ was not confined to this single event, since she is later reported to have killed Pelias, by pretending to perform a similar miracle on him, having first gained his confidence by apparently changing an aged sheep into a lamb!

In addition to these early mythical writing, there are several noted citations in the Old Testament indirectly bearing on (blood) transfusion. These have a social impact to the present day, relating to the denial of a blood transfusion by certain persons, on religious grounds.

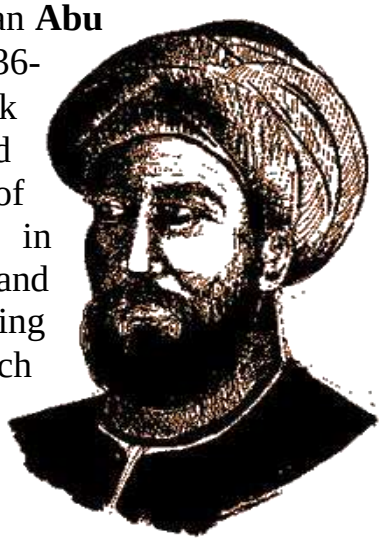
Although these references refer to the drinking of blood or the application of blood to the skin, an ancient Hebrew manuscript refers to an actual possible transfusion as follows[17]:

> "Naam, leader of the armies of Bed-Adad, King of Syria, afflicted by leprosy, consulted physicians, who in order to cure him, drew out the blood from his veins and put in that of another."

An early recognition of the dangers of the custom of ‘ingestion’ of blood, as well as probably the first rather fanciful description of what could be described as the management of an adverse reaction, is contained in the works of the 13th Century Italian writer **Pietro d'Abano** (1250-1316)[WS35], who wrote[18]:

> *“* who drinks of menstrual blood or that of a leper will be seen to be distracted and lunatic, evil minded and forgetful, and his cure is to drink of daisies powdered and mixed with water of honey, and to bath in tepid water and to copulate with girls acc*ording to the law natural”*

The Arabic physicians practiced venesection, cupping and blood leech in order to treat diseases. The venesected veins differed according to the complaint of patient. The famous physician **Abu al-Qasim Al-Zahrawi (Albucasis)** (936-1013)[WS67], in the thirty Essay of his best work “Kitab al-Tasrif”[19], described the method and indications of venesection and drew pictures of the Scalpels that he designed and used in venesection. He also mentioned the benefits and procedure of Cupping, describing the Cupping vessels he used. He limited the use of blood leech in lips, gums, nose and finger where physician couldn’t use cupping. He also mentioned the method of positioning leech.



Albucasis (936-1013)[WS67]

II- Blood Transfusion in The Modern Era:

It is likely that all references to the transfusion of blood before 1628, the date of Harvey's Discovery of systemic circulation, must be considered at best, questionable. Since most of the ancient and medieval references probably refer to the ingestion of blood, rather than to its infusion, it is in fact difficult to determine when the first authentic attempt at transfusion was actually performed.

1- First Thoughts of Blood Transfusion:

One of the most frequently quoted candidates for this noteworthy honor is **Pope Innocent VIII** (1432-1492)[WS36], **Giovanni Cibo**, who was reputedly 'transfused' sometime between 1490 and 1492. Pasquale Villari (1827-1917)[WS33], the Italian historian, some considerable time later recounted the incident, claiming that the Pope had some sort of illness (in the light of present knowledge, this was probably chronic renal disease), that rendered him semi-comatose.

Pope Innocent VIII (1432-1492)[WS36]

This was described as being so profound at times that the Pope was mistakenly thought to be dead[20]. On one occasion, after all means to revive the Pope had failed, it is reported that a physician (or mystic) of dubious reputation, named Abraham Meyre, appeared in the court and promised to save the Pope's life by transfusing him with the blood of young 'donors'. Apparently, three young 10-year-old shepherd boys were selected as donors and Villari states that the blood of the dying Pope was passed into the veins of one of the boys, *"... who gave him his own in* exchange". The process was apparently repeated with the other two boys. All three boys apparently died shortly after the procedure, possibly as a result of air embolism, but there was no change to the Pope's condition. This story is however controversial and is open to interpretation, being based on translations from the original script. It is possible that this presumed
'transfusion' stems from an incorrect translation by Villari of an earlier account of the Pope's illness. If this is the case, what is likely to have happened is that the Pope was asked to drink the blood. In any event, all authors seem to agree that the three boys, *"... costing one ducat a* piece"[21], died shortly after the procedure, as apparently did the Pope (presumably from his renal condition. The physician who instigated the 'treatment' was apparently punished and subsequently disappeared (probably very quickly!).

The second incident of interest in this first period is the statement made in 1615 by the chemist, **Andreas Libavius** (1555-1616)[WS7]. He imagined how blood was taken from the artery of one young man and infused into the artery of another old man. He described blood transfusion accurately and vividly enough, but he never transfused anyone. He wrote the following comments while defending his chemical theories against critics[22]:

Andreas Libavius (1555-1616)

> "Let there be a young man, robust, full of spirituous blood, and also an old man, thin, emaciated, his strength exhausted, hardly able to retain his own soul. Let the performer of the operation have two silver tubes fitting into each other. Let him open the artery of the young man, and put it into one of the tubes, fastening it in. Let him immediately after open the artery of the old man and put the other tube into it, and then the two tubes being joined together, the hot and spirituous blood of the young man will pour into the old one as if it were from a fountain of life, and all of his weaknesses will be dispelled. Now, in order that the young man may not suffer from weakness, to him are to be given good care and food, but to the doctor, hellebore."

In 1628, Harvey's discoveries initiated considerable speculation regarding not only the possibility of the transfusion of blood, but also the infusion of other medications or potions. Harvey himself is in fact thought unlikely to have used blood transfusion in relation to his medical practice, though there is evidence that, in order to test his theories, he pumped water through the circulation of a dead man.

During the 25 years or so following the publication by Harvey of the description of the circulation of the blood and the role of the heart, it is only to be expected that several people in different European countries should be thinking along similar lines. This gave rise to conflicting priority claims as to the first person to actually transfuse blood.

In 1628, **Giovanni Colle da Belluno** (1558-1630)[WS2], a professor at the University of Padua (who may well have had knowledge of Harvey's work), whilst writing on the 'methods of prolonging life', mentioned blood transfusion as a possible means of achieving this goal. There is however no evidence that he ever attempted to carry out a transfusion in practice.

2- Blood Transfusion from an Animal to an Animal:

Based upon his readings of Ovid's story of Medea, **Francis Potter** (1594-1678)[23] is thought by some to possibly be the first person to conceive of transfusion on a practical basis. Potter was the vicar of Kilmarton in England and apparently something of an eccentric and recluse, whose efforts were documented in the writings of his contemporary friend **John Aubery** (1626-1697)[WS25], an English antiquary and writer. According to these writings, Potter originated the idea of transfusion as early as 1639, and devised quills (as 'needles') and tubes for the purpose. In 1649 he wrote to John Aubery reporting that he had attempted the procedure of transfusion between two chickens, though it is likely that because of the size of such birds, it probably proved unsuccessful[24]:

> "I am as yet frustrated in ipso limine, but it is my own inexpertness, who never attempted any such thing on a creature before; for I cannot, although I have tried divers times strike the veins so as to make him bleed in any considerable quantity. I have prepared a little clear transparent vessel (like unto a bladder) made of the craw of a pullet; and I have fastened an ivory pipe to one of the necks of it, and I have put it into a veins which is most conspicuous about the lower joint of the hinder legs; and yet I cannot produce above 2 or 3 drops of blood to come into the pipe or bladder."

The above account didn't refer that the Reverend Francis Potter greatly advanced the science of blood transfusion to any great degree. No record remains of the fate of the chickens!

Francesco Folli (1624-1685)

One certainly false claim of priority in blood transfusion is made by Florentine physician, **Francesco Folli** (1624-1685)[WS4], who published a book in 1680 setting out his claim to be the originator of blood transfusion. He stated that he read of Harvey's work in 1652 and thereupon formed the idea that the transfusion of blood should be possible to cure diseases and to rejuvenate the aged. In 1654 Folli wrote[25]:

> "This I pointed out in my pamphlet on life culture which was published for no other reason than to make known to all that blood transfusion had been invented by me at the end of 1654 and demonstrated to his Serene Highness Ferdinand II, Grande Duke of Tuscany, of undying memory. The novelty of it had pleased him, or the fascinating ingenuity or the considerable experimental elaboration. To no one

else did I impart my idea, believing that if such an invention were successful, Monarchs alone were worthy of it."

Later Folli described in some detail the apparatus required and the method of using it. He even postulates the presence of twenty young men as blood donors, so that the patient may receive blood of a fresh donor every day over a considerable period. The apparatus apparently used, consisted of a funnel, connected by a tube formed from a goat's artery, with a gold or silver cannula to be inserted into the patient's vein. Though Folli describes the theory of transfusion, near the end of the book comes the confession, which spoils it all from a practical viewpoint, where he identifies that he did not actually carry out the process![26]:

"Finally I know that I have said too much concerning the manner of carrying out the operation, not having made the experiment...but I have done it solely so that everyone, however simple or ignorant, could understand, be inspired, and even make the experiment with the least possible expense, and to this end only I have written in the vulgar tongue."

The French may also lay some claim to being the first to perform a transfusion. At a meeting of a learned society, held in Paris in July 1658, **Robert des Gabets** (1610-1678)[27], a French Benedictine monk, discussed the discovery of the circulation of the blood by Harvey, and claimed that he was convinced that he could establish another type of movement of the blood. He termed this "communication", by which he meant *"... the* effective passage of blood of a healthy man or other animal to the veins of an individual weak or diseased". He also claimed that seven years earlier, a friar called Pichot, had prepared an instrument consisting of two small silver tubes, connected by a leather purse about the size of a walnut, which could be used for this purpose.

The 'established' priority claim however for proposing and demonstrating the intravenous administration of medications (into the veins of dogs) is made by Dr (later to become Sir) **Christopher Wren** (1632-1723)[WS15], who was to achieve far greater fame as an English astronomer and architect. He developed in 1656 an animal bladder attached to two quills for this purpose. Dr **Thomas Sprat** (1635-1713)[WS43], in his history of the Royal Society in 1657, records the following [28]:

Christopher Wren (1632-1723)

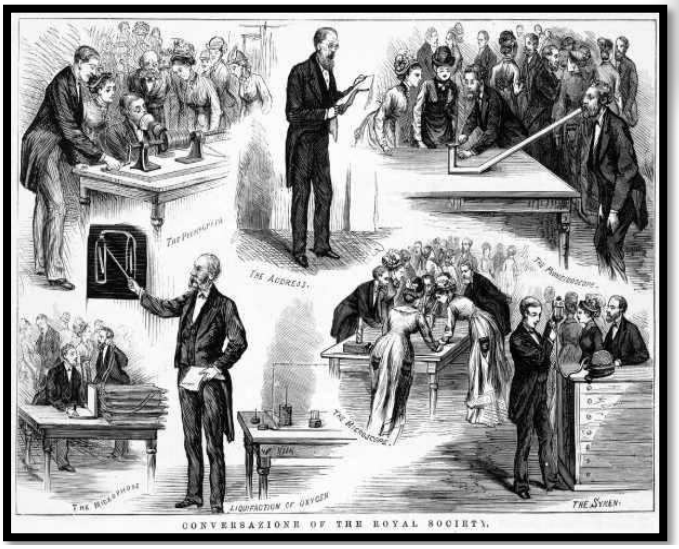
"…. Wren was the first author of the Noble Anatomical Experiment of Injecting Liquors into the Veins of Animals: an experiment now vulgarly known, but long since exhibited to the Meetings at Oxford, and thence carried by some Germans, and published abroad. By this operation, Creatures were immediately purged, vomited, intoxicated, killed or revived, according to the quality of the Liquor injected. Hence arose many new experiments and chiefly that of transfusing blood, which the Society has prosecuted, in many instances, that will probably end in extraordinary success."

Robert Boyle (1627-1691)[WS39]

Wren's experiments were later to be described in some detail by his associate **Robert Boyle** (1627-1691)[WS39], in his book, "Usefulness of Experimental Philosophy", published in 1663.

The Royal Society was founded in London during 1661 and received its Royal Charter in 1662[29]. It was founded by Thomas Willis, **Christopher Wren**, **Richard Lower**, Robert Hooke, **Robert Boyle**, Sir William Petty, Thomas Sydenham, and Samuel Pepys. It was this "philosophic assembly" of distinguished scientists that witnessed the beginnings of experiments of blood transfusion in animals. It was the practice of the time, that experiments should first be demonstrated in front of colleagues and peers, and then written down and published (usually by the Royal Society itself). Among several persons involved in these experiments was the Cornish Physician Richard Lower, a doctor practicing in Oxford, who claims priority for the first

The Royal Society



The Royal Society (Physicians Practicing And Discussing)

practical transfusion. **Richard Lower** (1631-1691)[30] was the first person to give a blood transfusion to animals successfully. He did this, early in February of 1665, when he bled one dog almost to the point of death. Then he tied the artery, and transfused this dying dog from a larger dog-a mastiff-and revived the bled dog. He did this three times, exhausting the donor each time, but he had very clearly saved the animal from dying by the performance of blood transfusion. Many of the early experiments were performed on dogs using "liquors", which included such substances as ale, wine and opium. Although the practice at the time, the animals used in these experiments were obviously treated unacceptably by present day standards, since they were reported to have undergone ″...suffering vomiting, intoxication and I fear death". These and many other various entries in the Journal Book of the Royal Society, record the earliest suggestions and attempts to carry out blood transfusions in animals or birds. In a report dated 31st May 1665, there appeared the first mention of a direct artery-to-vein transfusion from an animal to a human. The major part of future work was done by Dr Richard Lower, whose first statement, written in a letter to famous chemist Robert Boyle, was read to the Royal Society on the 26th September 1666. Lower's book on the heart "Tractatus de Corde", published in 1669, proves him to have been one of the great pioneers in anatomy and physiology. In it he makes the following statement about blood transfusion[31]:

Richard Lower (1631-1691)[WS38]

> ″..... *to reveal* the conduct of the whole affair and at the same time show by what train of thought reasoned it out and undertook it, and finally, by what means and aids it was carried into effect."

He then proceeds at great length to give an account of the first (published) description of a successful direct transfusion from artery to vein (having first attempted vein to vein direct transfusion and failed due to the blood clotting in the silver tubing used for the purpose). It seems clear that Lower was the first to define the appropriateness of the transfusion replacement of blood in severe hemorrhage, since he was able to demonstrate that a dog could be exsanguinated to the point of death and then be completely restored by transfusion.

Lower's efforts were the stimulus for a series of experiments on animals, by various people throughout Europe, and eventually led to the transfusion of blood from an animal to a man. The priority of this procedure occasioned a somewhat heated debate between Lower and a man he described as "a certain Denis", who was actually a Frenchman called Dr Jean Denys.

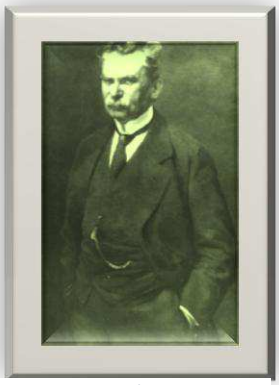
3- Blood Transfusion from an Animal to a Man:

On the 22nd of November 1666, **Richard Lower**, assisted by Dr Edmund King, transfused a 32 old man named Arthur Coga[32]. The event took place in England and was later detailed in the Transactions of the Royal Society. The initial part of the account describes the quills and silver pipes used to carry the blood between the carotid artery of the donor sheep and a vein of the recipient's arm. The account however concludes[33]:

"The blood did run all the time of those two minutes and we concluded.... upon the man's saying he thought he had enough. The man after this operation, as well as in it, found himself very well, and hath given in his own narrative under his own hand, enlarging more upon the benefit he thinks he hath received than we think fir to own as yet. He urged us to have the experiment repeated upon him within three or four days after this, but it was thought advisable to put it off somewhat longer."

Richard Lower And Edmund King Transfused Arthur Coga in 1666[34]

This second experiment did in fact occur (the following month) and apparently proceeded without mishap. Afterwards, the subject Arthur Coga said he felt better, although Pepys wrote in his diary *"... he is cracked a little in the head"* The excuse for performing a transfusion was that it was believed that it might improve his mind. Arthur Coga was a little cracked in the head, and the idea was that a transfusion might cure him. Lamb's blood was used for the transfusion too. It should be remembered that these early medical 'transfusion' experiments were carried out at a time when the popular medical treatment used by doctors to treat many illnesses was 'blood-letting', i.e. bleeding the patient, rather than transfusion them.!



Jean-Baptiste Denys (1640-1704)[WS23]

Dr **Jean-Baptiste Denys** (1640-1704)[WS23], a young French physician on the large staff attached to King Louis XIV, read of Lower's experiments in the Journal des Savants, of 31st January

1667. In association with a surgeon, Paul Emmerez (†1690)[35], Denys initiated his own trials approximately a month later, performing numerous dog-to-dog transfusions. On the 15th June 1667, Denys was asked to treat a 15-year-old boy, who had suffered from a fever for many months, for which he had been bled by his physicians twenty times, *"…. to assuage the excessive heat"*. Denys wrote[36]:

> "Before this disease, he had not observed to be of a dull spirit, his memory was happy enough, and he seemed cheerful and nimble in body; but since the violence of his fever, his wit seemed wholly sunk, his memory perfectly lost, and his body so heavy and drowsy that he was not fit for anything."

Accordingly he was bled to the extent of about three ounces and received in exchange nine ounces of blood from the carotid artery of a lamb. The change that ensued in the patient was described as *"startling"* and presently the boy was showing *"... a clear a smiling countenance"* where previously he had apparently passed the time *"... in an incredible* stupidity". The boy had also felt *"... a very great heat along his arm"* (a present-day indication of an incompatible transfusion reaction!), but there were apparently no further ill effects.

Denys' second transfusion was performed on a 45-year-old man using a reported 20 ounces of lambs' blood and described the man as feeling stronger than before the transfusion. Further transfusions were performed; one of which involved the description of a variety of reactions in the patient that would be indicative nowadays of a severe hemolytic transfusion reaction. Denys submitted a report of his transfusion of the teenage boy to the Royal Society in July 1667, which due to the editor of the Journal being in the Tower of London at the time, was not published until the 23rd September 1667. Therefore, although Lower performed the first animal-to animal transfusions, there now seems little question that Denys performed the first animal to man transfusion .

Denys favored the use of animal blood for his transfusion experiments because he believed it less likely[37] *"... to be rendered impure* by passion or vice". This way of thinking about blood, as carrying a person's (or in this case animal's) temperament, beliefs, strength or courage, was typical of the time. Following the transfusion of at least four individuals, Denys and his associate performed a further transfusion in 1668. This transfusion was to have far-reaching and significant repercussions, and in fact determined that the practice of transfusion was to lay dormant for nearly one hundred and fifty years. A 34-year-old man, Antoine Mauroy, was described by Denys as suffering *"a severe phrensy",* which apparently had lasted seven or eight years, and had

reportedly been due to an unfortunate love affair. Apparently one day the man escaped from his wife's control and paraded through the streets of Paris clothed *"... only* in nature's garb, followed by an admiring throng". Such an opportunity was apparently not to be lost by the enthusiastic researcher such as Denys, who pounced on this luckless fellow, proposing a transfusion to allay the *"... heat in* his blood ..". Shortly after, ten ounces of blood were removed from the vein of his right arm, being replaced with five or six ounces of blood from a calf, with no obvious untoward (or obviously beneficial) effects. Two days later, the man was transfused a second time. This resulted in what is now recognized as a hemolytic transfusion response. Denys' description of this second transfusion could in fact be considered to be a classic medical description of this phenomenon[38]:

Dr Jean-Baptiste Denys Transfused Antoine Mauroy 5 or 6 ounces of calf's blood[WS4]

> "As soon as the blood entered his veins, he felt the heat along his arm and under his armpits. His pulse rose and soon after we observed a plentiful sweat over all his face. His pulse varied extremely at this instant and he complained of great pains in his kidneys, and that he was not well in his stomach, and that he was ready to choke unless given his liberty. He was made to lie down and fell asleep, and slept all night without awakening until morning. When he awakened he made a great glass full of urine, of a colour as black as if it had been mixed with the soot of chimneys."

Denys also recounts that the following morning (the second day), Mauroy had further hemoglobinuria and epistaxis. However, by the third day, his urine had cleared and, his mental state having apparently improved, the man returned to his wife. Denys attributed the colour of the urine to a "black choler" which had been retained in the body and had sent *"*vapors *to the brain"*, causing the patient's mental disturbance.

Several months later, Antoine Mauroy again became violent and irrational and his wife persuaded Denys and his associate Emmerez to repeat the transfusion. A transfusion was attempted, but since the flow of blood was poor, it was apparently abandoned. Mauroy died the following evening. Through their transfusion experiments, Denys and Emmerez had acquired many enemies among the physicians of Paris, since the medical practice of the day involved bleeding the patient, principally by the use of leaches. Three of these physicians persuaded Mauroy's widow to accuse Denys and Emmerez of contributing to the death of her husband by the transfusion. Other physicians in the Faculty of Medicine of Paris, an apparently extremely conservative body who refused even to recognize Harvey's theory of circulation, were opposed to transfusion and published pamphlets condemning the practice. At one point the widow offered to withdraw the lawsuit provided she would receive payment from Denys, however he replied "That those physicians, and herself, stood more in need of the transfusion than even her husband had done". Denys lodged a counter-complaint against the widow, so that when the trail came to court, he appeared as the plaintiff, not the defendant. Following a prolonged legal battle, the outcome was that Denys was exonerated. The widow was in fact subsequently shown to have poisoned her husband with arsenic! More importantly however, due to the enemies that Denys had made, the Faculty of Medicine of Paris issued a decree based on the results of the trail, stating that the procedure of transfusion was not to be performed without the permission of a member of the Faculty of medicine. Since the Faculty was bitterly opposed to the whole idea, this permission was never given and the practice of transfusion rapidly fell into disuse. Eventually, in 1678, an edict from the French parliament ruled transfusion to be criminal act if performed in France. This had repercussions in London where the Royal Society rapidly washed its hands of transfusion as well. Finally, in 1679 the Pope joined the general outcry and also announced a ban on the procedure. As a result, quite understandably, interest in transfusion rapidly waned. Although the practice of transfusion had essentially ceased, some text books published in the 17th and 18th centuries still included classical accounts of how the procedure could be accomplished.

Apart from Lower's comments associated with his initial dog experiments, during this period, little consideration was given to the use of transfusion for the replacement of blood loss. The most popular use for transfusion was the possibility of it being able to alter the mental state of the patient and the possibility of restoring youth to the aged.

4- Blood Transfusion from a Man to a Man:

Following the decrees of the mid-17th century forbidding blood transfusion throughout most of Europe, the practice fell into general disrepute for more than a century and a half. The credit for placing transfusion on a scientific basis and re-awakening interest in its use must be given to **James Blundell** (1790-1877)[WS22]. James Blundell was a noted physician, physiologist and one of the outstanding obstetricians of his day. He is credited not only with rekindling interests in blood transfusion in the second decade of the 19th century and providing it with a semblance of a national approach, but he was also the first to transfuse human blood. Many people in fact regard Blundell as the 'the father of modern blood transfusion'. Even though he was one of the pioneers of blood transfusion, the Dictionary of National Biography makes no reference at all to his work on transfusion, but does note that he left a fortune of £350,000 at his death in 1877!

James Blundell (1790-1877)[WS22]

Blundell[39] initially became interested in transfusion as a method of treating postpartum hemorrhage. He wrote: "appalled at my own helplessness at combating fatal hemorrhage during delivery". His experiments began by exsanguinating dogs and then reviving them by the transfusion of arterial blood from other dogs. From his experiments, he concluded that the blood from one animal could not be substituted for that of another with impunity, and he therefore turned to the use of human blood for human transfusion. Besides, there is impracticability in using animal blood due to the difficulty of finding an appropriate animal in an emergency.

It must however be noted, that Blundell received his medical degree from the University of Edinburgh and was undoubtedly influenced in his early experiments by the work of American physician **John Henry Leacock** (1729-1802)[WS3]. Although Leacock's manuscript on the subject of transfusion was written whilst he was in Barbados, his experiments were performed during his tenure in Edinburgh, where one of his contemporaries was Blundell.

Utilizing[40] a six-inch length of ox ureter (as the 'tube') with crow quills (as the 'needles') attached to both ends, Leacock operated on dogs, resuscitating exsanguinated animals by transfusion. Although Leacock

did not perform a human transfusion, he argued against the mixing of blood from different species and his experiments quite clearly pointed to the advantages of such treatment. In 1817, Leacock eloquently concluded his dissertation on transfusion as follows[41]:

> "The consequences of hemorrhages where the functions are not dangerously affected, do not of course, require transfusion, since other remedies will suffice. But when the danger is imminent, and the common means are ineffectual, as when a parturient women trembles on the brink of the grave from uterine hemorrhage, or when a soldier is at the point of death from loss of blood, what reason can be alleged for not having recourse to this last hope, and for not attempting the recruit the exhausted frame and turn the ebbing tide of life."

Blundell initially advocated direct transfusion; however, shortly after he introduced the use of the syringe to facilitate vein-to-vein transfusions. He described transfusion by syringe in several papers, noting the necessity of removing air from the instrument before transfusion, as well as experiencing the problems of blood clotting, "....the blood is satisfactory only if it is allowed to remain in the container for but a few seconds."

The historic date assigned to the first documented transfusion of human blood is the 22nd December 1818. The procedure was published in 1819, under the title ‘Some account of a case of obstinate vomiting in which an attempt was made to prolong life by the injection of blood into the veins’. This case study describes how Blundell, with the help of the surgeon **Henry Crine Noyes**[42], his niece’s husband, transfused a 35-year-old man with what would now be called gastric carcinoma, but was then described as "scirrhosity of the phylorus". When first seen by Blundell, the patient was near to death. Approximately 14 ounces of blood were administered by syringe in small amounts, from several donors, at intervals of 5-6 minutes. Despite temporary improvement in his condition, the patient died 56 hours later. His disease was incurable and nothing could really have been expected from the transfusion.

Blundell then invented a rather strange instrument called an ‘impellor’,

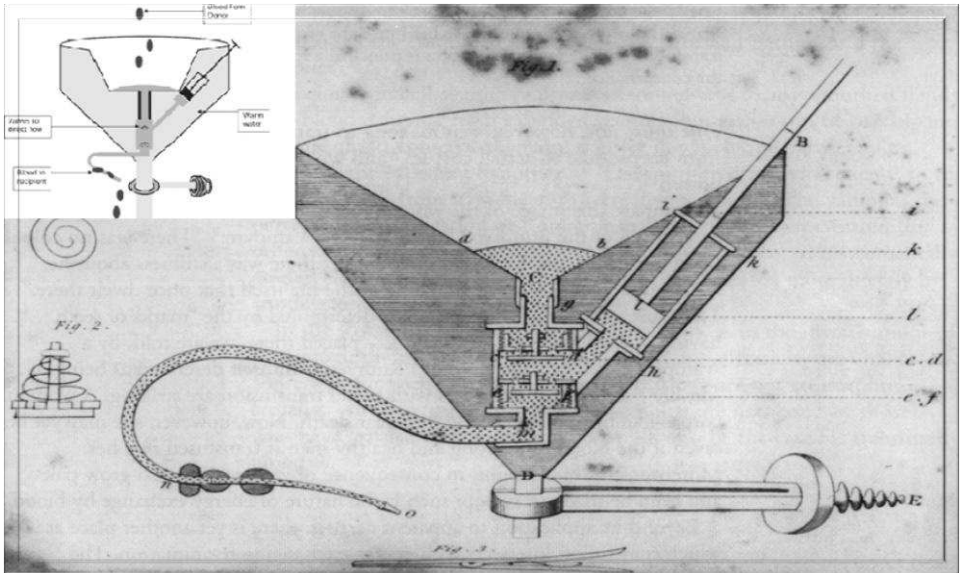


Diagram of The ‘Impellor’ of Blundell which appeared in his book, published in 1824[WS4]

which was essentially a funnel and pump combined; a diagram of which appeared in his book, published in 1824. The outer compartment of the funnel was first filled with warm water (to help keep the blood fluid) and the donor's blood was made to flow into the funnel. The action of the pump (within the water filled jacket of the funnel) forced the blood along a tube to a cannula inserted in the patient's vein, by means of two oppositely acting spring valves below the funnel. According to the illustration, the impellor was designed to be fixed to the back of a chair to give the equipment stability (as well as possibly being for the benefit of the blood donor!).

The Impellor of Blundell Fixed to a Chair[WS22]

Later Blundell[43] invented another instrument, the ‘Gravitator’, in which, as the name implies, gravity provided the motive force for pushing the blood into the patient's vein. The equipment consisted of a funnel at the end of a long flexible bracket, which was again attached to a chair or similar object for stability. The funnel is connected to a tube with a cannula, which was buckled to the patient's arm. Illustrations published in 1829 show the blood donor standing by the equipment while he watched his blood gushing into the funnel!

Blundell was at great pains, like a number of his contemporaries, to show (by extensive experiments) that the blood was not ‘injured’ by its passage through an instrument and that the introduction of "a few air

bubbles" into the circulation was, contrary to the belief of earlier observers "quite harmless"!.

Between 1818 and 1829, Blundell and his colleagues performed a total of ten transfusions using human blood, of which no more than four can have been successful – as two patients were in fact noted to already be dead when transfusion was commenced! The first successful transfusion was of a woman who recovered from severe post-partum hemorrhage after receiving eight ounces of blood from Blundell's assistant during the course of three hours.

This case was published in journal 'The Lancet' in 1829. Blundell still reported patients who "... suffered fever, backache, and headache and passed dark urine" (presumably due to ABO incompatibility).

Blundell Performed The First Human to Human Successful Transfusion in 1828 using his Gravitator[44]

Blundell also actively encouraged his contemporaries to practice transfusion. For the most part, these were obstetricians who used the procedure in cases of postpartum haemorrhage. One of the most active 'transfusionists' of the time was the English physician **Henry Doubleday** (1810–1902)[WS19] who described in great detail the transfusion of a woman (suffering postpartum haemorrhage) with her husband's blood. He noted that after six ounces had been given the woman, previously semi-comatose, suddenly exclaimed, "By Jesus, I feel strong as a bull". Similarly, in 1829 Blundell, describing a transfusion of postpartum hemorrhage, claimed that[45]:

"…. the patient expresses herself very strongly on the benefits resulting from the injection of the blood; her observations are equivalent to this - which she felt as if life were infused into her body".

James Blundell established, during his interest in transfusion, so many fundamental points that it is difficult to exaggerate the importance of his work in the history of transfusion medicine. However, after 1830, James Blundell's interest in blood transfusion waned. He retired from medical practice in 1847, at the age of 57, undoubtedly well facilitated by a fortune of approximately £500,000, which is recorded to have been accumulated from his medical practice and bequests. During this period, considerable debate continued regarding the use of transfusion and various views being recorded in the minutes of the Medical Society of London. Many people felt that the procedure was dangerous and that it may have hastened the death of some of the patients in whom it was used. Furthermore, it was claimed that most of the patients who benefited from the procedure would have recovered anyway without the use of a transfusion. Dr Blundell argued strenuously however on behalf of the use of transfusions, noting repeatedly that the dangers of haemorrhage, in these patients, far outweighed the possible danger from transfusion.

5- Establishing Transfusion Procedures:

It is obvious that one of the first problems that had to be solved before blood transfusion could be placed on a practical footing was the prevention of coagulation or blood clotting. During the 19th century, attempts to overcome this problem took several forms. James Blundell noted that vein-to-vein direct transfusions were impractical due to blood clotting, yet attaching the artery of the donor to the vein of the recipient rendered the procedure feasible (if not presumably rather messy!).

Considerable use was also being made around this time of defibrillated blood, that is to say, blood from which the (platelet) clot has been removed. A variety of techniques were described to achieve this goal. One of the first people to use an 'anticoagulant' additive was J. Neudorfer, who in 1860 recommended the addition of sodium bicarbonate as an anticoagulant. Two other physicians who actively sought an answer to the problem of coagulation were the English doctor **John Braxton Hicks** (1823-1897)[WS26], who used a solution of sodium phosphate (in six notably unsuccessful transfusions), and the Mauritian physician **Charles-Édouard Brown-Séquard** (1817-1894)[WS14], who used defibrillated blood for his experiments performed in the early 1850's. Defibrillation of blood was generally accomplished by whipping or twirling the blood, then removing the clot and transfusing the remaining fluid. However, half a century was to elapse before a practical means of anticoagulation was devised. Efforts during the remainder of the 19th century were directed towards the development of (usually) unproved devices for direct transfusion or the refinement of surgical procedures to facilitate direct transfusion. Many of the devices for direct transfusion were quite ingenious, attempting to incorporate the features of rapid administration, measuring the amount injected and, in some instances, warming the blood. Although anticoagulation of blood was becoming more popular during the mid-19th century, one of the chief exponents of a more direct or immediate manner of transferring blood was another obstetrician in America, Dr **James Hobson Aveling (1828–1892)**[WS3]. His apparatus was described and illustrated in an article published in 1873. It consisted of a simple tube with a central rubber bulb, which provided a pumping action produced by squeezing the bulb together with

John Braxton Hicks (1823-1897)[WS26]

Transfusion Apparatus of Aveling[WS4]

the tube at alternative sides of the bulb. Aveling described the apparatus as being extremely convenient, so much so that he wrote, "I carried the apparatus around in my pocket to every confinement I attended for eight years until at length the opportunity for using it arrived". From this statement it may be correctly inferred that the concept of sterility was unknown at this time! Dr Aveling finally used his direct transfusion apparatus in 1872, when he attended a lady, aged 21 years, "in extremis" from post-partum haemorrhage. She received 60 drachms of blood from her coachman and apparently soon recovered, certainly enough to reportedly be able to remark that she was dying! Dr Aveling added in his report that[46]:

> *"... the mental improvement of the patient was not as marked and* rapid as I anticipated, but this was perhaps due to the quantity of brandy she had taken."

The coachman, he was pleased to record, was not only "collected and cheerful", but able to make several useful suggestions during the transfusion process, though unfortunately Dr Aveling does not record what these suggestions actually were! No reason was given as to why this man was chosen as a donor, other than presumably because he was a servant, or even if he was a willing donor!

Defibrillated blood was used by Sir **Thomas Smith** (1809-1881)[WS59] who, in 1873, used the procedure in St Bartholomew's Hospital for in the first reported case of a transfusion to an infant (who was suffering from Hemolytic Disease of the Newborn). His defibrillating apparatus, on this occasion, included a wire eggbeater and a hair sieve, with which to remove the clot. Defibrillated blood has been used until relatively recent times by various operators, but the process results in the removal of a large part of the protein content of the blood, as well as some of the cells, and is also time consuming and difficult to perform correctly. A somewhat important instrument modification was introduced in 1857 by **M.B Higginson**[47], who applied the principle of a rubber sealed syringe with ball valves for transferring the blood from the receptacle into which it was drawn to the vein of the patient. 'Higginson's syringe' was later used for a different purpose (in the treatment of syphilis in men), but it was successfully applied by its inventor in a series of seven transfusions. One of these transfusions is recorded to have been given to a woman, who, having been transfused with about 12 ounces of blood from a healthy servant, fell into *"... a state of quietude following her previous* restlessness". A few minutes later the patient was seized with a rather severe rigor. It did not last long, but led to a state of reaction and excitement during which she "sang a hymn in a loud voice". Although this is a somewhat unique description of a patient experiencing a

transfusion reaction, the final outcome was apparently satisfactory and Higginson reported that some benefit was obtained from five of the seven transfusions he performed.

Although so much of the early work on blood transfusion had been performed in England, and its revival during the 19th century was started in the United Kingdom, most of the references to transfusion up to 1874 are to be found in continental publications.

During the final quarter of the 19th Century, frustration and discouragement with blood as a transfusion product resulted in a brief period of enthusiasm for the transfusion of milk, which was thought of as a 'blood substitute'. This form of treatment achieved its greatest popularity in the United States between 1873 and 1880, with the milk of cows, goats and humans being used. The most outspoken advocate of milk transfusions was **T.G. Thomas**, who was discouraged by the use of blood because of its "tendency to coagulation". However, by 1880 increasing numbers of adverse reactions associated with the administration of milk led to its general abandonment. A major contributing factor in the final decline of the use of animal blood and milk for transfusion must however have been the introduction, between 1875-1880, of physiological saline solution for infusion use, with its associated convenience and lack of danger to the recipient.

During the latter part of the 19th Century, the Franco-Prussian war was raging in Europe and the possibility of using blood transfusions on the battlefield naturally came to the fore. The chief authority at the time was Dr **J.Roussel**. He had first used his method of direct arm to arm transfusion with success in 1865 for a patient with puerperal haemorrhage.

Dr J.Roussel used his apparatus in direct arm to arm transfusion[48]

The apparatus he used was described in the Gazette des Hospitaux in 1867 and later in various other publications. The basis of the transfusion technique was to place a glass vessel over the donor's arm, the apparatus was filled with water and a lancet operated through the top of the vessel then punctured the donor's vein. The operator, by means of a two-way

tap, then rejected the water through one cannula and injected the blood into the recipient through a second cannula inserted in a vein.

In 1882, in Paris, he reported on a total of sixty transfusions performed since 1865 in Switzerland, Austria, Russia, Belgium, England and France. Roussel's 'transfuseur' apparatus was subsequently officially adopted for use by the French Army and apparently used in time of war.

The dangers of infection (both local and systemic) relating to safe transfusion methods started to be resolved when in 1865 **Louis Pasteur** (1822-1895)[WS68] recognized that bacterial / fungal contamination causes putrefaction and the work of **Joseph Lister** who in 1867 discovered antiseptics. As a result, the sterilization of instruments and antiseptic methods began to be introduced.

Throughout the 19th century, the main use of transfusion was however in the treatment of obstetric cases. Beyond this fact, a number of major practical problems remained to be solved.

Karl Landsteiner (1868-1943)[49]

One of these was the number of severe transfusion reactions which were, for a long time, attributed only to the introduction of air bubbles into the recipient's circulation. The discovery (in 1900) of the human ABO blood groups by Dr **Karl Landsteiner** (1868-1943)[WS69] in Vienna was the major step in understanding that these reactions were in fact due to what is now known to be blood group incompatibility (probably associated with intravascular haemolysis).

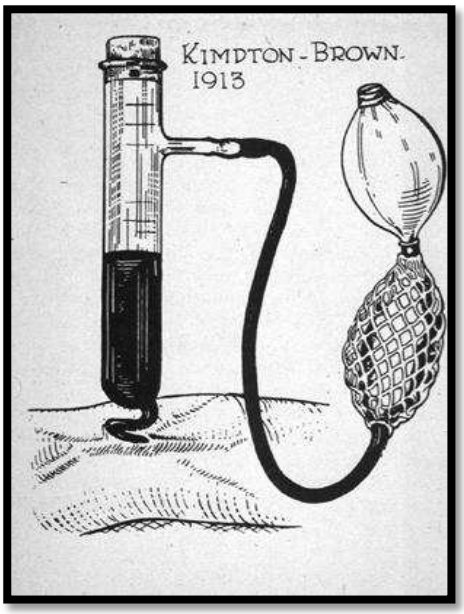
Landsteiner discovered the ABO blood group system by mixing the red cells and serum of each of his staff. He demonstrated that the serum of some people agglutinated the red cells of other. From these early experiments he identified three groups, called A, B and C (C was later to be re-named O). The forth much rarer blood group AB, was discovered a year later. He was awarded Nobel Prize in Physiology or Medicine in

1930. Landsteiner identified that most people had 'naturally occurring' antibodies in their serum that reacted with the antigens present on the red cells of a person of a different blood group. The presence of these antibodies, together with the variable frequencies of the different blood groups in European populations, identified why blood transfusion from one person to another had been so unpredictable, as receiving the 'wrong ABO group blood' can be fatal. For example, if a group O person receives red cells from a group A person, the antibodies present in their plasma will react with and destroy the donor red cells, releasing the hemoglobin out of the red cell into the person's circulation. If present in large amounts, the free hemoglobin is poisonous, possibly resulting in renal failure and death. However, it wasn't until 1907 that American surgeons **Reuben Ottenberg** and **Schultz** suggested that it might be a good idea if both donor and recipient were ABO grouped before transfusion and their blood mixed in the laboratory ('cross matched') to ensure compatibility.

At Mount Sinai Hospital in New York, American Doctor **Reuben Ottenberg** (1882-1959)[WS56] performs the first transfusion using cross matching, and over the next several years successfully uses the procedure in 128 cases, virtually eliminating transfusion reactions. He was also the first to suggest that human blood groups are inherited according to Mendel's law.

In 1911, Dr. **Ludvig Hektoen** of Chicago recommends checking the blood of donors and recipients for signs of incompatibility (or cross matching) prior to transfusion.

In 1913, The **Kimpton-Brown** transfusion apparatus[50], developed by dr. Kimpton and dr. Brown, was commonly used before using citrate. It consisted of a paraffin-coated gradient glass cylinder with a horizontal side tube for suction. It was in use until approximately 1918.



The **Kimpton-Brown** transfusion apparatus used (1913-1918)

In a series of reports between 1916 and 1918, Bruce Robertson of the Canadian Army, explained the advantages of the syringe-cannula technique, which he had introduced into the British Second Army area. The method was far simpler than the Kimpton-Brown technique, but at that it was not simple, and it required a team of three persons to carry it out.

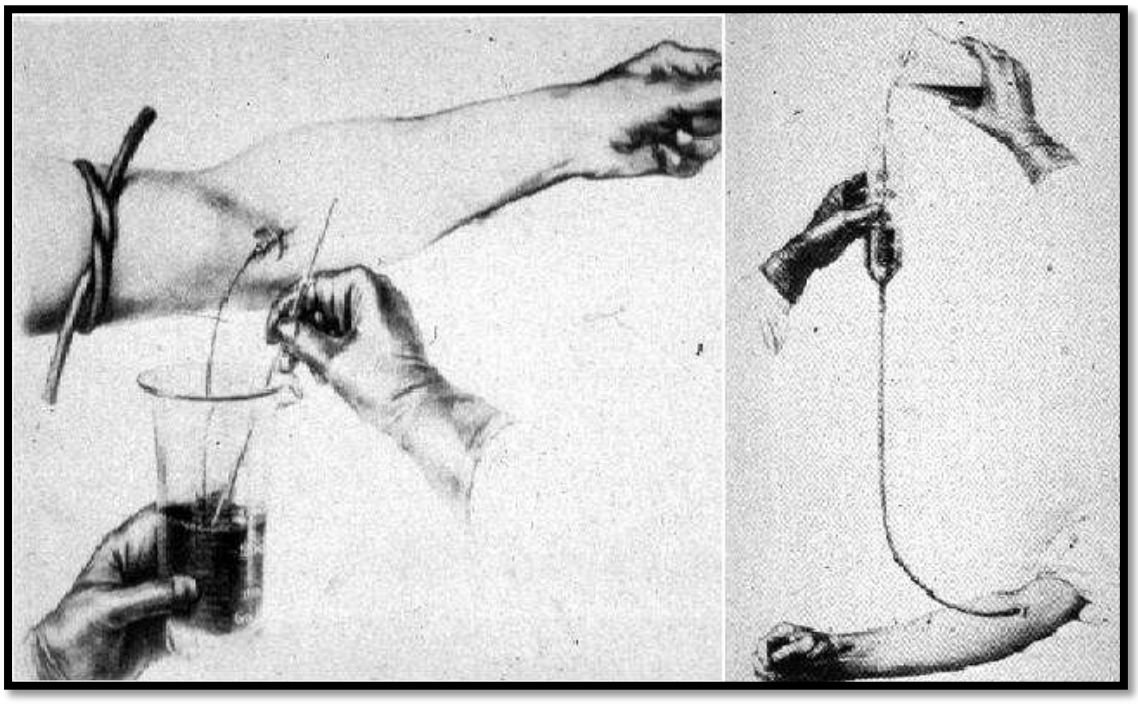
6- The Impact of War:

From the First to the Second World War, scientists and physicians inspired rapid progress in the large-scale storage and use of blood. War was not an incidental factor to these developments, as it created unprecedented demand for the life-saving fluid. Much as the Spanish Civil War was a prelude to World War II, so was blood first transported to the front lines of battle in Spain. By the time war had spread through Europe, the Allied forces were aided by a well-organized blood supply.

Science and technological developments became more and more involved in the development of transfusion during the 20th Century. One of the other previously identified practical problems associated with blood transfusion was that of blood clotting (coagulation), which effectively meant that blood was transfused by direct techniques and could not be stored for even short periods.

In 1914, almost simultaneously, researchers **Albert Hustin** of Brussels and **Luis Agote** of Buenos Aires discover that adding sodium citrate to blood will prevent it from clotting.

In 1915, the American physician **Richard Lewisohn** (1875- 1961)[WS55], at New York's Mount Sinai Hospital, formulates the optimum concentration of sodium citrate that can be mixed with donor blood to prevent coagulation, but pose no danger to the recipient. He carried out blood transfusion using the method described in the illustration. Blood is



Richard Lewisohn's Method in performing blood Transfusion[WS51]

collected in a citrated flask, and immediately transfused. At the beginning of World War II, it had become the exclusive method of blood transfusion used in surgery and medicine.

Dr. **Richard Weil** determines that citrated blood can be refrigerated and stored for a few days and then successfully transfused.

In 1916, At the Rockefeller Institute in New York, **Francis Peyton Rous** and **J.R. Turner** used a glucose additive as a red cell energy supplement to improve red cell preservation. Thus, they develop a citrate-glucose solution that allows blood to be stored for a few weeks after collection and still remain viable for transfusion. This mixture made the blood extremely dilute (1:1 solution: blood ratio), so it had to be removed prior to transfusion.

In 1917, While serving in the U.S. Army, the British physician **Oswald Robertson** (1886-1966)[WS58], familiar with the work of dr. Peyton Rous and dr. Turner, collected and stored type O blood, with citrate-glucose solution, during the Battle of Cambrai in World War I. Thereby, he establishes the first blood depot.

The voluntary blood donor scheme was pioneered in London in 1921 by the British librarian **Percy Lane Oliver** (1878-1944)[WS57] following a request of the Red Cross service to provide two blood donors at short notice. Oliver's work attracted attention worldwide and many countries sent representatives who sought and acted upon his advice on setting up similar organizations. The development of electrical refrigeration resulted shortly after in the first 'blood bank' being set up in Barcelona in 1936.

Percy Lane Oliver
(1878-1944)[WS57]

In 1937, an exhibition at a meeting of the Voluntary Blood Donors Association featured the idea of stored blood which, although originally used by Canadian doctor **Henry Norman Bethune** (1890-1939)[WS51] in the First World War, set up a mobile blood-transfusion service to rush bottled blood in refrigerated trucks to the wounded at the front in the Spanish Civil War. During the Spanish Civil War, the Republican Army banked 9000 liters of blood later administered at casualty stations and base hospitals. This was to become the basis of the war-time blood bank which Oliver helped to create at Luton in 1939. Small-scale refrigerated storage of whole blood had been used first in World War I, and this had been developed in Russia into a larger-scale system of blood depots.

Charles Drew (1904-1950)[WS53] was asked to be the medical supervisor on the "Blood for Britain" campaign, launched by the Blood Transfusion Betterment Association in 1939. At the height of World War II, Nazi warplanes were bombing British cities regularly and there was a desperate shortage of blood to treat the wounded. In order to meet the huge demand for plasma, Drew initiated the use of "bloodmobiles" trucks equipped with refrigerators. In 1941 after the success of "Blood for Britain," Drew became director of the American Red Cross Blood Bank in New York. He was asked to organize a massive blood drive for the U.S. Army and Navy, consisting of 100,000 donors.

Charles Drew
(1904-1950)[WS53]

Bernard Fantus (1874-1940)[WS10], at Chicago's Cook County Hospital, established the first blood bank in the United Stated in 1937. He conducted further experiments in blood storage, culminating in the preservation of blood for up to ten days. He established a "Blood Preservation Laboratory" at the hospital. However, he changed its name before launch to "Cook County Hospital Blood Bank. Thus, he invented the name "blood bank".

Dr **Philip Levine** (1900-1987)[51] co-discoverer with Karl Landsteiner and **Alexander Wiener** (1907-1976)[52] the 'Rhesus' (now termed Rh) blood group system factors, associated with the potentially fatal condition of Hemolytic Disease of the Newborn, described a severe reaction in a Type O woman given a transfusion of her husband's Type O blood following a stillbirth. Her serum agglutinated 80% of Type O blood. Landsteiner and Wiener, later in 1940, described the method of Rh typing. This leads to dramatic decrease in the incidence of hemolytic disease of the newborn.

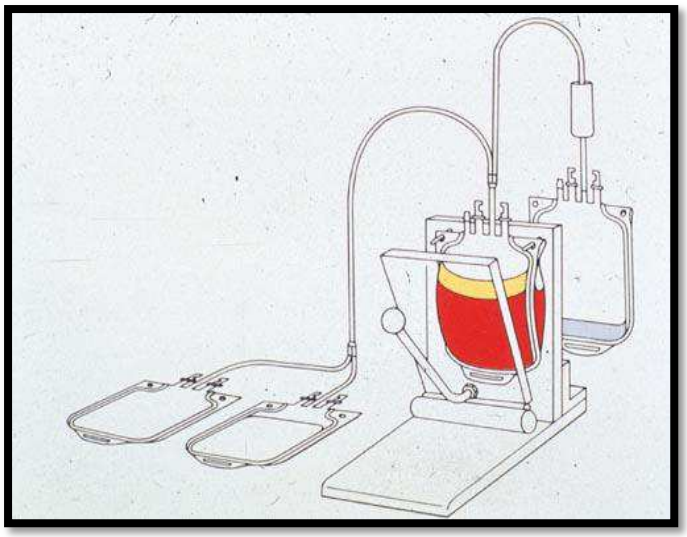
During the world war II, a development in the instrument used in blood transfusion occurred.

Effective preservation and refrigeration lead to the ability to blood bank. It began in 1940 when Freeze dried plasma was developed.

In 1943, acid-citrate-dextrose (ACD) anticoagulant preservative solution, was developed for the storage of blood by

World War II syringe for direct inter human blood transfusion

Australian doctor **John Loutit** and British Professor **Patrick Mollison** (1914-2003)[53], which extended the vitality of blood units to 21 days.



Edwin Cohn developed Plasma fractionation in 1944[54]

Plasma fractionation was developed by **Edwin Cohn** (1892-1953)[WS52] in 1944. The basis of the chemical procedure used was the differential precipitation of the plasma proteins with ethyl alcohol at low temperature, with careful control of salt concentration, temperature, and acidity or alkalinity of the medium. The most urgently needed plasma protein was serum albumin, for transfusion in treatment of shock; useful albumin preparations were obtained by 1942. Therefore, every unit of blood could treat more people. Nowadays, At least 17 different components are available through a blood bank.

Later, there was a development of a method of freezing blood.

In 1945, the British Professor **Robin Coombs** (1921-2006)[WS41] described anti-globulin testing, which is nowadays referred to as "Coombs Test". This test has formed the base of a large number of laboratory investigations in the fields of hematology and immunology.

7- Blood Transfusion in The Last Sixty Years:

Most of the important developments in transfusion medicine have only been achieved in last sixty years.

Blood was collected into reusable glass bottles in the first half of the twentieth century. Whole blood was transfused. Pyrogenic reactions from contamination due to incomplete cleaning were frequent. Air embolism was also a common complication due to the vacuum systems used on glass bottles.

Reusable Glass Bottles used in the first half of 20th century for blood collection[WS4]

Current Plastic Bags

In 1949, trials of plastic bags were conducted by the American Red Cross. Plastic bags were disposable and, because of their flexibility, facilitated the separation of blood components and the advent

ACD preservative solution was supplanted in 1957 by citrate phosphate dextrose (CPD), which extended the vitality of blood units to 28 days. CPDA-1 was developed in 1979 and extended the shelf time of blood units to 35 days, CPDA-2 (Citrate Phosphate Dextrose Adenine) was developed in the 1980s. It extended the shelf time of blood units to 42 days.

Cryoprotective agents, such as glycerol, gain use in the 1960s, enabling freezing of blood for long-term storage.

Dr. **Judith Graham Pool** (1919-1975)[WS27] was an American physiologist at Stanford University. She is best known for the discovery of cryoprecipitation in 1965, a process for creating concentrated blood clotting factors (especially Factor VIII). The cryoprecipitates (or cryo) are found to have much greater clotting power than plasma and given to hemophiliacs to stop bleeding episodes. It prevents the need for hemophiliacs to travel to the hospital to be treated, since cryo can be kept frozen at home and infused, after being thawed, by a physician.

Dr. **Kenneth Merle Brinkhous** (1908–2000)[WS28], a professor at the University of North Carolina at Chapel Hill, discovered Factor VIII and showed that it was lacking in hemophiliac patients in 1939. He also investigated other clotting disorders, including Von-Willebrand disease.

Besides, he discovered PTT test. In the Late 1960s he produced a highly concentrated form of Factor VIII by pooling large quantities of plasma that generate vast amounts of cryo, which are then re-dissolved, treated, filtered, and centrifuged. The resulting powder's clotting power is 100 times stronger than raw plasma, easily stored in a portable vial, and can be injected with a syringe by the hemophilia patient.

In 1967[WS50], Rh immune globulin is commercially introduced to prevent Rh disease in the newborns of Rh-negative women.

In 1969, **S. Murphy** and **F. Gardner** demonstrate the feasibility of storing Platelets at room temperature, revolutionizing platelet transfusion therapy.

In 1970, Blood banks move toward an all-volunteer blood donor system.

In 1971, Hepatitis B surface antigen (HbsAg) testing of donated blood begins.

In 1981, The first cases of a syndrome initially called GRID (Gay-related Immunodeficiency Disease), due to its prevalence among gay men, are reported. It is later renamed AIDS (Acquired Immune Deficiency Syndrome).

In 1983, the French doctor **Luc Montagnier** (1932-now)[WS29] at the Pasteur Institute, in France, isolate the virus that causes AIDS. They locate it in the swollen lymph node in the neck of a Parisian AIDS patient and label it LAV (lymphadenopathy-associated virus). He was awarded the Nobel Prize in Physiology or Medicine in 2008.

Luc Montagnier (1932-now)[WS29]

After dozens of Americans are infected with AIDS from blood transfusions, the first blood-screening test to detect the presence or absence of HIV antibodies -- the ELISA test -- is licensed by the U.S. government in 1985. The test is universally adopted by American blood banks and plasma centers.

A legal battle ensues over who deserves credit for the discovery of the AIDS virus, which finally ends in 1987 when the U.S. and French

governments agree to share credit and royalties from the sales of test kits for the virus.

In 1987[WS50], Two tests for screening for indirect evidence of hepatitis C are developed and implemented, hepatitis B core antibody (anti-HBc) and the Alanine Aminotransferase Test (ALT).

In 1989, Human T Lymphotropic Virus I antibody (anti-HTLV-I) testing of donated blood begins.

In 1990, Introduction of first specific test for hepatitis C, the major cause of "non-A, non-B" hepatitis, although the hepatitis C virus (HCY) has never been isolated.

In 1992, Testing of donor blood for HIV-I and HIV-2 antibodies (anti-HIV-I and anti-HIV-2) is implemented.

In 1996, HIV p24 antigen testing of donated blood begins. Although the test does not completely close the HIV window, it shortens the window period.

From 1987 to 2008, a series of more sensitive tests are developed and implemented to screen donated blood for infectious diseases:

- Detect HBV: by using ELISA test to detect HbsAg.
- Detect HCV: by detecting Anti-HCV.
- Detect Syphilis: by carrying out VDRL or TPHA.
- Detect AIDS: by using ELISA test to detect Anti-HIV1 or Anti-HIV2 or by detecting the HIV p24 antigen test.
- Detect Malaria: by carrying out Blood Film.
- Detect Toxoplasmosis Gondi: by using ELISA test to detect IgM or IgG Antibody.
- Detect CMV: by detecting Anti-CMV.
- Detect Human T-Lymphotropic Virus I antibody test (anti-HTLVI)
- Recently, Polymerase Chain Reaction (PCR) directly detects the genetic material of viruses like HCV and HIV.

Blood banks now standard in communities and hospitals, with regional blood centers collecting approximately 75% of the blood supply for the United States. 13,588,000 units collected in the US in 1992.

In the late 1990s, there was a transition in terminology from Blood Banking to Transfusion Medicine.

Nowadays, Progress in the medical field has caused many to consider bloodless medicine. Where will this lead us? Professor Luc Montagnier[WS62], discoverer of the AIDS virus, states: "The evolution of our understanding in this field shows that blood transfusions must one day die out." In the meantime, alternatives to blood are already saving lives.

Current voluntary blood donation process together with the sophisticated methods for the collection, storage, processing and testing of blood required by the complex medical and surgical procedures of the present day are a long way from the early beginnings of drinking the blood of gladiators.

Finally, it is a strange thing that after waiting more than two and a half centuries to learn how to make blood transfusion safe, men in clinical medicine paid no attention to **Landsteiner** when he told of his discovery in 1900. It was not until thirty years later that he was awarded the Nobel prize. It is a regrettable fact that we frequently pay no attention to valuable information.

Abstract

The transfusion time line highlights many of the discoveries, inventions, observations, and practices, which, since ancient times, have led to remarkable progress and resulted in the effective treatments that are now taken for granted.

The recent practice of transfusion isn't the result of one man's effort; but, it is the glamorous consequence of many inventors and physicians of deferent eras and regions.

In my treatise, I tried to shed light on the most important events in the history of blood transfusion epic. First of All, I discussed the development in the social and religious point of view towards blood. Then, in chapter two, I summarized the major points in the history of discovery of the blood circulation, which was very essential in the understanding of the importance of blood transfusion. Finally, in the third chapter, I tried to follow the steps in the development of blood transfusion, from the ancient and medieval eras to the modern era. I conventionally divided the history of transfusion in the modern era to seven periods, according to the main concern of every period.

Although the major development of blood transfusion was in the last sixty years, we can't ignore the contributions of the Ancient physicians who created the dream that has recently become true.

Comments and Notes

1- Brailey, Transfusion Medicine. Page 2.

2- Brailey, Transfusion Medicine. Page 2.

3- Brailey, Transfusion Medicine. Page 3.

4- Learoyd, A Short History of Blood Transfusion. Page 2.

5- Brailey, Transfusion Medicine. Page 3.

6- Brailey, Transfusion Medicine. Page 3.

7- Learoyd, A Short History of Blood Transfusion. Page 7.

8- McGraw, Swammerdam, Jan (1637–1680). Page 13.

9- Brewer, Max Schultze (1865), G. Bizzozero (1882) and the discovery of the platelet. Page 252.

10- Al-Ghazal S, Ibn al-Nafis and the discovery of Pulmonary Circulation. Page 4.

11- Al-Ghazal S, Ibn al-Nafis and the discovery of Pulmonary Circulation. Page 4.

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18- Learoyd, A Short History of Blood Transfusion. Page 3.

19- Kaadan, The Surgery of al-Zahrawi. Page 318-344.

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21- Sturgis, The History of Blood Transfusion. Page 116.

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23- Bauer, From Blood Transfusion to Haemotherapy – the Anniversary of the German Society for Transfusion Medicine and Immunology (DGTI) from a Medicinal-Historical and Bioethical Perspective. Page 3.

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39- Learoyd, A Short History of Blood Transfusion. Page 12.
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51- Zallen D.T., The Rhesus Factor and Disease Prevention, Page 100
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