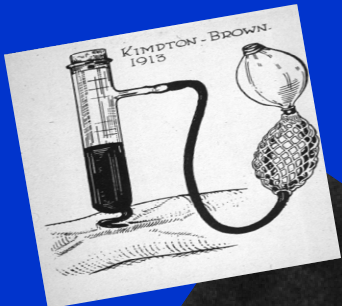
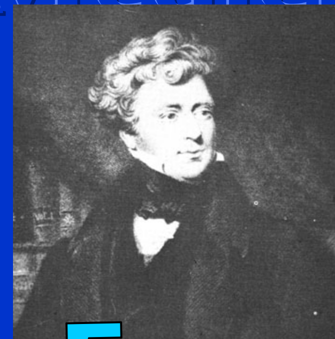
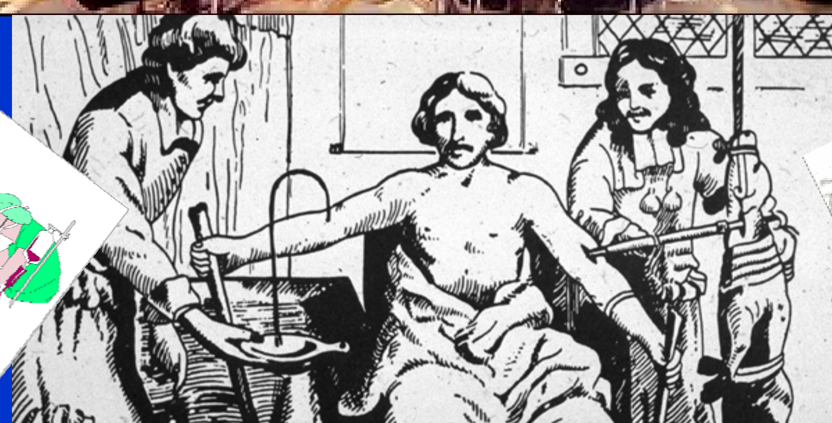
Transfusion Medicine: A History





John Freedman

St Michael's Hospital, Toronto



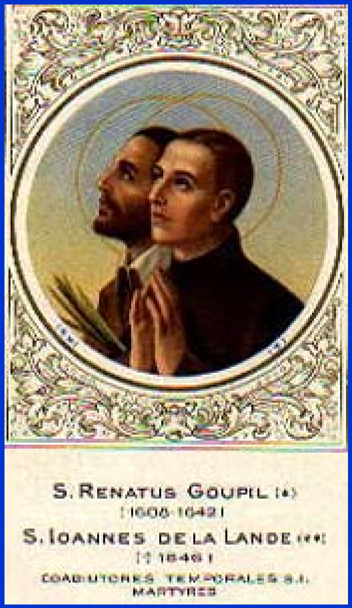
ONTraC
ontario transfusion coordinators

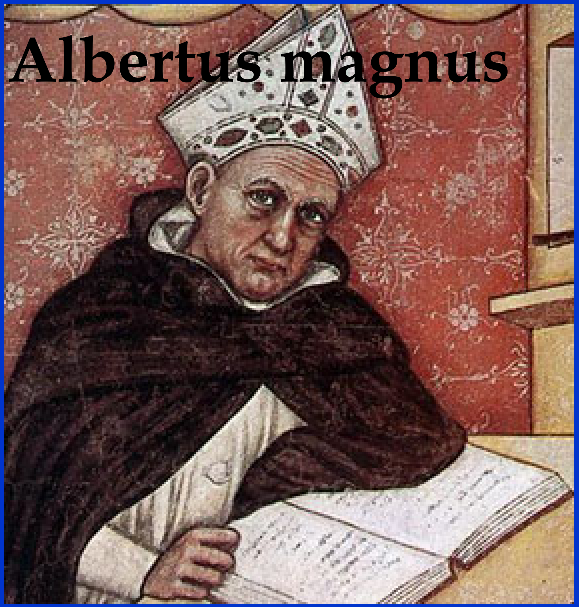

SAINT
JANUARIUS

Januarius/Gennaro

Bishop of Benventum, beheaded in 305 for refusing to worship pagan gods. 2 sealed phials of his blood and his head put in the Cathedral at Naples in 1497 and these have resulted in miraculous deliverance from the volcano of Vesuvius, 8 miles distant (e.g. 1631, 1707). On 19 Sept, 20 Dec and in May, these are examined. The congealed blood may liquify and 'boil' and re-solidify. Liquifaction of the blood seldom fails to occur on his feast days and may occur as much as 18 times during the year when it is exposed and placed near his head.

If liquified on the feast days, Neapolitans will have good luck.





Anaesthesiologists

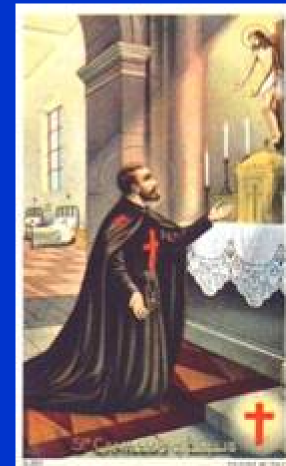
Missionary to the Hurons. Tortured and killed by Iroquois, enemies of the Hurons, for making the sign of the cross of a child's head. First North American martyr. His death by tomahawk in the head led to his patronage of people who work with or receive anaesthesia.

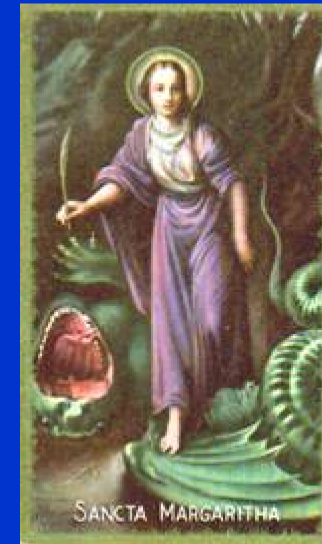
….

Medical technologists

Son of a military nobleman. Dominican Priest. Taught theology at Cologne and Paris. Teacher of St Thomas Aquinas. Introduced Greek and Arabic science and philosophy to medieval Europe. Known for his wide interest in what became known later as the natural sciences - botany, biology, etc. Wrote and illustrated guides to his observations, and was considered on a par with Aristotle as an authority on these matters.

Alexius





Agatha

Camillus of Lellis

Margaret of Antioch

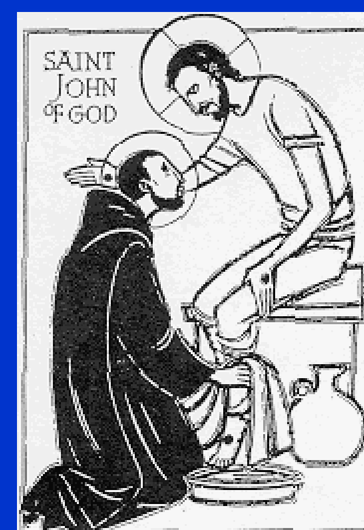
Hospital administrators

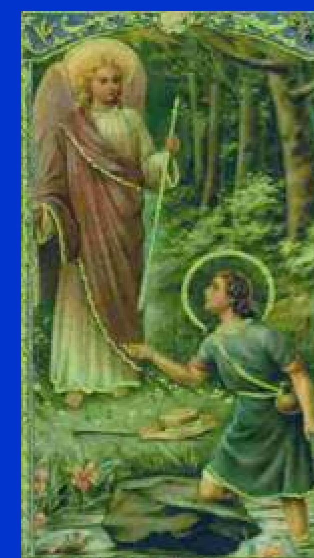
Frances Xavier Cabrini

Basil the Great

Catherine of Alexandria

Catherine of Sienna





Raphael the Archangel

Ovid: Metamorphoses, seventh book (43 BCE)

Jason pleaded that Medea restore the youth of his father, King Aeson.

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

Ovid's influence on Western art and literature cannot be exaggerated. The *Metamorphoses* is our best classical source of 250 myths. 'The poem is the most comprehensive, creative mythological work that has come down to us from antiquity.' Based on its influence, "European literature and art would be poorer for the loss of the *Metamorphoses* than for the loss of Homer" (Hadas). Ovid was a major inspiration for Dante, Chaucer, Shakespeare, Milton. If Virgil is Rome's greatest poet, Ovid is the most popular.

Medea’s Rx:

In a bronze cauldron:

“root herbs, seeds and flowers, strong juices and pebbles from the farthest shores of oceans east and west, hoarfrost taken at full of moon, a hoot owl’s wings and flesh, a werewolf’s entrails, the fillet of a snake, the liver of a stag, and the eggs and head of a crow which had been alive for nine centuries”

Blood in the Bible

Leviticus 17:11 *ויקרא*

כי נפש הבשר בדם הוא

"…the life/soul of the flesh is in the blood…
…no soul you shall eat blood"

Matthew 26:28

"…take drink…this is my blood, which is shed for you for the remission of sins…"

Blood in History

China, 1000 BCE: The soul was contained in the blood.

Egyptian kings bathed in blood for their health.

Taurobolium, the practice of bathing in blood as it cascaded from a sacrificial bull, was practiced by the Romans.

Pliny and Celsus describe Romans drinking the blood of fallen gladiators to gain strength and vitality and to cure epilepsy.

Galen advised drinking of blood of a weasel or a dog for rabies.

Ancient Norwegians drank blood of seals and whales as a remedy for epilepsy and scurvy.

[Brown HM: The beginnings of intravenous medication. Ann Med Hist 1:177, 1917]

Phlebotomy, or bloodletting, is the longest-running tradition in medicine, originating in the ancient civilizations of Egypt and Greece, persisted through the Medieval, Renaissance, and Enlightenment periods, flourished in Arabic and Indian medicine, and lasted through the second Industrial Revolution. The practice continued for 2,500 years until it was replaced by the techniques of modern medicine.

Doctors bled patients for every ailment imaginable. They bled for pneumonia and fevers, back pain and rheumatism, headaches and melancholia; even to treat bone fractures and other wounds. Yet there never was any evidence that phlebotomy did any good.

Bloodletting was based on an ancient system of medicine in which blood and other bodily fluid were considered to be "humors" whose proper balance maintained health. Sick patients were thought to have an imbalance of their humors, which bloodletting was thought to restore.

Bleeding was as trusted and popular in ancient days as aspirin is today. The Talmudic authors laid out complex laws for bloodletting. Medieval monks bled each other several times a year for general maintenance of health. Doctors devised elaborate charts indicating the most favorable astrological conditions for bleeding.

It wasn't until well into the 19th century that people began to question the value of bloodletting. Scientists such as Louis Pasteur, Joseph Lister, and Robert Koch showed that germs, not humors, were responsible for disease. Furthermore, medical statisticians tracking case histories began to collect evidence that bloodletting was not effective.

Eventually the practice died, although it continued in some parts of rural America into the 1920s.

Bleeders used an impressive array of hardware. The mainstay was the lancet, a small, sharp, two-edged knife. Wielding the lancet took quite a bit of skill; a false cut could slice a nerve or a tendon. To make the job easier a Viennese inventor produced a spring-loaded lancet, called a "Schnapper" in German or a phleam in English. It consisted of a case about two inches long with a spring-loaded blade emerging from the top. The bleeder would cock the blade, press the Schnapper against the skin and push a release, causing the blade to snap down and across. The Schnapper had the safety feature of not cutting beyond a certain depth.

Sometimes phlebotomists would use a scarificator -- a spring-loaded box containing anywhere from twelve to eighteen blades. This tool was often used in conjunction with "cupping" to relieve local inflammation. The bleeder would place a glass cup against the skin and warm it with a torch. The heat would create a vacuum strong enough to raise a large blood-filled blister. The bleeder would pull off the cup, spring the scarificator, and then reapply the cup to draw out more blood.

Today we regard leeches as loathsome, but for centuries these blood-sucking creatures were a mainstay of medical care. Derived from the Anglo-Saxon word loece, to heal, the leech was used as an adjunct to bloodletting, in places too sensitive or confined for the lancet or other blood-letting instruments e.g. the gums, lips, nose, fingers, or even "the mouth of the womb," according to a medical text from 1634.

The common medicinal leech, Hirudo medicinalis, produces natural anti-coagulants and anesthetics in its saliva, so patients bleed readily and generally feel nothing during the procedure. Leeches became popular in the 19th century -- so much so that the species became endangered in Europe. In 1833 alone, French doctors imported 41,500,000 leeches.

Today leeches have found renewed utility in certain surgical procedures, particularly after microsurgery. Doctors sometimes find it helpful, for example, to use leeches to restore circulation to a re-attached finger, or to portions of the skin following plastic surgery.

Barber-Surgeons

- During the Middle Ages a new category of medical practitioner emerged. The Pope had banned the clergy from performing bloodletting (although they were welcome to receive it), and physicians were discouraged by the fact that feudal lords could have them executed in cases of malpractice. So bloodletting and other minor procedures moved into the hands of barber-surgeons.
- More craftsmen than medics, they established their own guilds and competed for respectability with apothecaries and physicians. They advertised with a symbol that endures to this day -- a red and white striped pole. The pole represents the stick patients would grab while being phlebotomized; the white stripes represent the bandages and the red stripes, the blood.

"Na'am, leader of the armies of Ben-Adad, King of Syria, afflicted with leprosy, consulted physicians, who, in order to kill him, drew out the blood from his veins and put in that of another"

Dutton WF: Intravenous therapy: Its application in the modern practice of medicine. FA Davis, Philadelphia, 1925.

Petro de Abano, C13th:

"He 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 bathe in tepid water and to copulate with girls according to the law natural, and to play with pretty girls and young boys; and the antidote is to eat serpents whose heads and tails have been cut off with the edge of a palm frond."

[Brown HM: The beginnings of intravenous medication. Ann Med Hist 1:177, 1917]

“First Transfusion” Myth

Terminally ill with what was likely chronic renal disease

In 1492, Pope Innocent VIII is said to have received, at the behest of a Jewish physician, a transfusion of the blood of three ten year old boys, each of whom was paid a ducat and all of whom died. Probably the blood was drawn, but was intended to be taken orally. Indeed, there is no reliable evidence that the sickly pope accepted the blood at all.

This story has been told and retold over the last half millennium. It is most likely apocryphal and has the flavor of an early urban legend in its details and its anti-semitic and anti-Catholic overtones.

[Villari P: The life and times of Giralamo Savanorola. T Fisher Unwin, London, 1888;
Lindeboom GA: The story of a blood transfusion to a pope. J Hist Med 9:455, 1954.
Gottlieb AM: History of the first blood transfusion but a fable agreed upon: The transfusion of blood to a pope. Transfus Med Rev 1991;5:228-235.]

Circulation

- Understanding the concept of circulation was critical to developing the reality of blood transfusion.

- Ancient Greeks believed that blood was formed in the heart, then consumed as it flowed out to the body in veins, while air was passed from the lungs to the body in arteries.

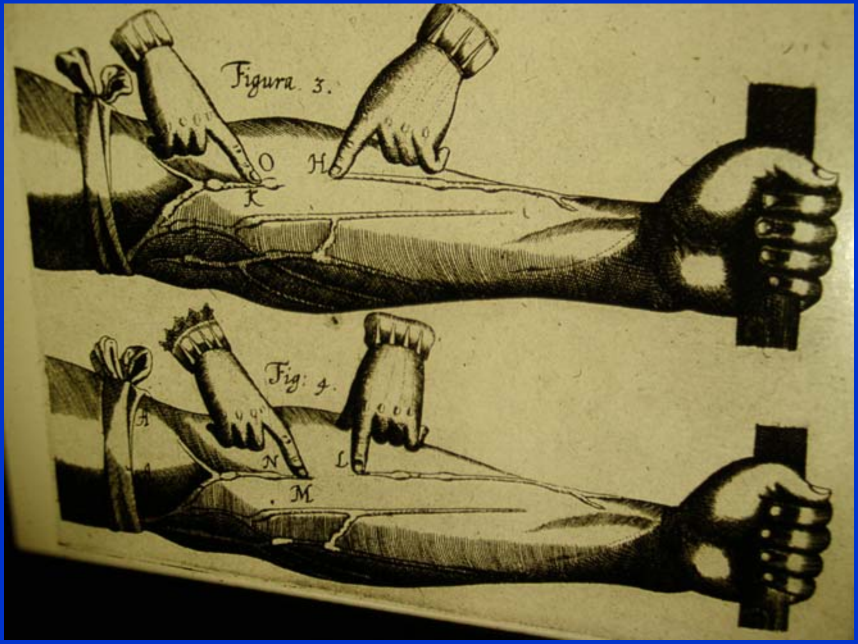
- Erasistratos (~270 BCE) envisioned the heart as a pump.

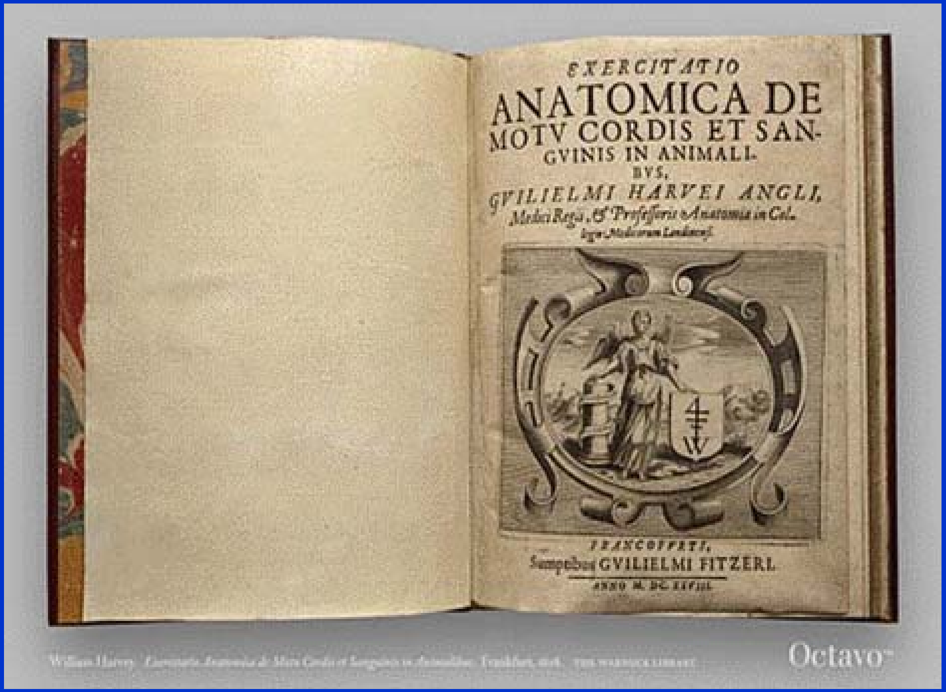
- Galen (131-201 CE) proved that arteries contain blood, but thought that blood was formed in the liver, not suspecting that arteries and veins are attached.

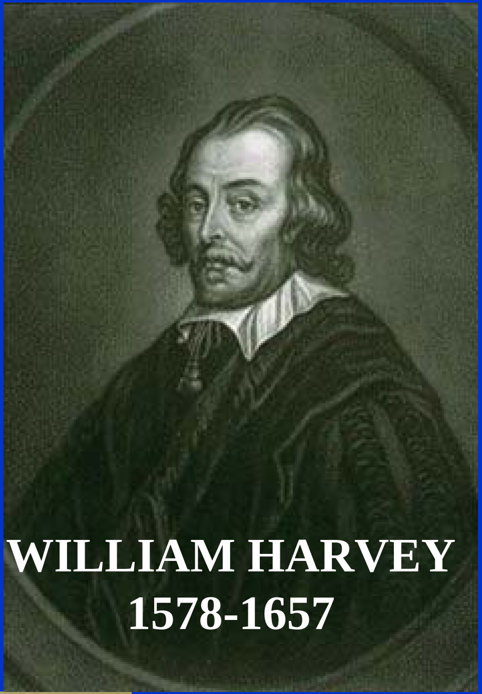
Circulation

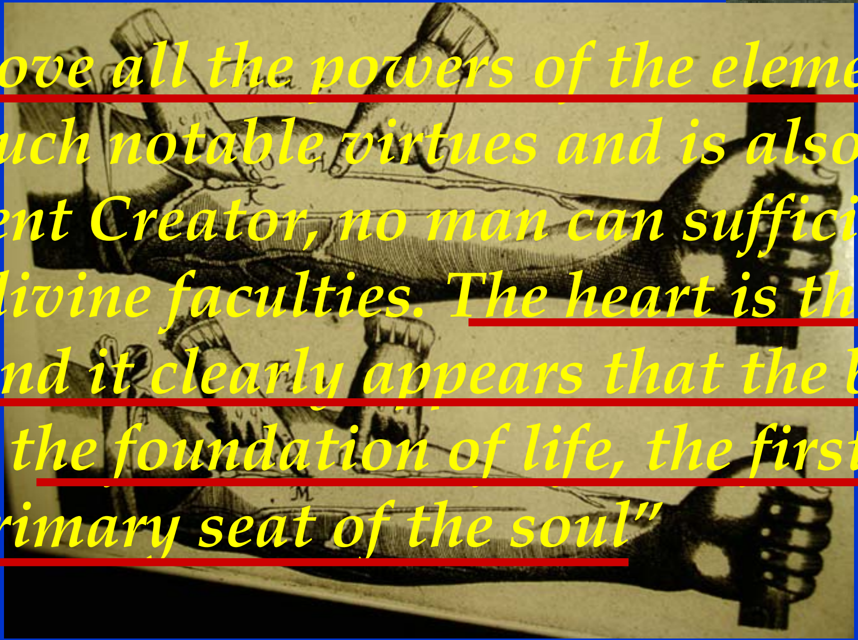
Andrea Cesalpino (1519-1603) used the term ‘circulation’ and believed that the veins and arteries were connected by a fine vascular network.

William Harvey is generally credited with the discovery in 1613 (published in 1628) of the circulation of blood as we know it today.









"Bloods acts above all the powers of the elements and is endowed with such notable virtues and is also the instrument of the Omnipotent Creator, no man can sufficiently extol its admirable and divine faculties. The heart is the mere organ for its circulation and it clearly appears that the blood is the generative part, the foundation of life, the first to live, the last to die and the primary seat of the soul"

Andreas Libavius, 1615

First to advocate transfusion, though not known to have actually attempted to perform a transfusion.

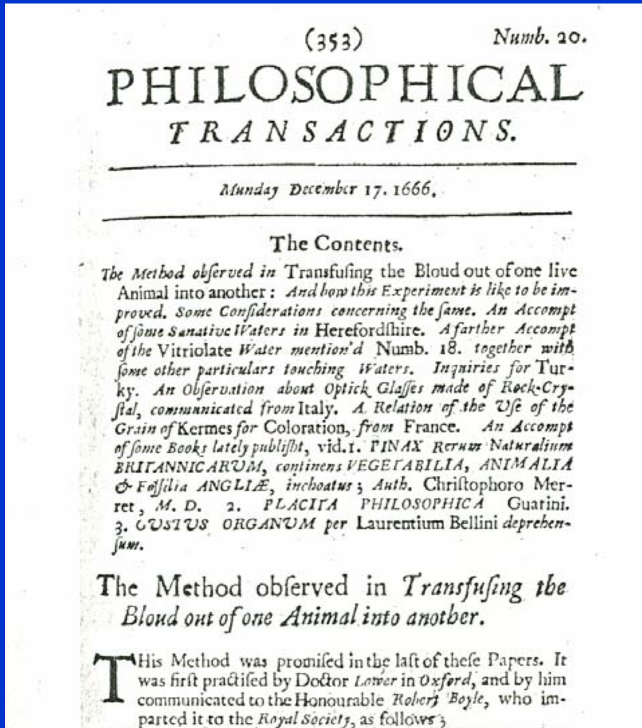
"Let there be a young man, robust, full of spirituous blood, and also an old man, thin, emaciated, his strength exhausted, hardly able to retain his soul. Let the performer of the operation have two silver tubes fitting into each other. Let him open the artery of the young man, and put it into one of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

In 1628, Giovanni Colle (Padua) suggested transfusion as a means of prolonging life but did not do it.
In the mid seventeenth century, many infusion experiments were performed.

In 1658, Christopher Wren and William Boyle performed a series of experiments injecting various medicaments into the veins of dogs utilizing a bladder with an attached quill and then observing the effects.

Infusion solutions included wine, beer, opium, emetics, water, nitric acid, and sulfuric acid.

Willis injected dyes into the blood vessels supplying the brain in order to trace its vasculature (thus the Circle of Willis).


(353) Numb. 20.

PHILOSOPHICAL TRANSACTIONS.

Munday December 17. 1666.

The Contents.

The Method obſerved in Transfuſing the Bloud out of one live Animal into another: And how this Experiment is like to be improved. Some Conſiderations concerning the ſame. An Accompt of ſome Sanative Waters in Herefordſhire. A farther Accompt of the Vitriolate Water mention'd Numb. 18. together with ſome other particulars touching Waters. Inquiries for Turky. An Obſervation about Optick Glaſſes made of Rock-Cryſtal, communicated from Italy. A Relation of the Uſe of the Grain of Kermes for Coloration, from France. An Accompt of ſome Books lately publiſht, viz. 1. PINAX Rerum Naturalium BRITANNICARUM, continens VEGETABILIA, ANIMALIA & Foſſilia ANGLIÆ, inchoatus; Auth. Chriſtophoro Merret, M. D. 2. PLACITA PHILOSOPHICA Guarini. 3. GUSTUS ORGANUM per Laurentium Bellini deprehenſum.

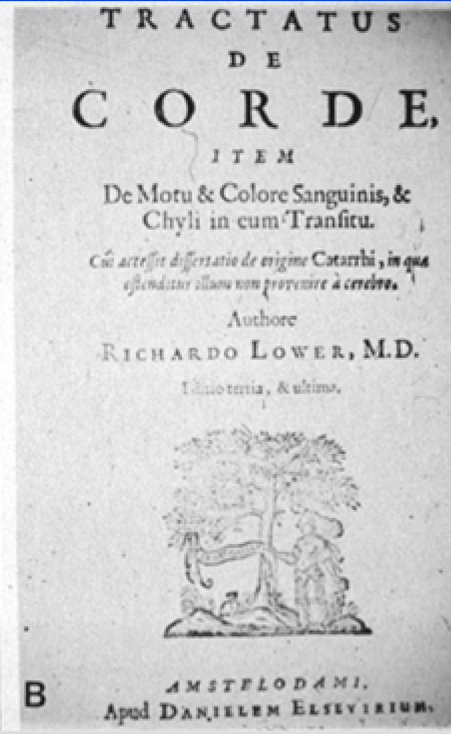
The Method obſerved in Transfuſing the Bloud out of one Animal into another.

THis Method was promiſed in the laſt of theſe Papers. It was firſt practiſed by Doctor Lower in Oxford, and by him communicated to the Honourable Robert Boyle, who imparted it to the Royal Society, as follows;

Richard Lower

(1631-1691)

A


TRACTATUS DE CORDE. ITEM De Motu & Colore Sanguinis, & Chyli in eum Tranſitu.

Cui acceſſit diſſertatio de origine Catarrhi, in qua oſtenditur illum non provenire à cerebro.

Authore RICHARDO LOWER, M.D.

Editio tertia, & ultima.

AMSTELODAMI, Apud DANIELEM ELSEVIRIUM.

B

Richard Lower is credited with performing, in 1665, the first authentic blood transfusion (animal to animal).

He kept exsanguinated dogs alive by connecting the carotid artery of the donor dog to the jugular vein of the recipient dog with a quill.

During his few, intensely active, years with the Royal Society, Lower did much of the work that established his reputation as perhaps the best seventeenth-century English physiologist after Harvey. He was concerned principally with 2 areas of investigation: transfusion and cardiopulmonary function. His interest in both can be traced to his days at Oxford, but the fame of his investigations and owed a great deal to his association with the Royal Society.

Apparently transfusion was attempted at Oxford in the late 1650s. Familiar with earlier attempts by Christopher Wren who tried to convey medicinal liquors directly into the bloodstream using quills and special bladders, Lower in 1661 expressed interest in using similar procedures to transmit broth and other nutritive fluids into the bloodstream. In a letter to Boyle dated 18 January 1661, Lower expressed, his "fancy to try, how long a dog may live without meat, by syringing into a vein a due quantity of good broth" and described his intended procedure as follows: *"I shall try it in a dog, and I shall get a tin pipe made, about two inches long, and about the usual bigness of a jugular vein, and hollow, which I may put into the vein."*

By 8 June 1664, Lower was able to write to Boyle in London about a more daring experiment: he intended to "get two dogs of equal bigness [and] let both bleed into the others vein. ..." As Lower was to explain retrospectively in his TRACTATUS DE CORDE (1669), he was led from the broth experiment to the transfusion attempt by observing how harmoniously the blood of different animals mixed with various injected substances.

It was natural to *"try if the blood of different animals would not be much more suitable and would mix together without danger or conflict." It is quite possible that Lower was influenced as well by reports of discussions at the Royal Society late in 1663. At one of these, Timothy Clarke had described his method of infusing certain medicinal preparations directly into the veins of dogs, and an unnamed fellow of the society proposed "to let the blood of a lusty dog into the veins of an old one, by the contrivance of two silver pipes fastened to the veins of such two dogs."*

- With his ideas crystallized, it took Lower only a few months to perfect the requisite experimental technique. He performed the first successful transfusion at Oxford late in February 1665, transfusing blood "from an artery of one animal into a vein of a second." The Royal Society soon heard of these results, and in early 1666, after several months interruption due to plague and the London fire, society members were busy making their own investigations into transfusion.

- In June 1666 John Wallis, who had been present at Lower's successful experiment at Oxford the previous February, reviewed Lower's success; and the society, through Boyle, requested a full account from Lower. This was officially received in September, replicated at the society in November, and printed in PHILOSOPHICAL TRANSACTIONS (December 1666). By mid-1667 Lower had joined the society.

(353) Numb. 20.

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The Method observed in *Transfusing the Bloud out of one Animal into another.*

THis Method was promised in the last of these Papers. It was first practised by Doctor *Lower* in *Oxford*, and by him communicated to the Honourable *Robert Boyle*, who imparted it to the *Royal Society*, as follows;

First, Take up the *Carotidal* Artery of the Dog or other Animal, whose Bloud is to be transfused into another of the

Aaa same

Fig. 6.—From the *Philosophical Transactions*, Dec. 17, 1666, describing Lower's blood-transfusion experiment in animals.

carried into effect". He goes on to say:—

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.

Fig. 4.—The title page of *Tractatus de Corde*, by Richard Lower.

For many years at Oxford I saw others at work, and myself for the sake of experiment injected into the veins of living animals various opiate and emetic solutions, and many medicinal fluids of that sort. . . . But when, in addition, The most probable ufe of this Experiment may be conjectured to be that one animal may live with the blood of another; and confequently, that thofe animals, that want bloud, or have corrupt bloud, may be fupplied from other with a fufficient quantity, and of fuch as is good, provided the Tranfufion be often repeated, by reafon of the quick expence that is made of the bloud.

[Lower R: Philosophical Transactions Royal Society London [Biol] 1:353, 1666]

The importance of Lower is that he was the first to define the appropriateness of transfusional replacement of blood in severe hemorrhage.

Samuel Pepys, November 14, 1666.

"Dr Croone told me that, at the meeting at Gresham College tonight, there was a pretty experiment of the blood of one dog let out until he died, into the body of another on one side, while all his own run out on the other side. The first died upon the place, and the other very well and likely to do well … but, as Dr Croone says, may if it takes, be of mighty use to man's health, for the amendment of bad blood by borrowing from a better body"

An Account
Of the Experiment of *Transfusion*, practised upon a *Man* in *London*.

This was perform'd, Novemb. 23. 1667. *upon one Mr.* Arthur Coga, *at* Arundel-*House*, *in the presence of many considerable and intelligent persons, by the management of those two Learned Physitians and dextrous Anatomists Dr.* Richard Lower, *and Dr.* Edmund King, *the latter of whom communicated the Relation of it, as followeth.*

THe Experiment of Transfusion of Blood into an *humane* Veine was made by Us in this manner. Having prepared the

Mmm

Lower's report of human transfusion, Nov 23rd, 1667

Samuel Pepys, November 21, 1667.

"…they discourse of a man that is a little frantic, that hath been a kind of minister…a poor and debauched man, that the College have hired for 20s to have some blood of sheep let into his body…propose to let in about twelve ounces, which they compute which is what will be let in in a minute's time by a watch… differ in the opinion they have of the effects of it; some think it may have a good effect on him as a frantic man by cooling his blood; others that it will not have any effect at all"

Samuel Pepys, November 30, 1667.

"…I was very pleased to see the person who had his blood taken out. He speaks very well and this day gave the Society a relation thereof in Latin, saying that he finds himself much better since, and as a new man, but he is cracked a little in the head, though he speaks very reasonably and very well…the first man that ever had it tried upon him in England, and but one that hear of in France, which was a porter hired by the Virtuosos"

Meanwhile, in Paris, Denis -- without proper citation -- had appropriated Lower's techniques and applied them to human transfusion. The Royal Society was outraged and Lower, sensitive to his colleagues' concerns, tried and succeeded at human transfusion. On 12 December 1667 the procedure was firmly established in England with its second successful trial, this a public one before a large crowd.

Jean Baptiste Denis

ig. 1. Jean-Baptiste Denis (c 1635 to 1704) (courtesy of lusée d'Histoire de la Médecine, Faculté de Médecine de aris).

Denis was a young physician of Louis XIV. He preferred animal (rather than human) blood for his experiments, as he believed it less likely "to be rendered impure by passion or vice"

Denis and Emmerez performed transfusion of lamb blood into the carotid artery of a young woman in June 1667.

Denis reported that the woman passed urine as black as soot following the transfusion, a finding indicative of a hemolytic transfusion reaction, but she survived.

Denis was born in Paris, in the 1640s, son of a hydraulic engineer who was Louis XIV's chief engineer in charge of the works distributing the water of the Seine from the pumps at Marly to the fountains at Versailles.

Denis is said to have studied medicine at Montpellier, but no records of this can be found in the very complete archives of the Faculty of Medicine. Niceron says that he obtained "un bonnet de Docteur en cette Faculté" and that "il fut aggrégé à la Chambre Royale". On the other hand, Martin de la Martinière, who was a physician in ordinary to the king, in a letter to Denis accuses him of taking the title of "maître" because of a "lettre de Médecine" that he obtained in Rheims. Nothing has yet been found in Rheims indicating that he obtained such a degree. In Paris he taught philosophy & mathematics, assuming the title of professor, which he placed at the head of his works. No evidence for a degree in mathematics or philosophy has yet been found.

Beginning in 1664, Denis gave public lectures in physics, mathematics, and medicine at his home on Quai des Grands-Augustins in Paris, and published these lectures as conference reports. He also joined the group surrounding Habert de Montmort, which met to discuss the new philosophy, much like the groups in London that preceded the Royal Society. When the Académie des Sciences was established in 1666, the Montmort group did not participate and continued its own meetings.

The discovery of the circulation of blood by William Harvey had stimulated experiments on the circulation. This was followed by the first trial of transfusion of blood in animals. After discussions at the Royal Society in England as early as its public meeting of 17 May 1665, an account of successful transfusion in dogs was given by Richard Lower in a letter written to Robert Boyle on 6 July 1665 and submitted by Boyle to the Royal Society. This led to another successful transfusion in November 1666 at the Royal Society.

When reports of the English experiments reached Paris late in 1666 or early in 1667, the Académie des Sciences immediately set about repeating them, appointing a committee including Louis Gayant, an anatomist; Claude Perrault, the physician noted for the east facade (the Colonnade) of the Louvre; and Adrien Auzout, the astronomer. Gayant performed the first transfusion in Paris on 22 January 1667, using dogs. Transfusion also attracted the interest of the Montmort Academy, which apparently appointed Denis and Paul Emmerez, a surgeon from St.-Quentin, to carry out independent studies. On 3 March 1667 Denis performed a transfusion experiment on two dogs. On 2 April 1667 various experiments involving transfusion from three calves to three dogs were made. These were published in the Royal Society's PHILOSOPHICAL TRANSACTIONS.

But it was the transfusion of blood in men which was of the greatest interest to Denis, gave him his celebrity, and started the greatest medical controversy of that time. In these experiments he was assisted by Paul Emmerez.

The first transfusion of blood in man was made on 15 June 1667, on a drowsy and feverish young man. From a lamb he received about twelve ounces of blood, after which he "rapidly recovered from his lethargy, grew fatter and was an object of surprise and astonishment to all who knew him".

The second transfusion was carried out on a forty-five-year-old chair bearer, a robust man who received the blood of a sheep. He returned to work the next day as if nothing had happened to him.

The recipient of the third transfusion was Baron Bonde, a young Swedish nobleman who fell ill in Paris while making a grand tour of Europe. He was in such a bad state that he had been abandoned by his physicians; and in despair, having heard of Denis's new cure, his family asked Denis to attempt transfusion of blood as a final recourse. After the first transfusion, which was from a calf, Bonde felt better and began to speak. This improvement lasted only a short time, however, and he died during a second transfusion.

The fourth transfusion patient was a madman, Antoine Mauroy, who died during a third transfusion. He may have been poisoned by his wife, who, perhaps to divert suspicion from herself or at the suggestion of the many Paris physicians antagonistic to Denis, accused Denis of having killed her husband. Denis brought the case before the court, and a judgment tendered on 17 April 1668 cleared him of any wrongdoing but forbade the practice of transfusion of blood in man without permission of the Paris Faculty of Medicine. Meanwhile, another transfusion had been made by Denis, on 10 February 1668, on a paralyzed woman. After this, however, the practice of transfusion faded out as suddenly as it had begun.

In 1673 Denis was invited to England by Charles II, who wished to learn about transfusion and other remedies purportedly discovered by Denis. He went to England and successfully treated the French ambassador and several personalities of the court. Despite offers to remain, he became dissatisfied and returned to Paris, where he continued his interest in science and mathematics but never practiced medicine or again concerned himself with transfusion. He died suddenly on 3 October 1704.

A LETTER

Concerning a new way of curing ſundry diſeaſes by Transfuſion of Blood, Written to Monſieur de MONTMOR, *Counſellor to the* French King, *and Maſter of* Requeſts.

By J: DENIS *Profeſſor of* Philoſophy, *and the* Mathematicks.

Munday July 22. 1667.

SIR,

THE project of cauſing the Blood of a healthy animal to paſſe into the veins of one diſeaſed, having been conceived *about ten years agoe*, in the illuſtrious Society of *Virtuoſi* which aſſembles at your houſe; and your goodneſs having received M. *Emmeriz*, & my ſelf, very favorably at ſuch times as we have preſum'd to entertain you either with diſcourſe concerning it, or the ſight of ſome not inconſiderable effects of it: You will not think it ſtrange that I now take the liberty of troubling you with this Letter, and deſign to inform you fully of what purſuances and ſucceſſes we have made in this Operation; wherein you are juſtly intitled to a greater ſhare than any other, conſidering that it was firſt ſpoken of in your *Academy*, & that the Publick is beholding to you for this as well as for many other diſcoveries, for the benefits & advantages it ſhall reap from the ſame.

But that I may give you the reaſons of our procedure & con-

Ccc vince

Fig. 7.—The opening page of the translation in the *Philosophical Transactions*, July 22 1667, of the letter of Jean Denys.

Denis' fourth transfusion recipient, suffering from luetic madness, following a symptom-free first transfusion of calf blood (December 19, Sunday—Gregorian calendar), developed a hemolytic reaction upon his second transfusion:

Wednesday: "As soon as the blood began to enter into his veins, he felt ...heat along his arm, and under his arm-pits…His pulse rose presently, and soon after we observed a plentiful sweat over all his face. His pulse varied extremely at this instant, and he complained of a great pain in his kidneys, and that he was not well in the stomach, and that he was ready to choke unless they gave him his liberty…he vomited of bacon and fat…He found himself urged to urine and asked to go to stool… When he awakened…a general lassitude he felt in all his limbs…He made a great glass full of urine, of a color as black as if it had been mixed with soot of chimney…he bled at the nose very plentifully… Saturday morning…his urine cleared up and after that time it resumed little by little its natural color "

Seemed improved, so another transfusion done which proved fatal

Gregorian calendar

24 Feb 1582; Gregory VIII

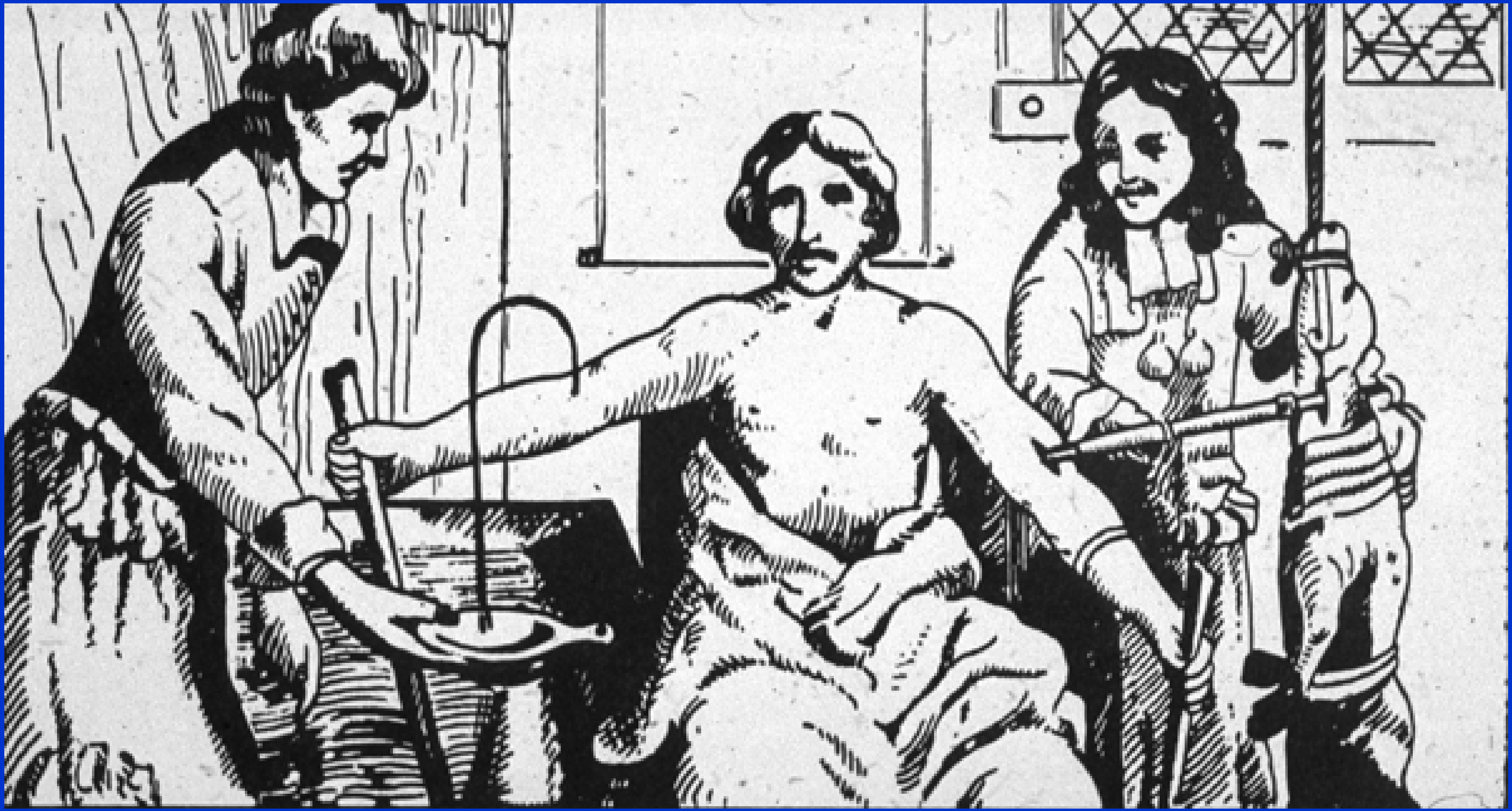
(i) Mean year in Julian calendar a little too long and vernal equinox had drifted back in the calendar year and (ii) because the lunar year was used to calculate Easter, there was a compounding error.

Deleted 10 days: Thursday 4 October 1582 was followed by Friday 15 October 1582.

But European countries took varying times to implement e.g. Venice in 1582, England only in 1752.

So what date to use???

Animal to Human Transfusion



Early lamb blood transfusion

Engraving by Scultetus, 1693, Armamentarium Chirurgicum, Leyden

Fig. 3. Two physicians transfusing a dog's blood into a man from *Armamentarium chirurgicum* (1671), Pl. 11, p. 28 by Johannes Scultetus [28] (courtesy of Bibliothèque Interuniversitaire de Médecine, Paris).

Fig. 9.—Scultetus, transfusion, 1693.

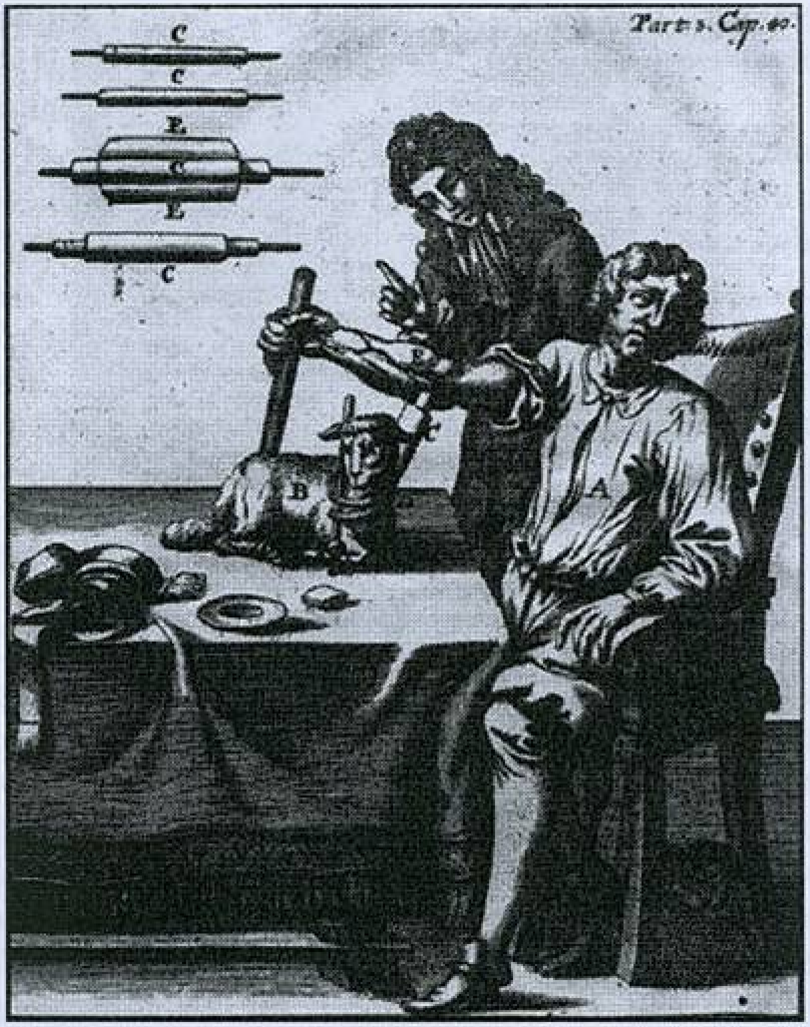


Fig. 2. Physician transfusing a lamb's blood into a man from *Grosser und gantz neugewundener Lorbeer-Krantz oder Wund-Artzney* (1692), p. 285, by Matthäus Gottfried Purmann [25] (courtesy of Bibliothèque Interuniversitaire de Médecine, Paris).

Fig. 4. The title page of the anatomical plates of Pietro da Cortona (1596 to 1669) published in 1741 shows a man receiving blood from a sheep [29].

Fig. 5. A man receiving a transfusion from a calf or a goat from *Tractatio medico curiosa de ortu et occasu transfusionis sanguinis* (1679) by Georges Abraham Mercklin [30], engraving by Cornelius Nicolaus Schurk (courtesy of Bibliothèque Interuniversitaire de Médecine, Paris).

RELAZIONE

DELL' ESPERIENZE

Fatte in Inghilterra, Francia, ed Italia
Intorno alla celebre, e famoſa

TRASFVSIONE DEL SANGVE

PER TVTTO MAGGIO 1668.

In cui, oltre all'oppugnationi, e difeſe, ſi vede la ſanità reſtituita ad alcuni infermi, e particolarmente à vn pazzo.

La maniera di facilmente pratticarla ne gli Huomini, e la minuta deſcrizione di eſſa,

Con nuoua Eſperienza in vn Cane vecchio, e ſordo reſtituito alla forza, & vdito.

DEDICATA

ALL' ILLVSTRISSIMO SIG[illegible]

VIRGILIO MARIA
DAVIA.

In BOLOGNA, Per Manoleſsi. M.DC.LXVIII.

Con licenza de' Superiori.

Prohibitions against Transfusions

Mauroy's wife charged Denis with poisoning her husband. Denis was exonerated (and the wife was charged with attempting to poison her husband!), but this incident led to prohibitions against blood transfusions:

- **1678 prohibition by the French Parliament**
- **The British Royal Society (1678), and**
- **the Vatican (1679).**

These prohibitions and the fear of adverse reactions led to a 150-year near-complete hiatus in transfusion work.

The Eighteenth Century

Transfusions done only sporadically; generally animal to human.

Transfusion generally thought of as a cure for mental aberration or as youth potion for the aged, rather than treatment for blood loss.

Reciprocal transfusions between husband and wife suggested as a cure for marital discord.

Blood thought to carry characteristics of the donor to the recipient: sheep blood would make a dog grow wool, hooves and horns; cat blood would make a girl feline, etc.

[Brown HM: The beginnings of intravenous medication. Ann Med Hist 1:177, 1917]

James Blundell

In 1818, James Blundell (obstetrician, Guy’s Hospital, London) attempted human-to-human transfusion.

He preferred human donors:

“What is to be done in such an emergency? A dog might come when you whistled, but the animal is small; a calf might have appeared better suited for the purpose, but then it has not been taught to walk properly up the stairs.”

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.

By JAMES BLUNDELL, M.D.

LECTURER, IN CONJUNCTION WITH DR. HAIGHTON, ON PHYSIOLOGY AND MIDWIFERY, AT GUY'S HOSPITAL.

Read Dec. 22, 1818.

Report of Blundell's first transfusion, in the Lancet

Between 1825 and 1830 he performed 10 transfusions, five beneficial.

James Blundell

- Although the possibility of transfusing whole blood from human to human had been discussed in the literature for centuries, Blundell made the hypothesis a reality. He completed four successful transfusions out of slightly more than twice this number. As he pursued his experimental trials in dogs, he performed, with a syringe, the first transfusion in humans in 1818. Complicated instruments were described subsequently.

- One device named an "Impellor" provided blood under pressure to the recipient; the Gravitator, a gravity feed apparatus, was described in the LANCET in 1829.

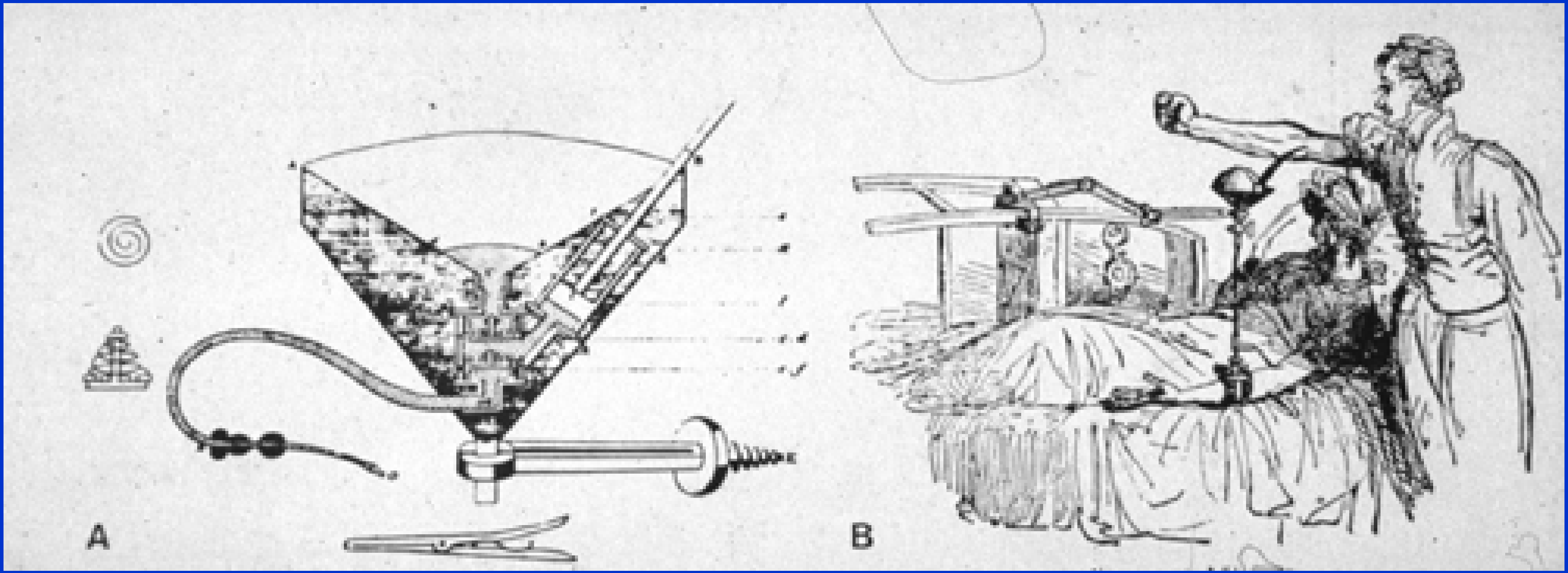
- The indications for transfusion included postpartum hemorrhage, extreme malnutrition, puerperal fever, cancer of the pylorus, ruptured uterus, and hydrophobia. Since each of his patients was critically ill at the time of decision, it is impossible to discover from the clinical notes whether a transfusion reaction appeared as a complication in any. Excerpts from the LANCET report follows:

“In the present state of our knowledge respecting the operation, although it has not been clearly shown to have proved fatal in any one instance, yet not to mention possible, though unknown risks, inflammation of the arm has certainly been produced by it on one or two occasions; and therefore seems right, as the operation now stands, to confine transfusion to the first class of cases only, namely, those in which there seems to be no hope for the patient, unless blood can be thrown into the veins.

The object of the Gravitator is, to give help in this last extremity, by transmitting the blood in a regulated stream from one individual to another, with as little exposure as may be to air, cold, and inanimate surface; ordinary venesection being the only operation performed on the person who emits the blood; and the insertion of a small tube into the vein usually laid open in bleeding, being all the operation which it is necessary to execute on the person who receives it.

Although the description of the instrument must appear complex, its use is simple; in truth, when the transfusion is once begun, the operator has little to do; his principal cares are -- first, to see that the cup never empties itself entirely, otherwise air might be carried down along with the blood. Secondly, to make sure that blood which issues by dribbling, from the arm of the person who supplies it, may not be admitted into the receiver, as its fitness for use is doubtful. Thirdly, to watch the accumulation of blood in the receiver, and to prevent its rise above the prescribed level; and, lastly, to observe with attention the countenance of the patient, and to guard, as before stated, against an overcharge of the heart. This latter cause is of great importance.”

James Blundell



Blundell's transfusion devices included the impellor (A), which consisted of a cup, tube , and syringe; and the gravitator (B), consisting of a receptacle held high above the patient with an attached tube through which the blood was injected into the patient.

Following transfusion of a woman with post-partum hemorrhage with her husband's blood, …after six ounces had been administered, the woman, previously semicomatose, suddenly exclaimed *"By Jesus, I feel as strong as a bull"*

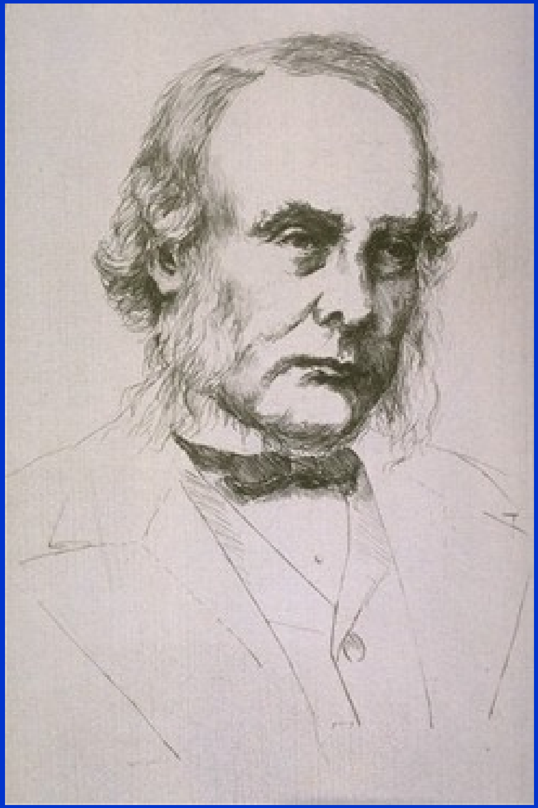
Doubleday E: Lancet 1:111, 1825

In 1849, Routh reviewed all the transfusion patients to that date.

48 reported cases, of which 18 had had a fatal outcome, which he estimated was ***"rather less than that of hernia, or about the same as the average amputation"***

Routh C: Med Times 20:114, 1849

Two instances of successful transfusion, both administered during leg amputation, are documented from the Civil War.



Joseph Lister, Lord

1827-1912

Founder of aseptic surgery

1867

Uses antiseptics to control infection during transfusions

The Nineteenth Century

- **Transfusions in the 1800s were plagued by the complications of transfusion reactions.**

- **Panum and Landois showed that same species transfusions were more efficacious than interspecies transfusions.**

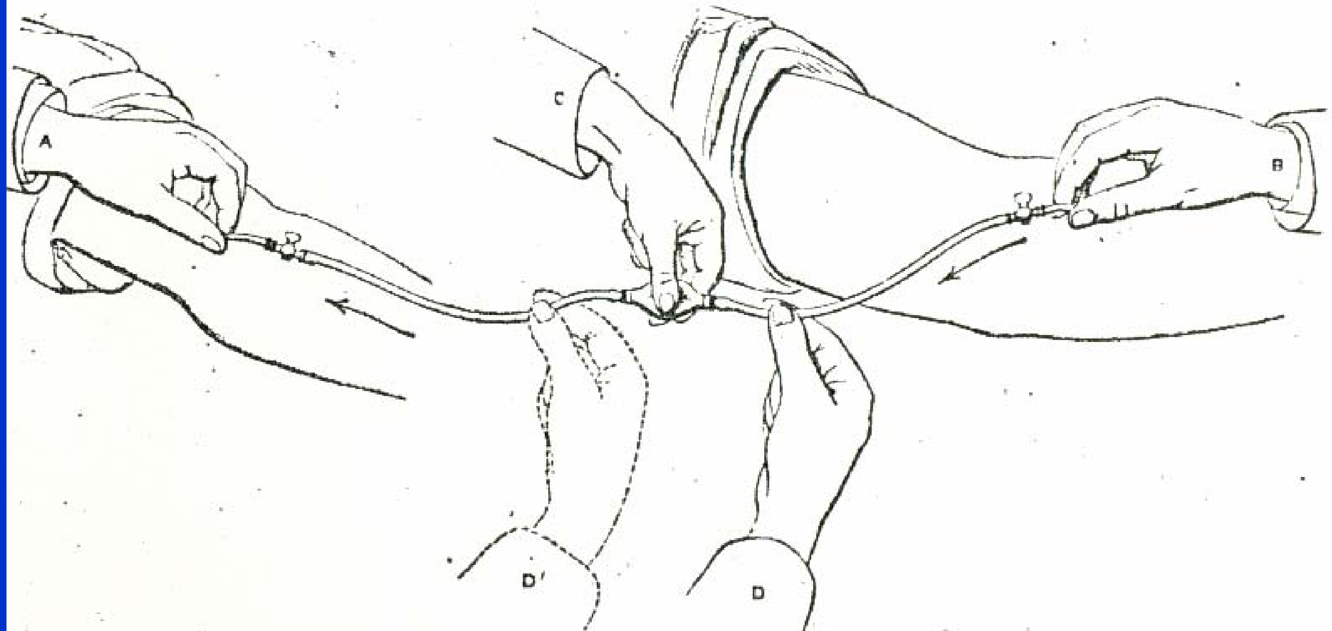
- **Landois noted that in interspecies transfusion red blood cells were hemolyzed and white blood cells would cease their amoeboid motion and die.**

- **Nonetheless, animal to human transfusions were performed as late as 1890.**

Fig. 24.—Roussel's apparatus in use during the Franco-German War.

Advances in technology

FIG. 3.



METHOD OF TRANSFUSING.

B represents the hand of an assistant holding the efferent tube and the lips of the small wound together, and A shows the afferent tube secured in the same manner. The india-rubber portion of the apparatus, filled with water, and kept so by turning the cock at each end of it, is now fitted into the two tubes. The cocks are then turned straight, and the operation commenced by compressing the india-rubber tube on the efferent side D, and squeezing the bulb C; this forces two drachms of water into the afferent vein. Next shift the hand D to D' and compress the tube on the afferent side, then allow the bulb to expand slowly, when blood will be drawn into it from the efferent vein.

Fig. 16.—Aveling's method, 1873.

1873

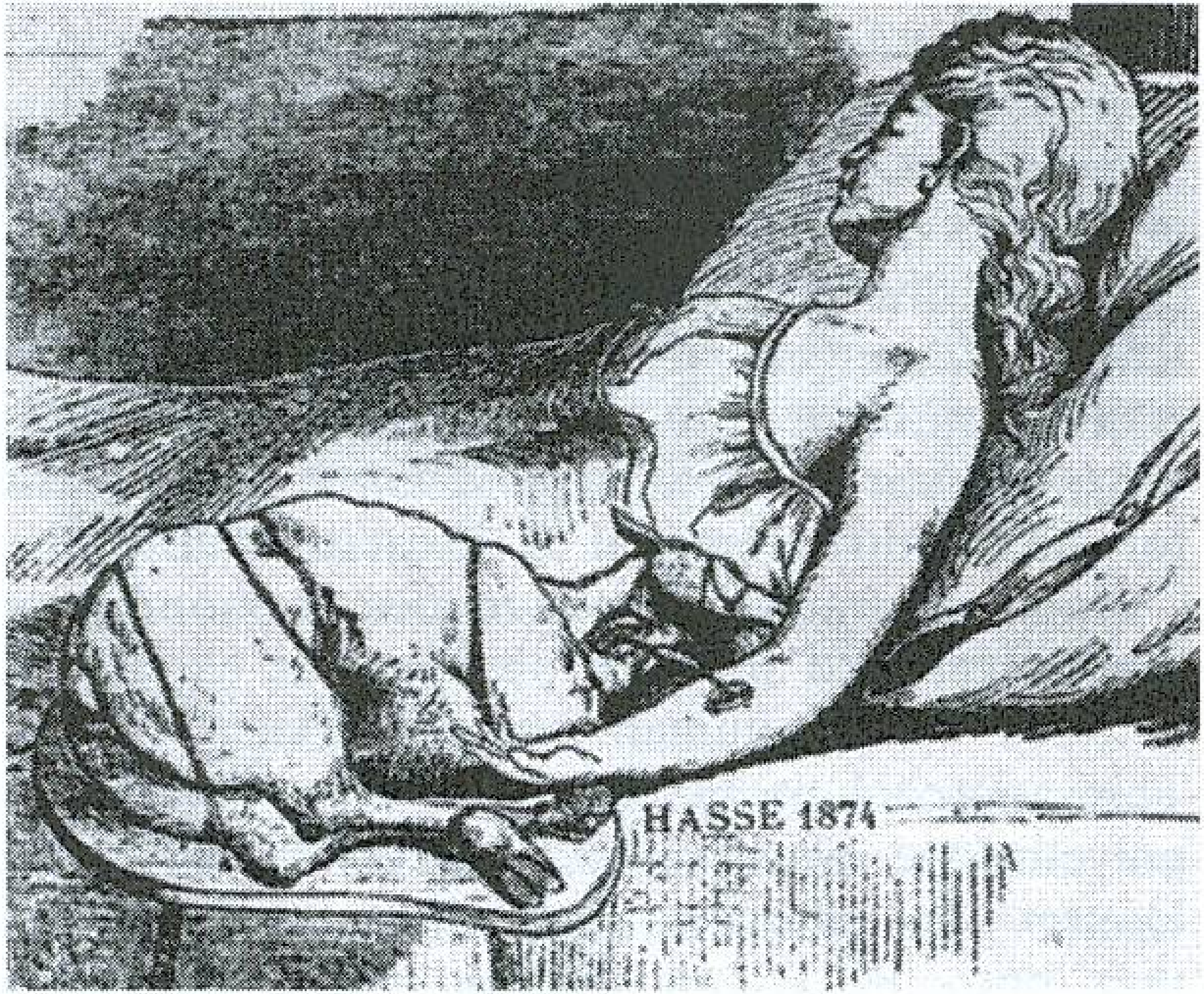


Fig. 6. A woman receiving blood from a sheep from *Die Lammblut-Transfusion beim Menschen* (1874) by Oscar Hasse [40].

In 1875, Landois*, in a comprehensive monograph on transfusion, collected 347 cases in which human blood had been used and 129 cases in which animal blood had been used. By this time, important studies on the physiology of the blood were being performed by a number of qualified observers, and some physicians, such as Fordyce Barker, advocated transfusion " ... not exclusively in those desperate cases where favorable results are hardly looked for but ... before patients have arrived at, and fallen into, this desperate condition."

Techniques in use included transfusion with defibrinated blood, mediate transfusion with pure blood, immediate transfusion from vein to vein, and immediate transfusion from artery to vein.

Although the indications and rationale of blood transfusion were by this time apparently quite well understood, the indications during the last quarter of the century again became vague and irrational, the procedure was employed indiscriminately, and the number of severe reactions and fatalities increased. As a result, transfusion again began to be considered as a hazardous, and even a disreputable, procedure, to be employed only as a last resort and in desperation.

*Landois, L.: DIE TRANSFUSION DES BLUTES. Leipzig: F. C. W. Vogel, 1875.

From BLOOD PROGRAM IN WORLD WAR II (SUPPLEMENTED BY EXPERIENCES IN THE KOREAN WAR) by Douglas Blair Kendrick. Washington, D.C.: Office of the Surgeon General, Department of the Army, 1989. (Provided by the Office of Medical History, Office of the Surgeon General/US Army Medical Command.)

“Human blood only should be employed…When lamb’s blood is used, an invariable result seems to be the escape, through the kidneys, of haemoglobin…”

Fagge & Pye-Smith, Textbook of Medicine, 1891

Anticoagulation:

Bischoff, 1835, proposed using defibrinated blood. Brown-Sequard also experimented with defibrination in the 1850s. Accomplished by whipping or twirling the blood, then removing the clot and transfusing the remaining fluid.

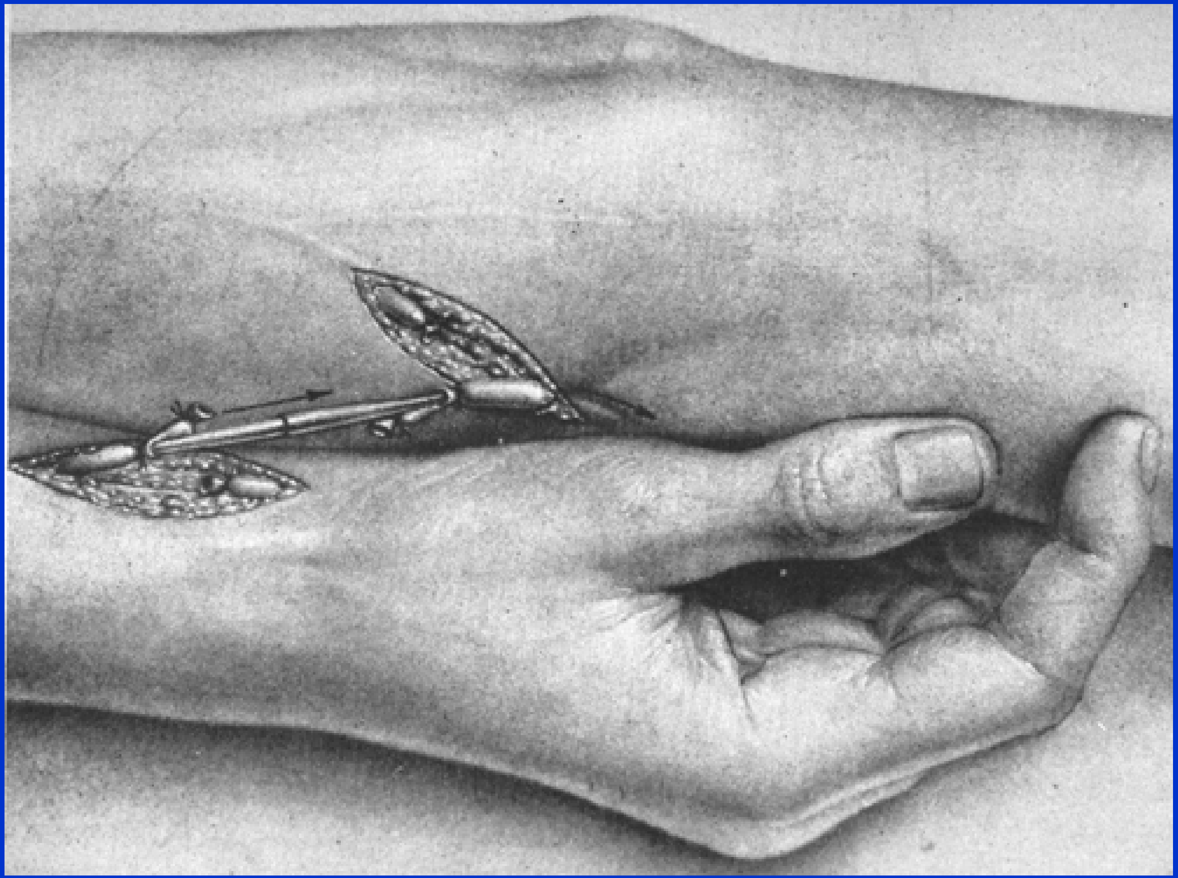
Neudorfer, 1860, used sodium bicarbonate

Braxton-Hicks, 1868, used Na phosphate

But transfusion was generally by:

- **Artery to vein cannulation**
- **Paraffin-coated tubes**

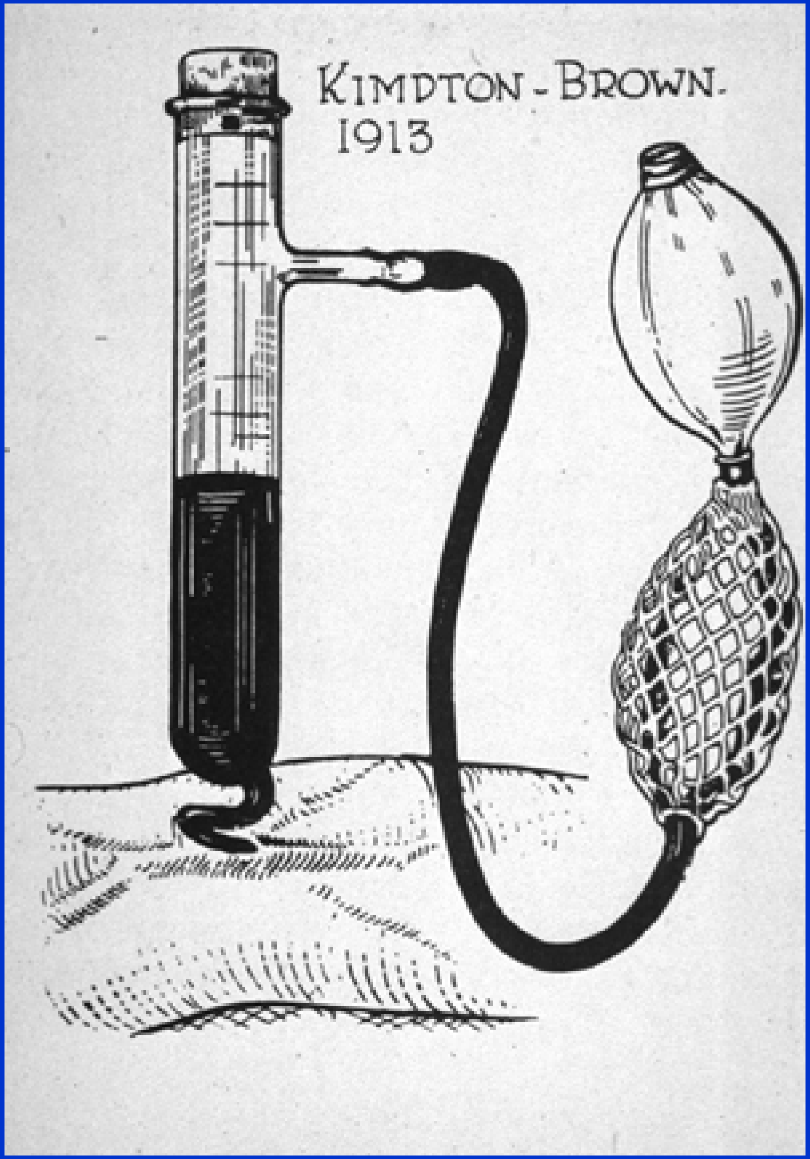
Direct transfusion (artery to vein for speed) advocated



1908:

French surgeon Alexis Carrel devises a way to prevent clotting by sewing the vein of the recipient directly to the artery of the donor. This vein-to-vein method practiced by a number of physicians, but was impractical.

(Did pave the way for organ transplantation, for which Carrel received the Nobel Prize in 1912)



The Kimpton-Brown transfusion apparatus was commonly used before citration. It consisted of a paraffin-coated gradient glass cylinder with a horizontal side tube for suction. It was in use until approximately 1918.

The Nineteenth Century

Saline used as blood substitute in 1884.
Saline infusion was observed to be safer than, and frequently as effective as, blood transfusion.

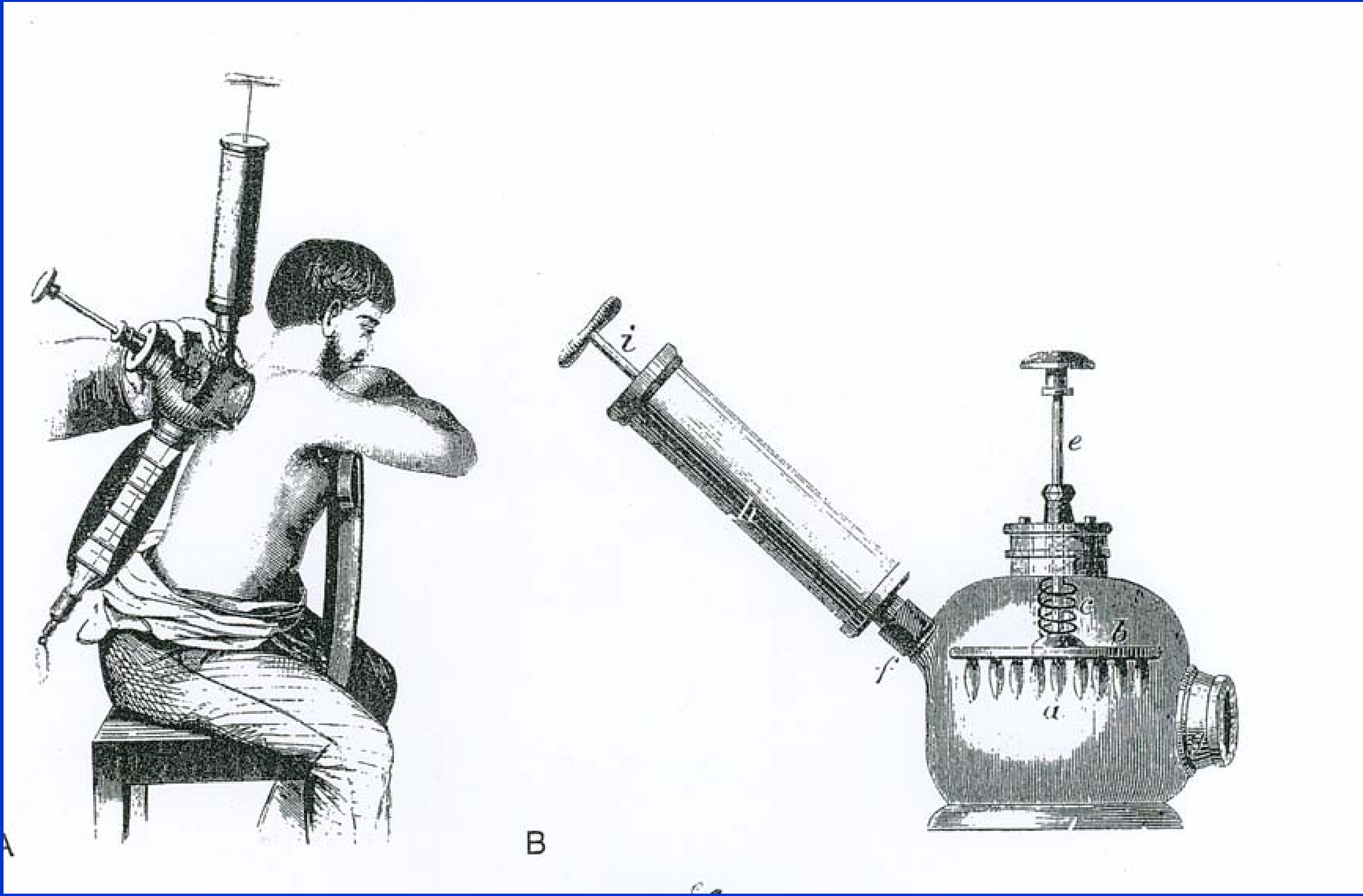
Milk was advocated as a potentially effective infusion, because it was thought that the “white corpuscles of milk were capable of being transformed into red blood corpuscles.”

Because of difficulty with coagulation, milk was used extensively as a blood substitute in the USA in the final quarter of the C19th

The complications of transfusion and logistical problems in obtaining blood led to a search for safer, more readily available substitutes. For example,

James Bovell & Edwin Hodder (Canadian Journal, 1855) transfused fresh cow's milk for treatment of patients during the cholera epidemic in Toronto in summer of 1854.

"…in a few seconds the pulse was distinctly felt…almost simultaneously, the eyes and…the lungs responded to the vital tide which now flowed toward them…the voice, which was unearthly before, was clear…"



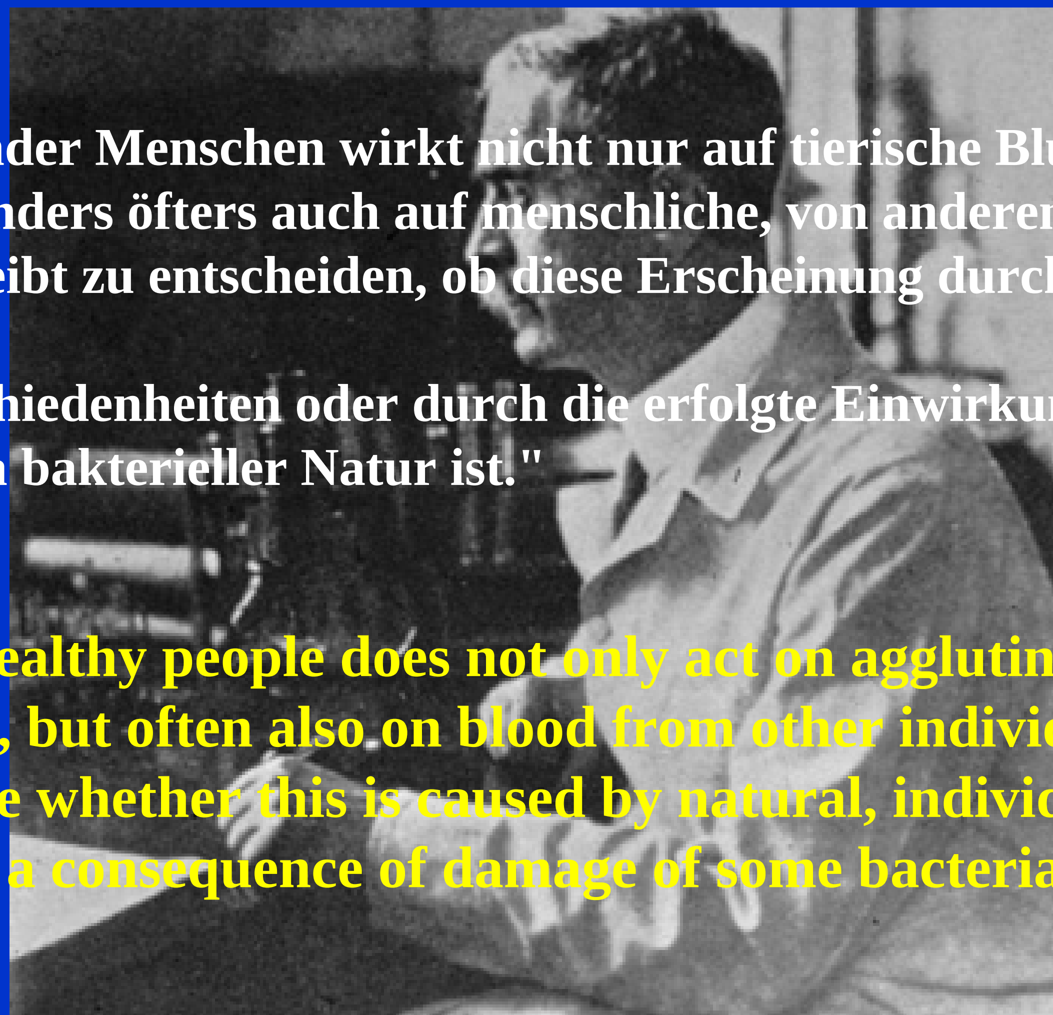
Gesellius, 1870s, capillary blood donation

Karl Landsteiner

1930 Nobel Prize Laureate

In 1900, Landsteiner showed that serum from some individuals could agglutinate or hemolyze the red blood cells of certain, but not all, other individuals. The serum of the latter would likewise agglutinate the red blood cells of the former. Still other individuals' red cells were unaffected by the serum from either of these. He named these three different types A, B, and C. Today these are types A, B, and O.

K. Landsteiner: *Zur Kenntnis der antifermentativen, lytischen und agglutinierenden Wirkungen des Blutserums und der Lymphe.* Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten. 1900, 27: 357-362.



"Das Serum gesunder Menschen wirkt nicht nur auf tierische Blutkörperchen agglutinierend, sonders öfters auch auf menschliche, von anderen Individuen stammende. Es bleibt zu entscheiden, ob diese Erscheinung durch ursprüngliche individuelle Verschiedenheiten oder durch die erfolgte Einwirkung von Schädigungenetwa bakterieller Natur ist."

"The serum of healthy people does not only act on agglutinating animal blood corpuscles, but often also on blood from other individuals. It remains to decide whether this is caused by natural, individual differences or as a consequence of damage of some bacterial nature.

Zur Kenntnis der antifermentativen, lytischen und agglutinierenden Wirkungen des Blutserums und der Lymphe.

[Aus dem pathol.-anat. Univ.-Institute des Prof. Weichselbaum in Wien.]

Von Dr. **Karl Landsteiner** in Wien.

I. Zur Serumdiagnostik der Fermente.

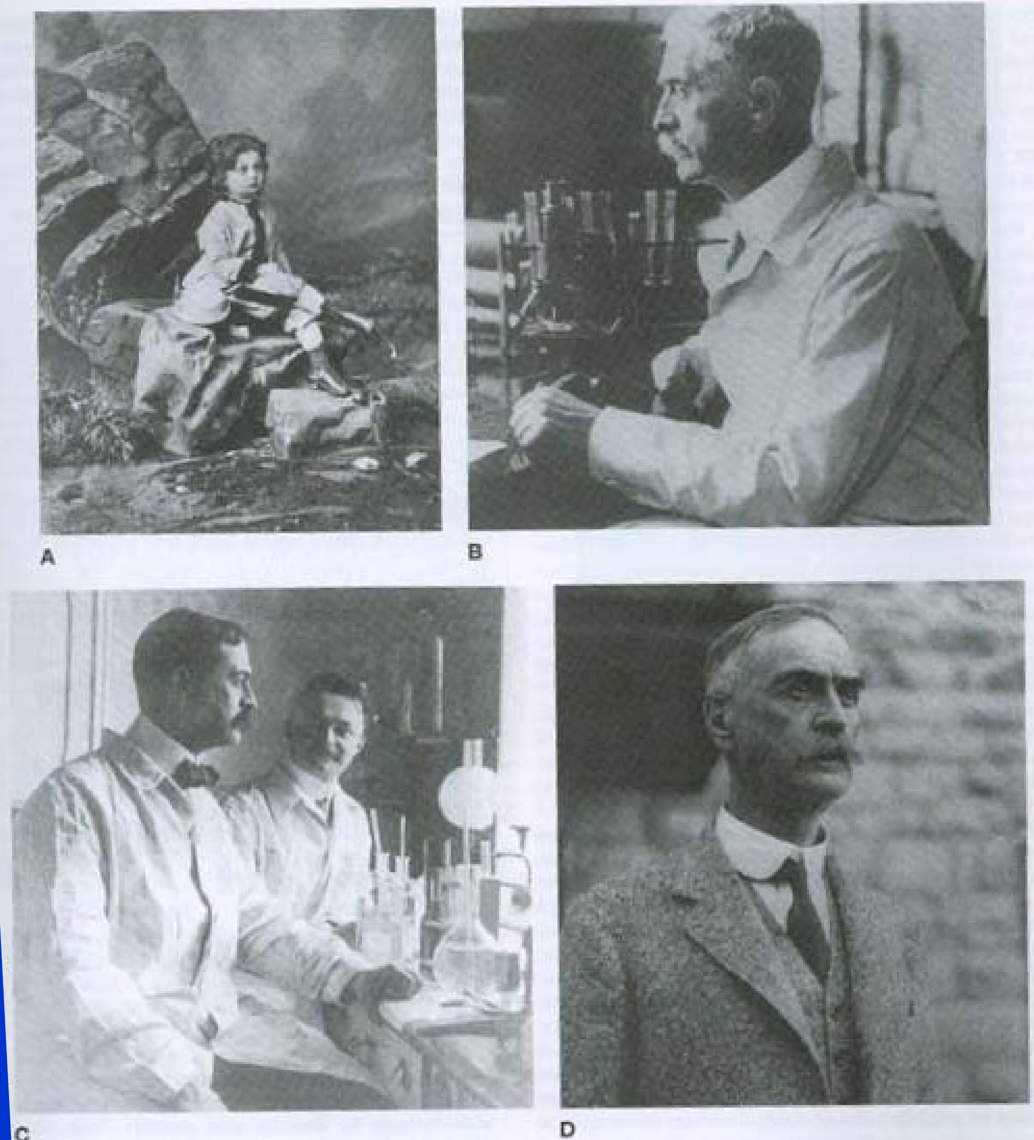
Durch die Arbeiten von Fermi[1]), Pernossi[1]), Hammarsten, Hahn[2]), Röden[3]), Hildebrandt[4]) und Morgenroth[5]) wurde festgestellt, daß dem Blutserum die Fähigkeit zukomme, die Wirkung mancher Fermente aufzuheben. Fermi und Hahn führten ihre Untersuchungen an verdauenden Fermenten aus, Röden und Morgenroth am Labenzym.

Die Hoffnung, dieses eigentümliche Verhalten des Serums zur Untersuchung der Fermente benutzen zu können, ist leicht begreiflich, und es hat Morgenroth[6]) Versuche in Aussicht gestellt, die mit Hilfe der Einwirkung von Serum beweisen, daß im Lab verschiedene wirksame Gruppen vorhanden sind. In anderer Weise versuchte v. Dungern[7]) die antifermentativen Serumwirkungen zu verwerten, indem er Tiere mit verschiedenen Mikrobien immunisierte und zeigte, daß das resultierende Serum spezifisch gegen die Fermente der eingeführten Bakterien wirke. Es handelt sich in diesen Versuchen also um eine Art von Serodiagnostik von Bakterien auf dem Umwege über ihre Fermente. Wie es scheint, ist eine praktische Verwertung dieses Verhaltens bis jetzt nicht erzielt worden.

Versuche, die ich anstellte, gingen darauf aus, das Serum als Hilfsmittel zur Unterscheidung solcher tierischen Fermente zu benutzen, die auf anderem Wege keine Differenzen erkennen lassen. Ich wählte das tryptische Ferment als Objekt der Untersuchung. Dabei ging ich von der Vermutung aus, daß die gleich benannten Fermente verschiedener Tierspecies ebenso jeder Art eigentümlich sein könnten wie die wirksamen Serumstoffe, die Hämoglobine und gewisse andere Bestandteile der roten Blutkörperchen und tierischen Zellen überhaupt.

Die Erkenntnis der gesetzmäßigen Besonderheit sehr ähnlicher, zunächst nicht unterscheidbarer Stoffe bei den verschiedenen Species gelang bisher zum Teil durch chemische Untersuchung, namentlich durch die Serumreaktionen, andererseits führten physiologische und morphologische Ueberlegungen zu ähnlichen Schlüssen. So hat erst vor kurzem Rabl[8]) auf Grund der Erfahrungen bei Transplantationsversuchen und seiner Untersuchungen über den Bau der Linse des Auges auf die Konstanz der Unterschiede homologer Strukturen bei den verschiedenen Tierspecies hingewiesen.

1) Zeitschr. f. Hyg. Bd. XVIII. u. a. a. O.
2) Berl. klin. Wochenschr. 1897. p. 499.
3) Cit. nach Hahn.
4) Virch. Arch. Bd. CXXXI.
5) Centralbl. f. Bakt. etc. Bd. XXVI. No. 11, 12.
6) l. c.
7) Ref. Münch med. Wochenschr. 1898. p. 1040.
8) 71. Versamml. deutscher Naturforscher.



RE 1-4. Karl Landsteiner at various times in his life. (*A*) Landsteiner at about the age of 5 (c. 1873), posing in a Husars riding costume on the pho-
pher's papier-maché rocks. (*B*) Photograph of Landsteiner probably taken at the Institute for Pathological Anatomy, where he worked from 1897
07. (*C*) Landsteiner and his coworker, Emil Prášek from Belgrade, December 1913. The two worked together on the chemical manipulation of the
ficity of serum albumin. (*D*) Landsteiner at about the time he left Europe for the United States. (From Mazumber MH: Species and Specificity: An
pretation of the History of Immunology. Cambridge, UK: Cambridge University Press, 1995.)

Compatibility testing

Landsteiner pointed out the importance of his findings in his original paper (1900)

Ottenberg and Schultz were the first to apply this information in an actual transfusion (1907)

In 1911, Hektoen suggested that blood groups be made the basis for selection of donors for blood transfusion.

World War I experiences led to the universal adoption of blood typing to select blood donors.

Reuben Ottenberg

Appointed the George Blumenthal, Jr. Fellow in pathology in 1908, Dr. Reuben Ottenberg served Mount Sinai Hospital with distinction for 50 years and became one of its most productive physicians in the first half of the 20th century. Born in New York, Ottenberg received his B.A. from Columbia University in 1902 and his M.D. degree from the College of Physicians and Surgeons three years later.

Ottenberg's first paper, "Transfusion and Arterial Anastomosis" (ANNALS OF SURGERY, 1908), won the prize for the best paper of the year by a member of the house staff. Ottenberg describes an experimental study of performing sutureless arterial anastomoses utilizing tiny silver rings held in place by silver wire, rather than sutures, in animals for use in direct transfusion and then describes its use in two patients being transfused. He notes that the blood was tested for compatibility prior to use; the first report anywhere of the clinical use of compatibility testing. Years later Dr. Ottenberg was to note, ***"The subject is only brought in incidentally in a footnote. I was still an intern and did not realize how important the testing was to become. I should have made a separate article."***

In 1923, Ottenberg reported that jaundice and hemolytic anemia of the newborn might be due to blood incompatibility of mother and child. Landsteiner's & Levine's discovery of the Rh factor almost 20 years later proved Ottenberg correct. He was also the first to suggest that human blood groups are inherited according to Mendel's law, and described a new method of counting platelets using sodium citrate, a technique that remained in standard use for decades.

Ottenberg also wrote important papers based on his clinical work, including on the diagnosis of painless jaundice, the toxic effect of sulfonamides, and septicemia following trauma. Suffering from stenosis of the internal carotid artery, Ottenberg reported his own case in 1955, four years before his death. In a matter of fact manner, he described his TIAs, his episodes of amaurosis fugax, and the stroke from which he recovered.

In 1954, Ottenberg received the Karl Landsteiner Award of the AABB for ‘distinguished pioneering contributions to blood banking & hemotherapy’. After noting his many contributions the award went on to state *‘Everyone of these were milestones in the growth of our knowledge of blood groups and formed the basis for the subsequent development of blood transfusions’*

- **1908**
- **Moreschi: the antiglobulin reaction**

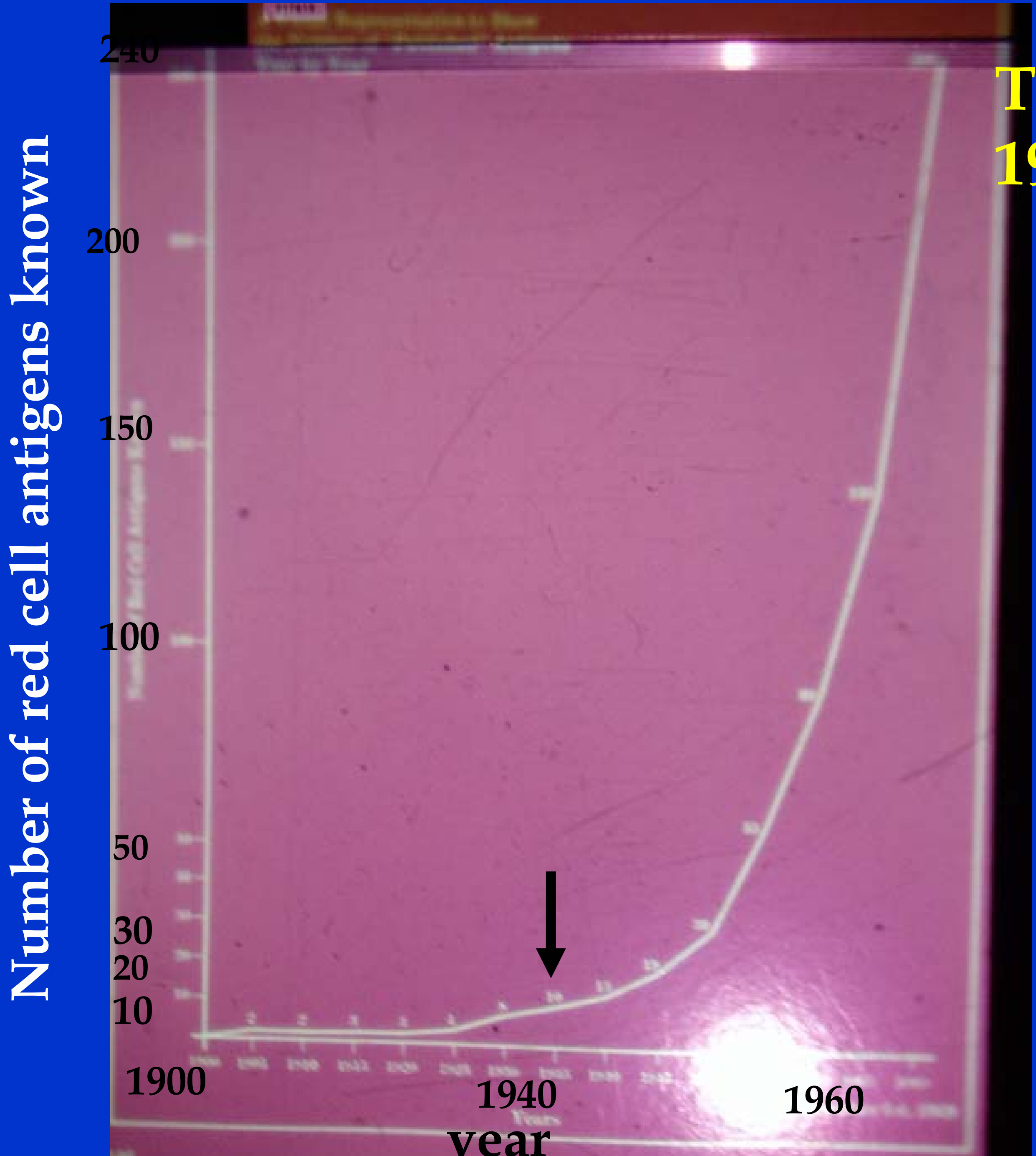
Blood Typing

Sturli and DeCastello described the fourth blood group, AB, in 1902.

Levine and Stetson, in 1939, describe 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, in 1940, describe Rh typing. This leads to dramatic decrease in the incidence of hemolytic disease of the newborn.

Over 250 different antigens categorized into 23 major discrete systems are now known.



To Sept 1, 1969 = 249

Why do we have blood group antigens on our red cells ?

“Hangover” is more pronounced in persons of group A; members of group B defecate the most (Warnowsky, 1927)

Increased incidence of group B among criminals (Bohmer 1927)

Persons of group O have the best teeth, followed by AB, while A and B persons have the worst (Suk, 1930)

Group O individuals have less satisfactory strength of character and personality…group B individuals are impulsive (Schaer, 1941)

Other associations were made with homosexuality, lesbianism, platonism, sadism and flat feet.

Wood et al, Nature, 1972

Anopheles Gambiae (species A from Nkolmekok, Cameroon) is selective in its feeding habits: extracted blood from mosquito's gut and typed it.

Persons who are group O had a mean of 5.045 bites on their forearms; persons who are group A had a mean of 3.276 bites

Giles et al, Nature, 1973

Group A2 highest IQ, then group O, then A1 phenotype

Statistical association of ABO blood groups with disease:

Malignancy:

stomach, colon, rectum, salivary glands, uterus, cervix, ovaries

Other diseases:

pernicious anemia, cholecystitis, rheumatic disease, peptic ulcer

Loss of ABH antigens from malignant cells

Appearance of new and ‘illegitimate’ ABH/Lewis/Ii antigens on malignant cells

Association of ABH/Lewis/Ii antigens with CEA

Association of ABO with bleeding and with clotting

Bacterial infections (also other blood group associations)

Proven relationships of blood groups with disease:

- Hemolytic disease of the newborn/fetus
- Autoimmune hemolytic anemia
- Hemolytic transfusion reactions
- Graft rejection and ABO antibodies
- Early abortion and P system antibodies

Neonatal/fetal alloimmune thrombocytopenia

Post-transfusion purpura

RBC morphology	Transmembrane protein
Acanthocyte	Kx polypeptide
	Lutheran polypeptide
Elliptocyte	glycophorin C and D
Stomatocyte	Rh polypeptides

Urea transport and Jk(a-b-) phenotype

PNH and glycosylphosphatidylinositol (GPI)-anchored proteins (Cromer, Gy^a, Hy, Yt^a, JMH, Do^a and Do^b

Intestinal disorders and Inab phenotype

SLE and Chido-negative, Rogers-negative phenotype

Malaria resistance with the Fy(a-b-) phenotype

In Japan: Toronto Star, 26 June, 1991

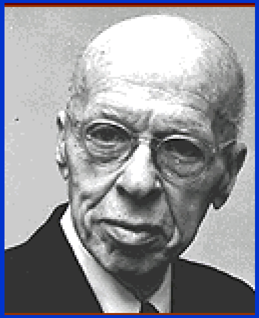
Type A: cautious, eager to please, indecisive, sympathetic and conformist

Type B: decisive, known for originality and versatility, are occasionally obnoxious and stand out in a crowd

Type O: produces team leaders, confident and cool-headed people, who meet challenges with courage, but may be domineering and moody

Type AB blood is said to produce complex, mysterious folks with tendency to eccentricity and talent for specialized fields

Lewisohn



- In 1913, Richard Lewisohn, a surgeon at the Mount Sinai Hospital, introduced the modern technique of blood transfusion, developed from his discovery of a method of preventing coagulation of the blood outside the body. Dr Howard Lilienthal, who performed the first transfusion on a human using Lewisohn's citrate method, wrote: The ease and simplicity of this transfusion was most amazing to me, who had so often suffered more than the patient in performing this life-saving operation.

- Lewisohn was educated in Germany and received his medical degree from the University of Freiburg in 1899, with a doctors thesis on "Malignant Tumors of the Kidney." In 1906, he immigrated to New York, and after obtaining his medical license, joined the staff of the Mount Sinai Hospital. He retired in 1937.

Anticoagulation:

1914, 1915: sodium citrate as anticoagulant:

Belgium, Argentina, New York (Lewisohn)

1915: refrigeration

1916: Rous & Turner: salt, citrate, glucose solution

1940's: minor modifications by DeGowin, Alsever, etc

1943: Loutit & Mollison: ACD; adopted by the army in 1945

WWI: O Robertson: creates blood depots: 1st blood bank

First World War posters

Oswald Robertson

After his house officership he was appointed as an assistant in bacteriology and pathology at the Rockefeller Institute for Medical Research, where he planned to continue his studies on the physiology of blood in the laboratories of Peyton Rous. He moved to New York in the autumn of 1915, but he had barely started his experiments on reticulocytes when World War I called for his services on the Harvard team of Dr Harvey Cushing. In France, his early interests in hematology stood him in good stead as he was assigned the task of seeking better ways of reducing the risks of excessive transfusions. At the same time he initiated experiments to learn whether a fluid devised by Rous in the laboratory to preserve human blood cells "in vitro" had a practical use for transfusions at the battle front and in military hospitals. He demonstrated that the preserved cells were indeed an acceptable substitute, and Robertson now is recognized as the creator of the first blood bank. For this work he received decorations from both the American and British governments and was discharged in 1919 from the U.S. Army after attaining the rank of major.

Early transfusions were a complex affair

First transfusion St. Michael's Hospital, Toronto, 1917

Percy Oliver

In October 1921, in his capacity as honorary secretary of the Camberwell Branch of the Red Cross, he received a telephone call from nearby King's College Hospital. They were in urgent need of a blood donor and sought his help. He and a few colleagues went to the hospital, and from them Sister Linstead, a Red Cross worker, was chosen, becoming the first voluntary blood donor.

The results of this exercise so impressed Oliver that with the help of his wife he set about devising and organizing a system for a panel of donor volunteers. The donor's health and blood details were checked by the hospital and kept on record cards in his home, where there was continuous telephone cover. In the first year there were 4 members of the panel and they had one call; 5 years later there were 400 members and > 700 calls. Oliver was convinced that organized panels of volunteer donors were the answer and he worked hard at setting up similar panels, particularly in London, with the help of groups such as St. John Ambulance and the Rover Scouts. To cope with the organization and the paper-work it was also necessary to move to a larger house -- 5 Colyton Road, Camberwell. Much of his free time was spent travelling around the country, explaining the system, and encouraging the formation of yet more local groups of volunteers.

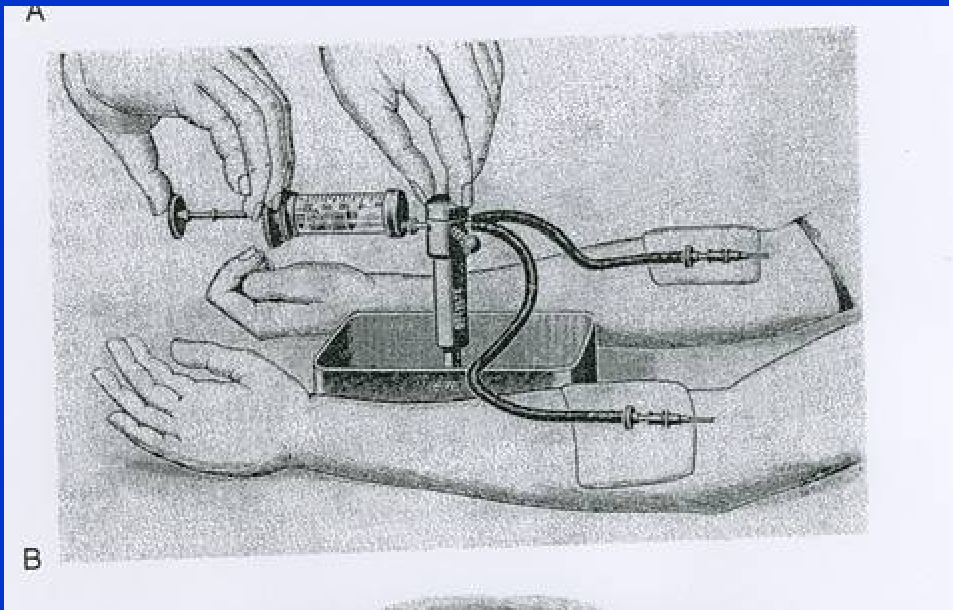
Although on its inception in 1921 Oliver called it the London Blood Transfusion Service, it was really a voluntary donor service for local hospitals. It progressed to the stage where the official support of the British Red Cross Society was considered essential. This was forthcoming and in 1926 it became the British Red Cross Blood Transfusion Service, later changed to the Greater London Red Cross B.T. Service and eventually developed into the National Blood Transfusion Service. General hospitals were not charged for the service and no payment was ever made to, or expected by, the donors. The expenses of running the organization from the house in South London were met by charging private clinics, by grants from institutions, and by Oliver's own efforts.

Oliver had the support of many eminent surgeons and doctors, but there were others who resented this intrusion into medical preserves by a layman. Many donors had to keep their involvement secret from families and employers, and as recently as 1940 Percy Oliver was still travelling the country trying to dispel apprehensions and encourage the supply of donors and the setting up of panels.

Oliver's work attracted attention worldwide and many countries sent representatives who sought and acted upon his advice on setting up similar organizations. 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 doctors in the First World War, had been brought to the fore in the Spanish Civil War. This was to become the basis of the war-time blood bank which Oliver helped to create at Luton in 1939. Surprisingly, Oliver received no official recognition for his work in the development of voluntary blood donor panels, although in later years he was invited back to Buckingham Palace to talk with the King about his work.

Percy Lane Oliver died on April 16, 1944, but his achievements are not forgotten. A memorial consisting of a portrait and a panel with an appropriate inscription was unveiled in the entrance hall of the hematology department of King's College Hospital, London, in 1972 by Her Royal Highness The Duchess of Gloucester. A framed copy of this is in every Regional Transfusion Centre in Britain, and another is in the Donor Centre in Rome, bearing a suitable translation. In 1979 the Greater London Council provided an appropriate plaque on the house in South London where so much of Oliver's work was undertaken.

More advances



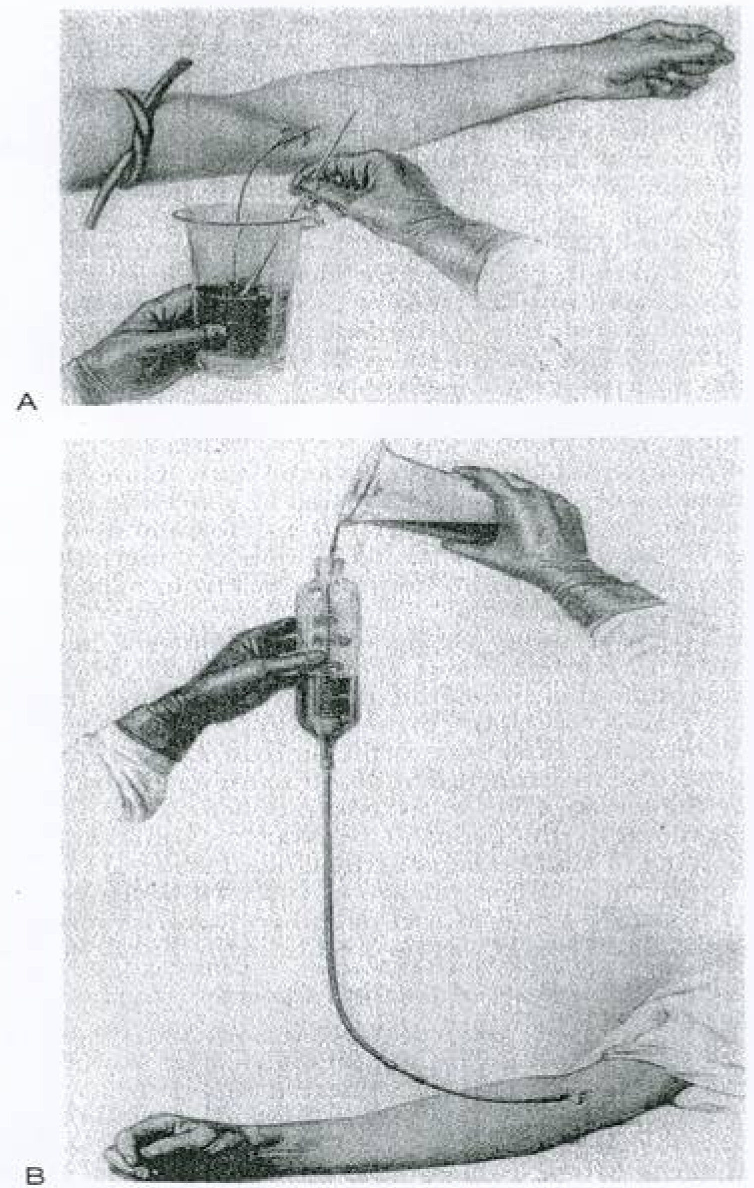


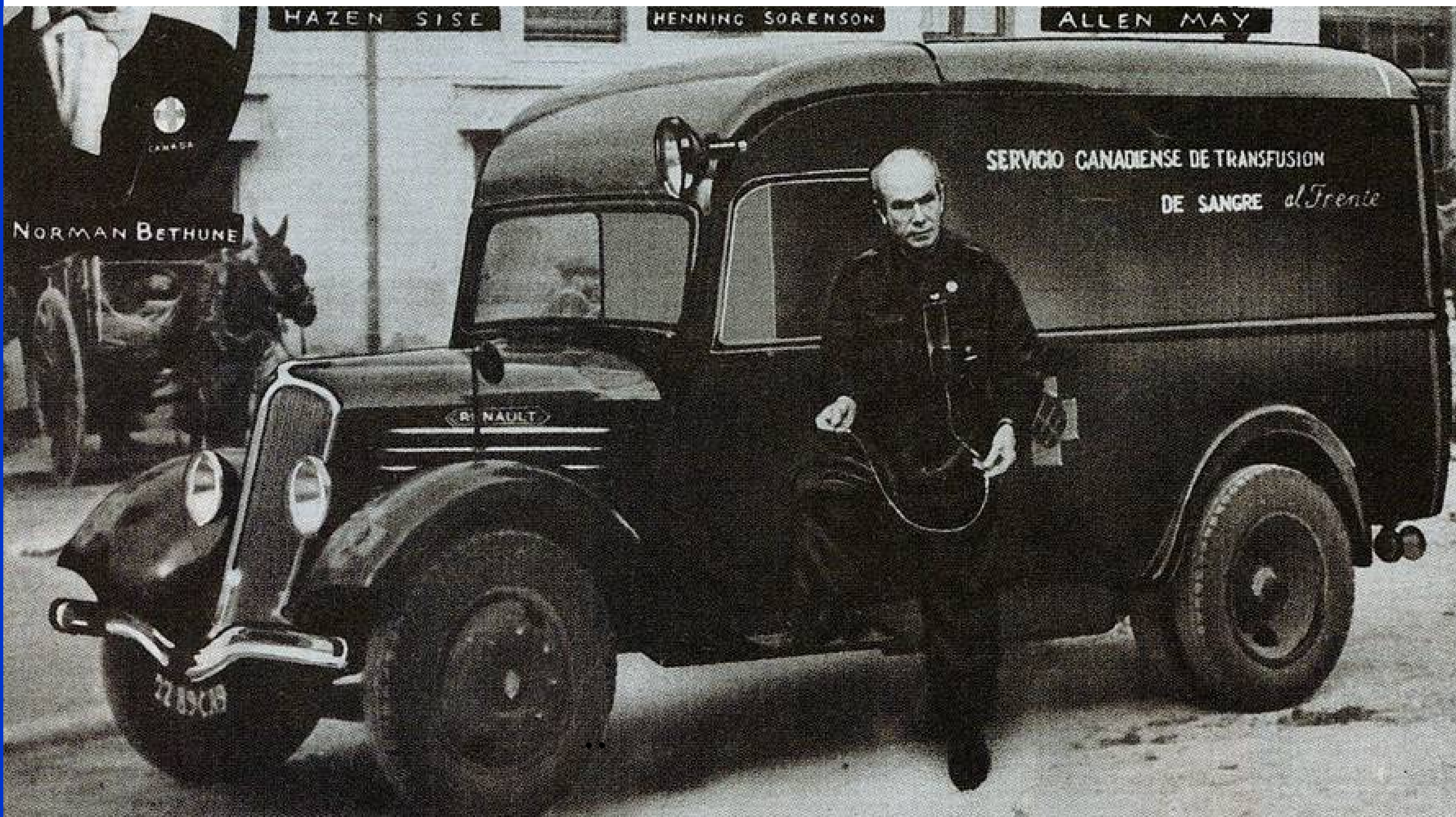
Fig. 2-13. Lewisohn's method of transfusion of citrated blood. **(A)** Blood is collected in a graduated flask and **(B)** is promptly transfused to the patient. (From Lewisohn,[69] with permission.)

Alternative sources of blood:

Cadaver blood, Russia, 1938

Placental blood, Lancet, 1939

- **First Blood Bank formulated in Leningrad in 1932**
- **First functional blood bank in Barcelona, 1936**
- **First transfusion service in the field: Spanish Civil War, 1937-1939 *[Norman Bethune]* .**



Born: March 3, 1890 in Gravenhurst, Ontario, Canada
Died: November 12, 1939 in Huang Shikou, Heibei, China

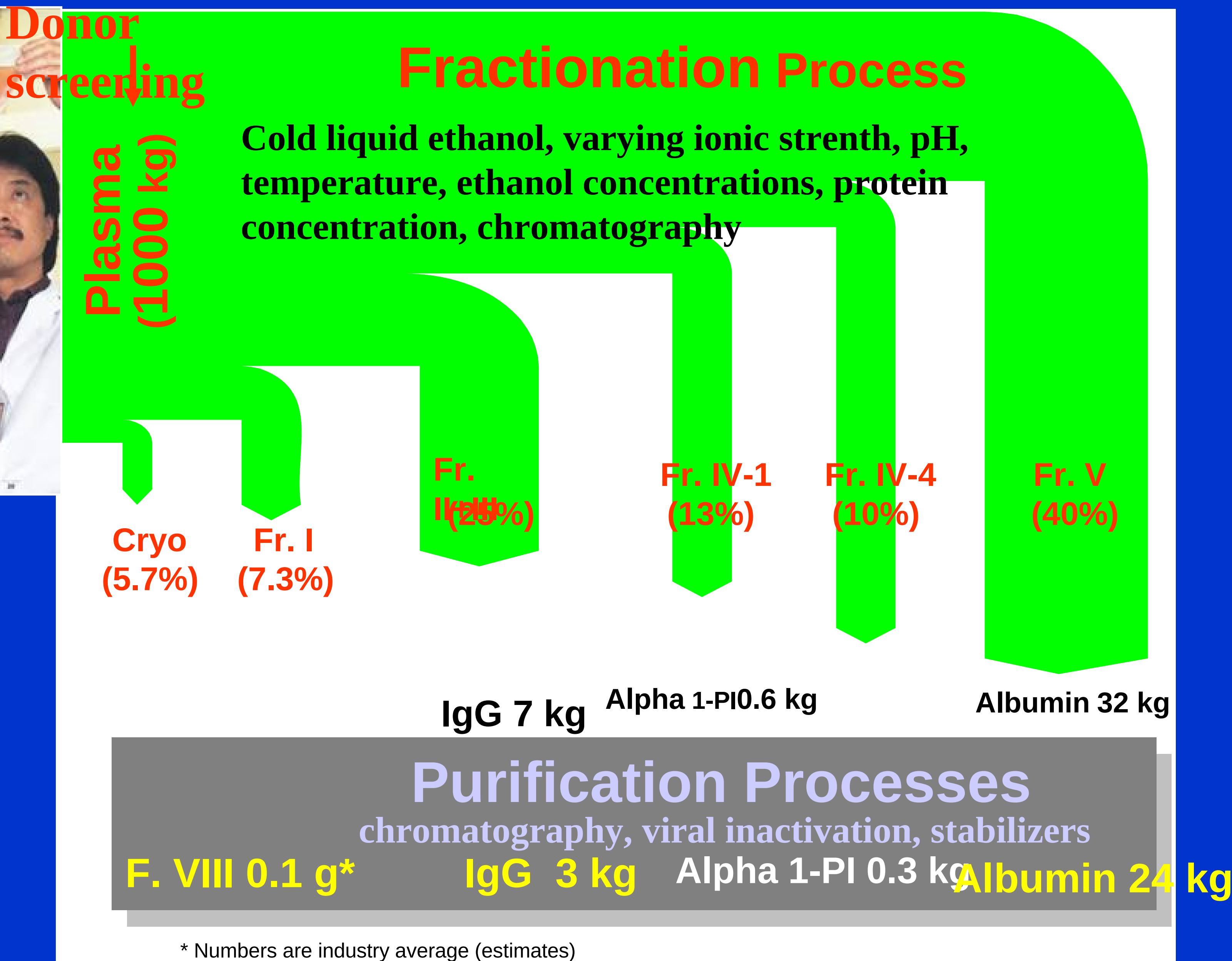
- Bethune's death received little attention in Canada or in China until the Cultural Revolution (1966-1976). During that decade of social and political upheaval the Chinese Communist leadership used Bethune as a symbol of selflessness, dedication, and responsibility -- characteristics that they wanted the Chinese people to adopt. They published hundreds of millions of copies of an essay written by Mao Zedong called "In Memory of Norman Bethune." Everyone was expected to read it, and many committed it to memory. Since the 1960s through books, movies, and study in the schools, Bethune has become a national hero in China.

  In Canada, belated recognition was granted in 1972 when the federal government declared him "a Canadian of national historical significance." The Presbyterian manse in which he was born was restored to period and a portion of it converted into a museum. It was opened in 1976 as the Bethune Memorial Home.

1940: Edwin Cohn at Harvard develops cold ethanol fractionation, allowing separation of plasma components e.g. albumin, γ globulin, fibrinogen.

1940: Charles Drew develops the "Plasma for Britain" program in the USA.

Overview of Material Flow



- Charles R. Drew was a renowned surgeon, teacher, and researcher. He was responsible for founding two of the world's largest blood banks. Because of his research into the storage and shipment of blood plasma -- blood without cells -- he is credited with saving the lives of hundreds of Britons during World War II. He was director of the first American Red Cross effort to collect and bank blood on a large scale. In 1942, a year after he was made a diplomat of surgery by the American Board of Surgery at Johns Hopkins University, he became the first African American surgeon to serve as an examiner on the board.

In 1928 he was finally able to apply to medical school. However, African Americans who wished to become doctors at that time did not have many opportunities. There were two colleges open to them. Drew applied to Howard University and was rejected because he did not have enough credits in English. Harvard University accepted him for the following year, but he did not want to wait so he applied to and was immediately accepted to McGill University in Montreal, Canada.

At McGill, Drew continued to excel in sports and academics. In 1930 he won the annual prize in neuroanatomy and was elected to Alpha Phi Omega, the school's honorary medical society. During this time, under the influence of Dr. John Beattie, a visiting professor from England, Drew began his research in blood transfusions. The four different types of blood -- A, B, AB, and O -- had recently been discovered. Subsequently, doctors knew what type of blood they were giving to patients and were avoiding the negative effects of mixing incompatible blood types. However, because whole blood was highly perishable, the problem of having the appropriate blood type readily available still existed. In 1930 when Drew & Beattie began their research, blood could only be stored for seven days.

- In 1933 Drew graduated from McGill with his Medical Degree and Master of Surgery degree. He interned at the Royal Victoria Hospital and finished his residency at Montreal General. During this time, he continued researching with Beattie.

- Because of his father's death in 1934, Drew decided to return to Washington, D.C., to take care of his family. In 1935 he accepted a position to teach pathology at Howard University Medical School. The next year he obtained a one-year residency at Freedmen's Hospital in Washington, D.C.

- In 1938, having accepted a two-year Rockefeller Fellowship, Drew continued his work in blood at Columbia University-Presbyterian Hospital in New York. Under the auspices of the Department of Surgery, he worked with Drs John Scudder and EHL Corwin on the problem of blood storage. Drew began to study the use of plasma as a substitute for whole blood.

- In 1939, while supervising a blood bank at Columbia Medical Center, Drew developed a method to process and preserve blood plasma so that it could be stored and shipped to great distances. (Dehydrated plasma could be reconstituted by adding water just before the transfusion.)

- Drew graduated from Columbia University in 1940, with a Doctor of Science degree, the first African American to receive this degree. In his dissertation, "Banked Blood: A Study in Blood Preservation," Drew showed that liquid plasma lasted longer than whole blood. He was asked to be the medical supervisor on the "Blood for Britain" campaign, launched by the Blood Transfusion Betterment Association. 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.

- 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. However, when the military issued a directive to the Red Cross that blood be typed according to the race of the donor, and that African American donors be refused, Drew was incensed. He denounced the policy as unscientific, stating that there was no evidence to support the claim that blood type differed according to race. His statements were later confirmed by other scientists, and the government eventually allowed African American volunteers to donate blood, although it was still segregated. Ironically, in 1977 the American Red Cross headquarters in Washington, D.C., was renamed the Charles R. Drew Blood Center.

- First blood bank in USA at Cook County in 1937 (actually recently shown to be at the Mayo Clinic in 1935*)
- First large-scale blood transfusion service: World War II
- National Blood Transfusion Service in England: 1946

*Transfus Med Rev 19:241, 2005

Before 1939:

- 3 blood group systems – ABO, MN, P
- 3 known plasma proteins – albumin, euglobulin, pseudoglobulin
- Complement was only a vague entity
- No Coombs test

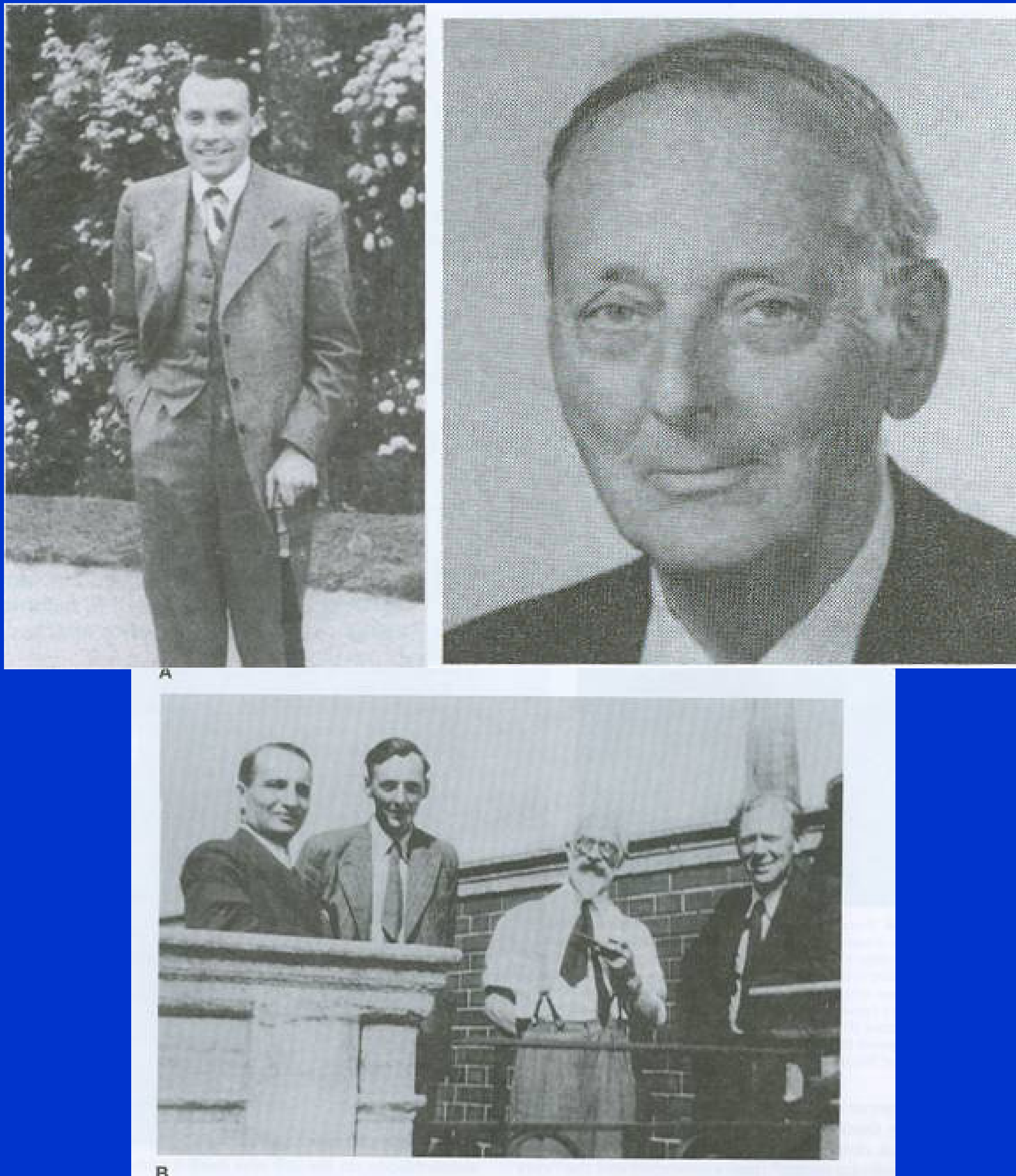


FIGURE 1-25. *[A)* Patrick Mollison. (8) A 1947 photograph taken at the Lister Institute in London showing, from left to right: Louis K. Diamond whose research clarified the pathogenesis of hemolytic disease of the fetus and newborn as well as the optimal management of that disorder; Patrick L. Mollison, a pioneer in the field of blood transfusion and editor of ten editions of the famous text, *Blood Transfusion in Clinical Medicine;* Robert R. Race, an eminent immunohematologist who, along with his long-time collaborator. Ruth Sanger. made innumerable contributions to the field of RBC genetics and serology; and Sir Ronald A. Fisher. a famous geneticistjbiostatistician who, together with Race, devised a classification of the Rh blood group system that is still used. [Courtesy of Professor P. L. Mollison.)

In 1939, red cell storage was 7 days (sodium citrate)

Extended to 21 days in ACD (1943)

28 days in CPD (1957)

35 days in CPD-adenine (1965)

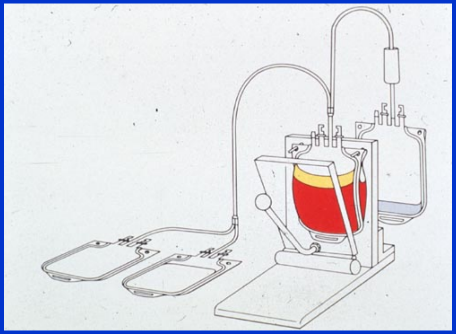
49 days in Adsol (increased glucose, mannitol)

1960s: Cryoprotective agents, e.g. glycerol, provide the technology to freeze and reclaim cells i.e. long-term storage.

In 1939, there was just whole blood and plasma

The extension of blood component therapy was one of the great advances of the last 50 years

Plastic Blood Bags



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 a common complication due to the vacuum systems used with glass bottles.

In 1949, trials of plastic bags were conducted by the American Red Cross [Walter].

Plastic bags were disposable and, because of their flexibility, facilitated the safe separation of blood components and the advent of component therapy.

At least 17 different components are available through a blood bank.

Preservation

ACD preservative was supplanted by citrate-phosphate-dextrose (CPD) in 1957, CPD with adenine in 1965, and CPD-A1 in the 1980s.

Effective preservation and refrigeration lead to the ability to bank blood.

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

In less than 30 years, Rh hemolytic disease of the newborn moved full cycle, from hypothesis to prevention

Mid 1950s: In response to increased demand created by open heart surgery and advances in trauma care, blood transfusion enters its most expansive growth period.

1961: Platelet concentrates: reduces mortality in cancer patients

1969: Platelets stored at room temperature

1962: AHF to treat hemophiliacs

1965: cryoprecipitated AHF for hemophilia treatment

1967: Rh immune globulin commercially introduced for HDN

Major Innovations in the 20th Century

Compatibility testing

Anticoagulant preservative solutions

(1943: ACD: Loutit & Mollison: allowed reduced volume of anticoagulant, longer storage and larger volumes of blood to be transfused;

1983: shelf life red cells 42 days)

Refrigeration

1945: Coomb, Mourant & Race: Antiglobulin test

Blood Banks (1947: AABB formed)

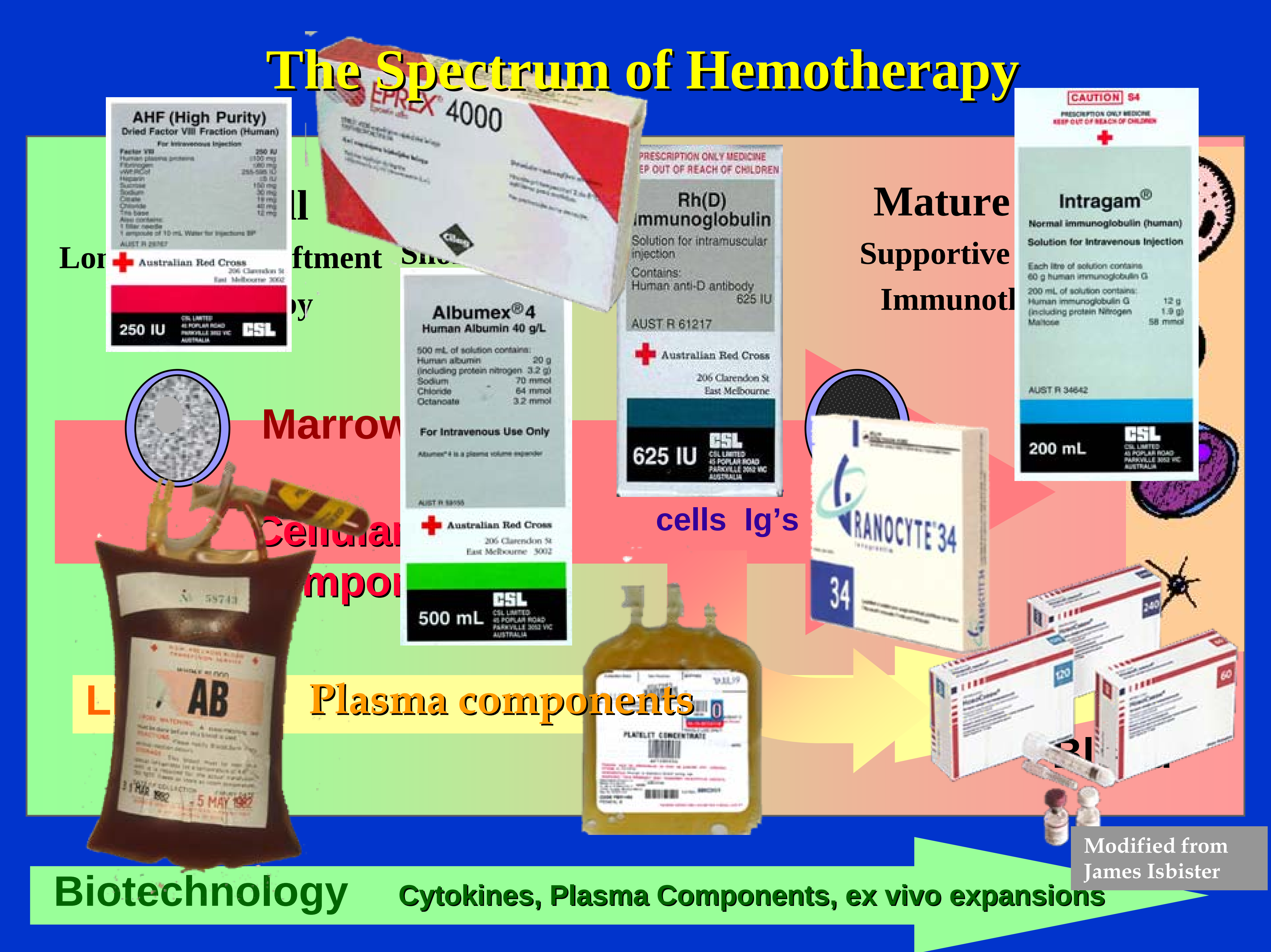
Plasmapheresis: for collecting plasma for fractionation (1964)

Plastic blood bags (Walter & Murphy, 1950)

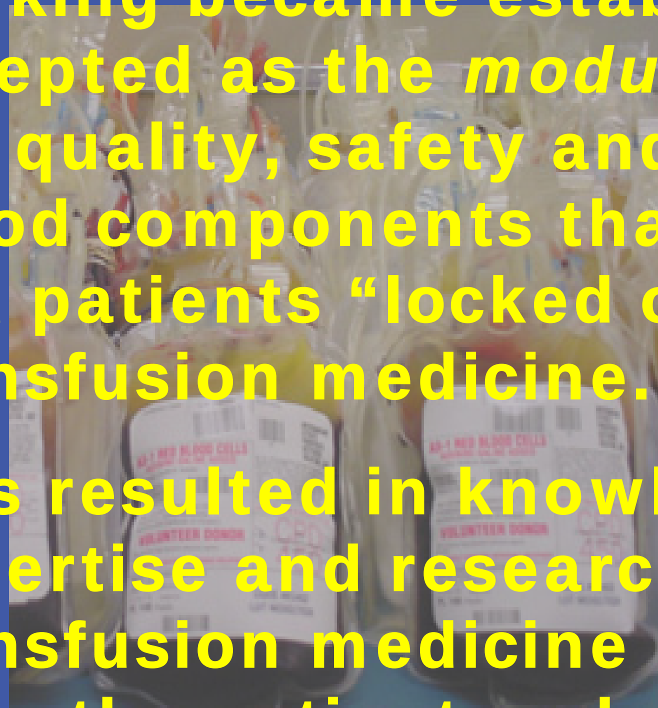
Component administration

Infectious disease testing (1943: Beeson: transfusion-transmitted hepatitis; 1971: HBsAG testing begins)

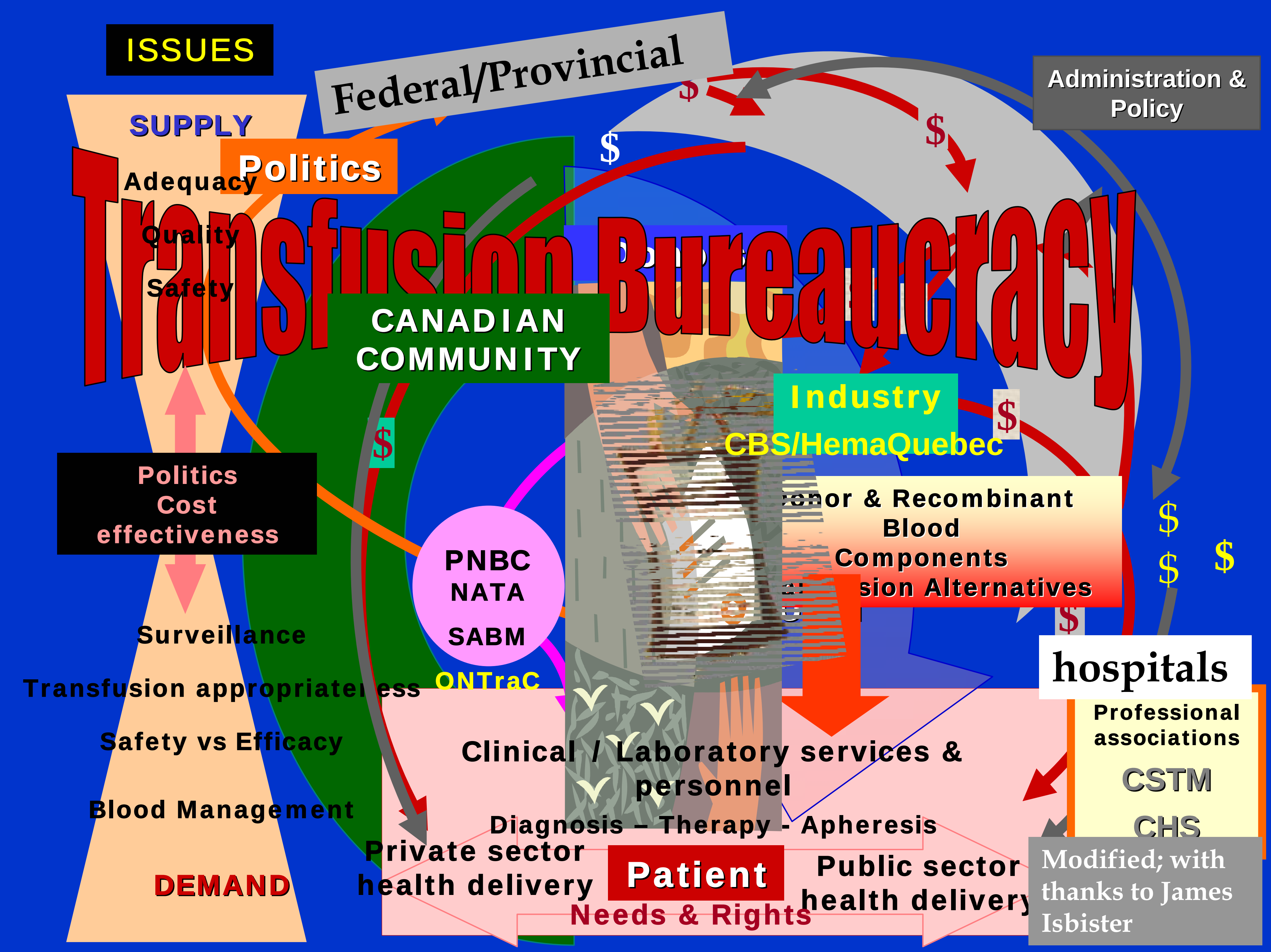
High-risk donor screening (1985: HIV screening test; 1987: anti-HBc, ALT)


The Spectrum of Hemotherapy
AHF (High Purity)
Dried Factor VIII Fraction (Human)
For Intravenous Injection
Australian Red Cross
250 IU
CSL
EPREX 4000
Rh(D) Immunoglobulin
Solution for intramuscular injection
Contains: Human anti-D antibody 625 IU
AUST R 61217
625 IU
Mature
Supportive
Immunot
Intragam®
Normal immunoglobulin (human)
Solution for Intravenous Injection
200 mL
Albumex®4
Human Albumin 40 g/L
For Intravenous Use Only
500 mL
Marrow
Cellular
cells Ig's
RANOCYTE 34
AB
Plasma components
PLATELET CONCENTRATE
Biotechnology
Cytokines, Plasma Components, ex vivo expansions
Modified from James Isbister

Ironically, it was when blood banking became established and accepted as the *modus operandi* for the quality, safety and supply of blood components that clinicians and patients “locked out” of transfusion medicine.



This resulted in knowledge, expertise and research of transfusion medicine moving away from the patient and clinical workface, focusing less on pathophysiology of disease and more on supply, safety and cost.


ISSUES
Federal/Provincial
Administration & Policy
SUPPLY
Politics
Adequacy
Quality
Safety
Transfusion Bureaucracy
CANADIAN COMMUNITY
Industry
CBS/HemaQuebec
& Recombinant
Blood
Components
Alternatives
Politics
Cost
effectiveness
PNBC
NATA
SABM
ONTraC
Surveillance
Transfusion appropriateness
Safety vs Efficacy
Blood Management
DEMAND
Clinical / Laboratory services & personnel
Diagnosis – Therapy - Apheresis
Private sector health delivery
Patient
Public sector health delivery
Needs & Rights
hospitals
Professional associations
CSTM
CHS
Modified; with thanks to James Isbister

21st century ???

Bloodless medicine/blood conservation/blood management

"Artificial" blood components and blood products

Pharmacologics

Error prevention

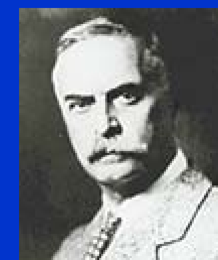
Adverse event prevention (including infectious)

Molecular techniques/nanotechnology

Proteomics/genomics

? ? ?

A brief history of transfusion



Jean-Baptiste Denis

1640 - 1704

Transfused humans with Animal blood

June 15, 1667

*James Blundell**

1770-1878

Transfused humans with human blood

Karl Landsteiner

Born 6/14/1868; died 6/26/1943

Discovered ABO and (with Levine) Rh blood systems

1900

1600 — **April 17, 1688** — *1800* — **1907** — *2000*

TRANSFUSION FORBIDDEN

By Paris Faculty of Medicine

BAN PERSISTED For 130 years!

First successful ABO-matched human-human transfusion at Mt Sinai hospital by Reuben Ottenberg

***Relied strongly on Leacock’s work in Caribbean**