Theory and Practice of Transfusion Therapy April 2021

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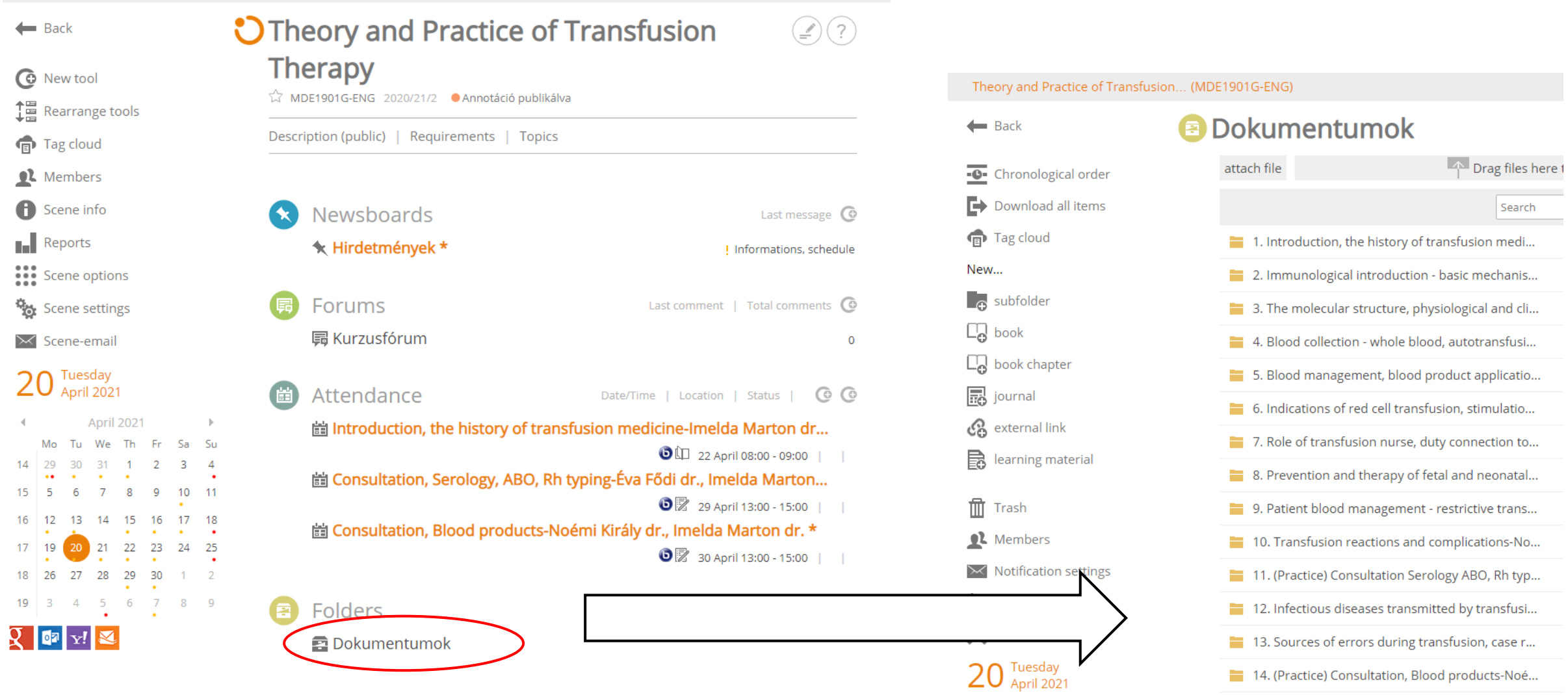
Slides, videos



Key information on slide (important to know!)

Homework : details in Newsboard: Hirdetmények

Exam: Coospace test exam (25 question)
Time:?

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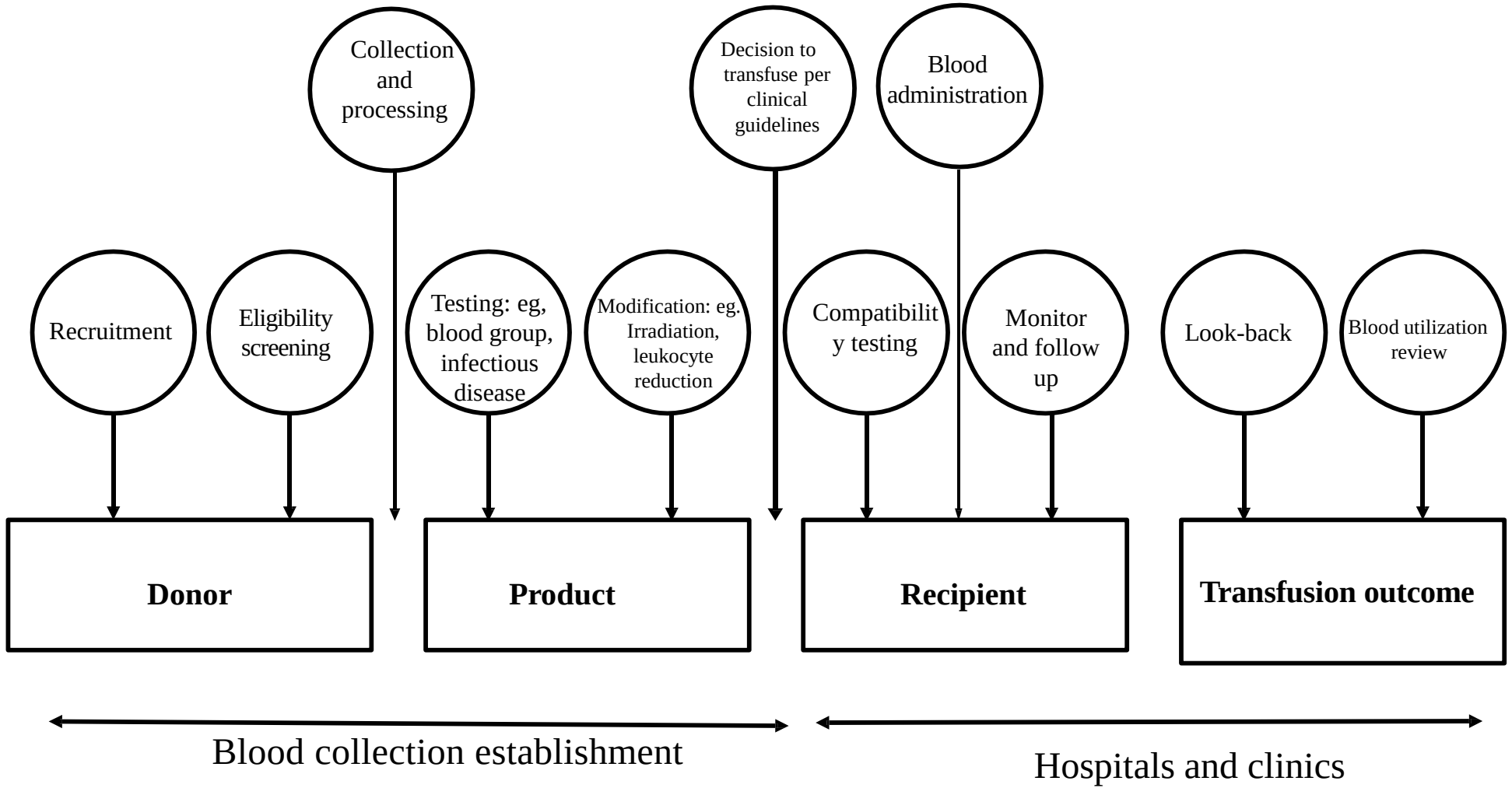
Introduction to transfusion medicine,

Transfusion medicine as a medical service

- The main focus of transfusion medicine is the provision and administration of generally allogeneic (occasionally autologous) blood products as a form of special, potentially life-saving medical treatment.



Transfusion medicine as product generation

- Strictly regulated – GMP (good manufacturing process), FDA, EMA;
- Outstanding role of quality control and assurance;
- A strong tend towards standardization
- Processes: donation+production+storage/transport+screening and quality tests;
- Unstable/stable blood products;
- Stem cell preparations: generation+storage.

Transfusion medicine as laboratory diagnostics

DONOR RECIPIENT

- Immunhematology diagnostics/blood group serology
  - Blood group typing
  - Antibody screen/identification
  - Compatibility testing
  - Molecular diagnostics
- Screening for infectious agents
- Related fields: (i) histocompatibility (HLA); (ii) coagulation. History: paternity/origin testing.

Transfusion medicine as patient care

- Clinical transfusion:
  - RBC,
  - platelet
  - FFP,
  - GRC
- Apheresis: (i) therapeutic, (ii) donation;
- Stem cell collection, storage, cell-therapy;
- Regenerative medicine.

Potential research projects in tranfusion medicine

- Epidemiology of special infectious agents: population, geography, temporal aspects;
- Frequencies of genetic varriants-population genetics;
- Recognition of new processes/phenomena in immunhematology;
- Case-series, clinical research.

Transfusion medicine facts (2015) from USA
AABB (American Association of Blood Banks)

- Number of blood donors: 6.8 million/year (32% first time),
- Number of blood units donated: 13.6 million (2013),
- Estimated daily need: 36000 RBC, 7000 platelet, 10000 plasma,
- Main donor eligibility criteria: older than 16 (no upper age limit), at least 110 pounds (50 kg),
- Significant population differences, USA:

U.S. FREQUENCIES (%) (ROUNDED TO THE NEAREST WHOLE NUMBER)

Phenotype	Whites	Blacks	Hispanic*	Asian**
O	45	50	56	40
A	40	26	31	28
B	11	20	10	25
AB	4	4	3	7

	Caucasians	Asians- China, Japan, Korea, Indonesia
RhD+	85-87%	>99%
RhD-	13-15%	<1%

Harmening ed. Modern Blood Banking 6th ed. 2012

Organisations involved in transfusion medicine

Blood banks:

- Usually centralized,
- In most countries, government controlled,
- Strictly regulated,
- High level of internal and external quality assurance,
- Many similarities (e.g. regulatory authorities) with pharmaceutical companies,
- Diverse activities besides blood collection processing and procurement.

Organisations involved in transfusion medicine: Sanquin, Netherlands (2015)

Key numbers (2017) of Sanquin and Hungarian National Blood Transfusion Service (HNBTS)

Indicator	Sanquin	HNBTS
Employees	2500	1400
Yearly budget	470 M EUR	46 M EUR
Yearly donation units handled	350 000	300 000
Research papers in PubMed – 2012-2018	1330	39
Population served	17 M	10 M

Professional societies in transfusion medicine

- International Society of Blood Transfusion (ISBT)
- American Association of Blood Banks (AABB) -- USA,
- British Blood Transfusion Society (BBTS) -- UK,
- Deutsche Gesellschaft für Transfusionsmedizin und Immunhämatologie (DGTI) -- Germany,
- Australian & New Zealand Society of Blood Transfusion (ANZSBT) – Australia,
- Hungarian Society for Hematology and Transfusion (MHTT)

Transfusion medicine as a medical speciality

Special fields to be covered:

- issues of blood donation,
- immunohematology and other laboratory testing,
- transfusion practices,
- therapeutic apheresis,
- stem cell collections,
- cellular therapy,
- coagulation,
- laboratory management
- understanding of state and federal regulations of blood products

• **USA**: sub-speciality within clinical pathology together with (i) clinical chemistry, (ii) hematopathology, (iii) clinical microbiology, (iv) cytogenetics and (v) molecular genetics.

• **UK**: sub-speciality of hematology.

• **Denmark**: sub-speciality within clinical immunology.

• **Norway**: independent basic sub-speciality: immunology & transf. medicine.

• **Germany, Austria & Hungary**: independent basic speciality to be obtained after obtaining M.D. (4 years).

History of transfusion medicine

- **1492: first historical attempt of blood transfusion.**

It was believed that the transfusion of blood from a young, healthy person into the aged or delibitated would restore youth and health.

Pope Innocent VIII sank into a coma, the blood of three boys (10 years old) was infused into the dying pontiff (probably through to mouth – concept of circulation and methods for iv. access did not exist at that time!).

The boys had been promised a ducate (money) each.

The attempt was unsuccessful: *all four involved died.*

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

- Ancient Greeks believed that blood was formed in the heart and arteries contain air.

- Galen (a prominent Greek physician, 131-201 AD) made many *animal dissections* → proved that arteries contain blood, but he thought that blood was formed in the liver.

- **1555: Andreas Vesalius (1514-1564, Italy)**

broke with medieval ideas about the anatomy of the circulatory system. He carried out *human body dissections.*

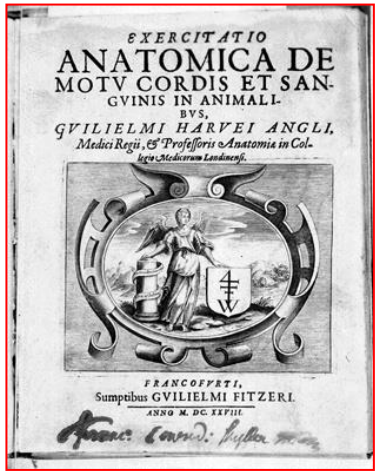
He is the founder of modern anatomy.

- **1628: William Harvey (1578-1657, England)**

discovered the circulation of the blood.

He published his treatise :

***De Motu Cordis* (1628).**


EXERCITATIO
ANATOMICA DE
MOTV CORDIS ET SAN-
GVINIS IN ANIMALI-
BVS,
GVILIELMI HARVEI ANGLI,
Medici Regii, & Professoris Anatomia in Col-
legio Medicorum Londinensi.
FRANCOFVRTI,
Sumptibus GVILIELMI FITZERI.
ANNO M. DC. XXVIII.

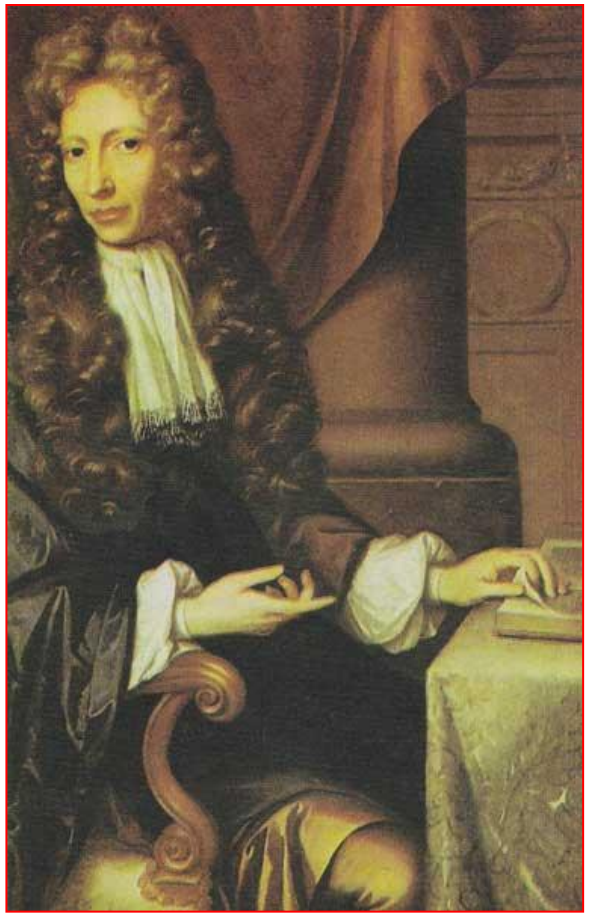
First iv. injections were done in 1656 (Oxford), by

Christopher Wren (1632-1723)

(astronomer, mathematician, architect)

Robert Boyle (1627-1691)

(physicist)



- **1665: Richard Lower (1631-1690, England)**

He performed the first documented blood transfusion *between animals* (dogs).

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

He recognised the appropriateness of transfusional replacement of blood in severe hemorrhage.

- **1667 (Jun. 15):**

Jean-Baptiste Denis (1635-1704, France) performed the first documented human transfusion *(animal blood into human*).

He transfused the blood of a sheep into a 15-year-old boy with a febrile illness, who had been bled many times. After the transfusion he *was recovered.*

Denis used the procedure on several other patients.

After the second transfusion of calf blood to a man Denis recorded the *first case of acute hemolytic transfusion reaction:*

„ 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 extremly 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 choak unless they gave him his liberty…When he awakened… He made a great glass full of *urine*, of a color *as black, as if it had been mixed with the soot of chimneys”.*

Denys perfomed calf blood transfusion into Mr. Antoine Mauroy (a 34-year-old madman). His madness seemed improved, so another transfusion was undertaken. He on the third account had died.

Denys was accused of his murder. *(In fact, Mr. Mauroy's wife poisoned her husband with arsenic).*

The Faculty of Medicine of Paris stated: the procedure of transfusion was a criminal act.
1670: French parliament forbade transfusion in France, it also was outlawed by Royal Society in London.
1679: the pope joined the outcry and banned the procedure.

Only sporadic efforts at transfusion were during the 17th and 18th century.

Transfusions of animal blood into humans (in the 1600's)

1667

To replace the patient's bad blood with good.

Armamentium Chirurgiae, 1693

In the Eighteenth Century:

Transfusions were done *only sporadically,* and were generally *animal to human.*

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

***Reciprocal transfusions* were suggested as a cure for marital discord.**

Blood was *thought to carry the 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.

Blood transfusion reborned only in the 19th century

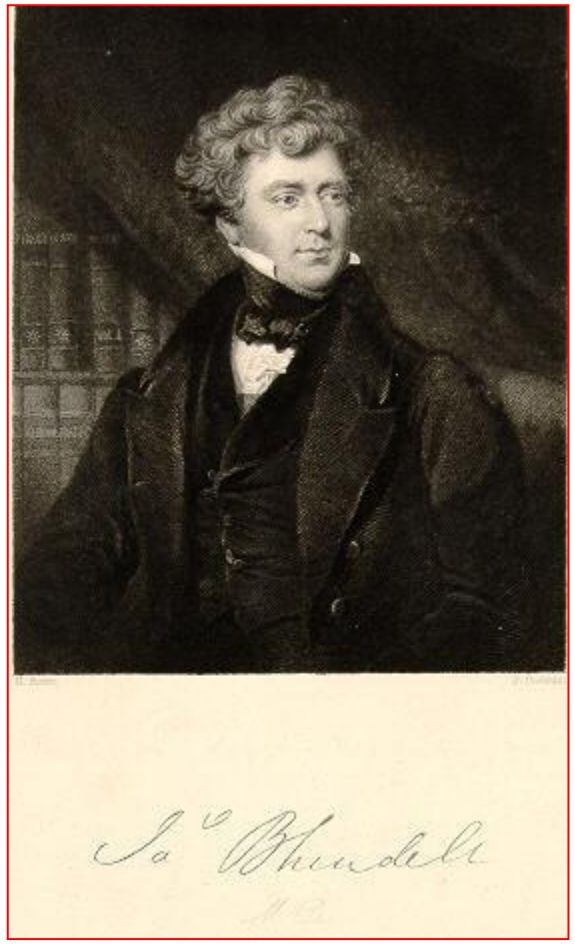
- **1818:**

James Blundell (1790-1877, obstetrician, England)

performed the first successful transfusion of *human blood.*

He transfused a 35-year-old man with gastric carcinoma. 14 oz (398 ml) of blood was administered by syringe in small amounts at intervals of 5-6 minutes.

Despite temporary improvement, *the patient died* 56 hours later.



Subsequently Blundell transfused several women with postpartum hemorrhage. He used the patient's husband as a donor. 5 from 10 transfusions was successfull.

He offered the use of human rather than animal blood for transfusion.

- **1840:**

Samuel Armstrong Lane,

(1802-1892)

aided by consultant Dr. Blundell, performed the first successful whole blood transfusion to treat hemophilia.

(St. George's Hospital Medical School, London)

Transfusion in Paris – 1874

(Hopital de la Pitie)

First photo about blood transfusion

1870. Bellevue Hospital, New York (O.S. Mason)

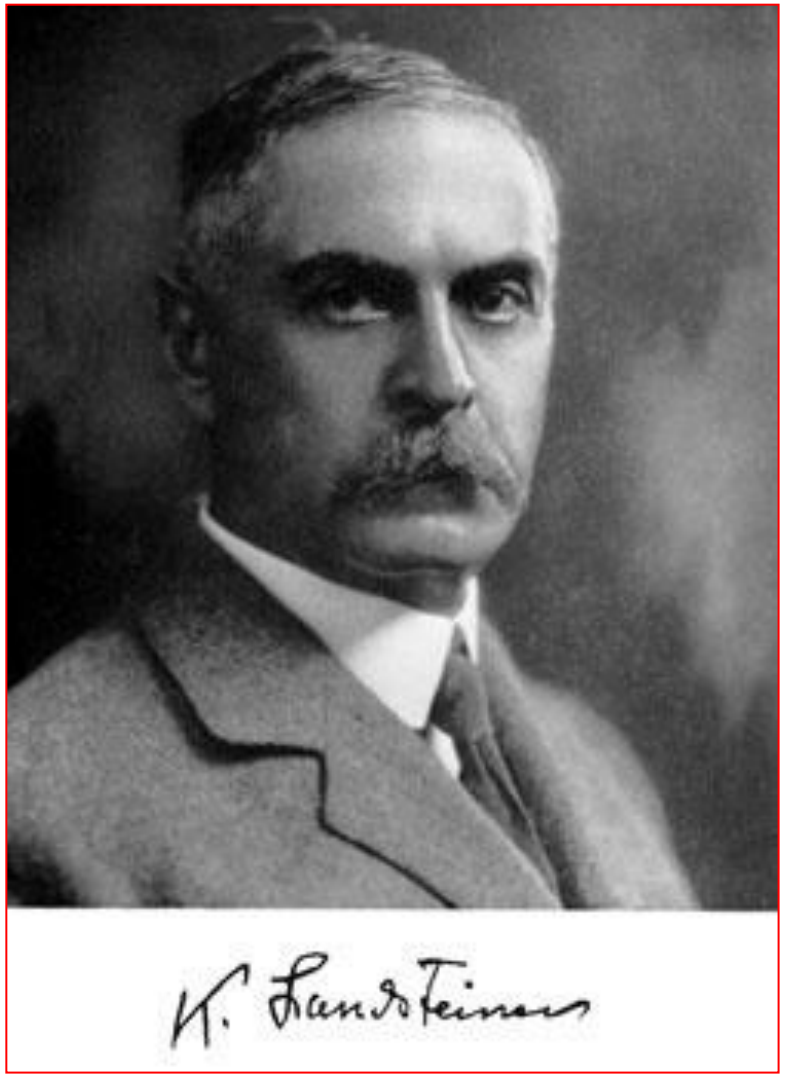
- **1901: Karl Landsteiner**

(1868-1943, Vienna)

He established the basis of modern transfusion.

Discovered of the three main human blood groups: A, B, C (C is later changed O)

(Wiener Klinische Wochenschrift, 14, 1132, 1901)



A Nobel Medal

For his discovery he got the Nobel Prize in Physiology or Medicine (1930)

1900, Discovery of ABO

Karl Landsteiner (1868-1943, Wien)

1930: Nobel Prize Laureate

translation

- Serum of some individuals (colleagues) could **agglutinate** or **hemolyze** the red blood cells of certain, but not all, other individuals**.**
- Specific reactivity pattern.
- Some RBCs do not react at all.
- New names of these three different types: **A, B, and C (today: O – „ohne”).**
- **AB** blood group was later described in 1902 by **Decastello & Sturli.**

First successful transfusion: New York, Mount translation Sinai Hosp. 1907

Further developments in blood typing: discovery of Rh

- **Landsteiner, Wiener, Levine and Stetson,** in **1939**, described Rh
- Severe reaction in a type O woman who received a transfusion of her husband's type O blood following a stillbirth.
- Her serum agglutinated 80% of type O blood.

translation

- This led to dramatic decrease in the incidence of **hemolytic disease of the fetus/newborn (HDFN)**.

Source: Lisa Louise Bradley, 2000

STUDIES ON AN AGGLUTINOGEN (Rh) IN HUMAN BLOOD REACTING WITH ANTI-RHESUS SERA AND WITH HUMAN ISOANTIBODIES.

By KARL LANDSTEINER, M.D., AND ALEXANDER S. WIENER,* M.D.

(*From the Laboratories of The Rockefeller Institute for Medical Research, and the Serological Laboratory of the Office of the Chief Medical Examiner of the City of New York, New York*)

(Received for publication, June 10, 1941)

From some observations made with immune sera, and particularly from the evidence provided by tests with occasionally occurring normal and post-transfusion human sera containing irregular agglutinins (*cf.* reviews in 1, 2) one can conclude that there exist individual properties of human blood other than those which are demonstrable by readily available reagents such as A_1, A_2, B, M, N. Doubtless numerous attempts have been made to discover additional agglutinogens by the familiar technique used for the demonstration of the factors M and N (3), that is, with immune sera prepared by the injection of human blood into rabbits, but only few results were obtained (*e.g.* 4, 5), and these were not followed up because it was difficult to produce the immune sera again. Other ways of approaching the problem were therefore desirable and it was thought that new results might be obtained by immunizing with animal instead of human blood, considering that the blood of some animals contains antigens related to agglutinogens present in individual human bloods, for instance the Forssman substance related to A in sheep cells. A result that favored this plan was the observation that certain anti-*rhesus* immune sera contain agglutinins specific for the human agglutinogen M (6).

Pursuing this idea, by immunizing rabbits with *rhesus* blood an immune serum was obtained with which an agglutinable factor different from A, B, M, N, or P was detected (7), and this new factor was designated as Rh to indicate that *rhesus* blood had been used for the production of the serum. The property was then found to be present in the blood of about 85 per cent of white individuals examined (7, 8).

Evidence that the property Rh is of clinical importance was obtained when one of the writers came into possession of blood samples from patients who had shown hemolytic reactions, one with fatal outcome, after receiving repeated

* One of the authors (W.) was aided in obtaining the human material by a grant from the Committee on Human Heredity of the National Research Council.

J. Exp. Med.

There are *reciprocal relation* between *antigens* (agglutinogens) and *antibodies* (agglutinins) according to Landsteiner's rule:

Landsteiner's rule states that if a given antigen is present in one individual (on RBC) its corresponding agglutinin should be absent (in plasma).

Blood transfusion should be of the *same, or compatible ABO type as the recipient.*

⟹ **During the transfusion process, blood matching must first be accurately done!**

In urgent situations, or when the correct ABO type is doubt, type O RBCs *(RBC concentrate, not whole blood!)* may be used.

Overview of major Innovations in the 20th Century

- 1907: Compatibility testing
- 1914: Anticoagulant solutions
- 1915: Refrigeration
- 1916: Preservative solutions
- 1932: Blood Banks, Leningrad
- 1936: Effects of wars
- 1940: Component administration
- 1949: Plastic blood bags
- 1971: Infectious disease testing HBsAg
- 2000: NAT-screening

Source: Lisa Louise Bradley, 2000

Preservation and anticoagulation

- 1916: Lewisohn and Weil, Rous and Turner developed a solution of **salt, isocitrate and dextrose** in order to both anticoagulate and preserve blood. This mixture made the blood extremely dilute, so it had to be removed prior to transfusion. (1:1 solution:blood ratio).
- 1943: Loutit and Mollison introduced **ACD (acid citratedextrose)** as a preservative in. It was adopted by the Army in 1945 (1:4 solution:blood ratio).
- 1957: ACD preservative was replaced by less acidic **citratephosphate- dextrose (CPD)**.
- In 1978, CPD was supplemented with **adenine (CPDA)** + **refrigeration**.

Source: Lisa Louise Bradley, 2000

Blood Banks, plastic bags

- **1932**: First blood bank in Leningrad, Soviet Union.
- **1936**: Spanish Civil War, the Republican Army banked 9000 liters of blood in Barcelona.
- **1937**: Bernard Fantus, at Chicago's Cook County Hospital, first blood bank in the United Stated.
- Problems with reusable glass bottles (whole blood):
  - **-pyrogenic reactions**
  - **-air embolism**.
- **1949**: trials of plastic bags were conducted by the American Red Cross.

Source: Lisa Louise Bradley, 2000

Transmissible diseases

- **1962**: Connection between paid donation and posttransfusion hepatitis.
- **1972**: Voluntary donation mandated in the US.
- **1980**: AIDS epidemic caused by the human immunodeficiency virus (HIV).
- **2000**: HIV & HCV nucleic acid testing (NAT) introduced.

Infectious agent	Risk by transfused units (2013)
HBV	1:1 M
HCV	1:1,2 M
HIV 1&2	1:1,5 M
HTLV I&II	1:2,7 M

Stramer SL. Transfusion 2013.

Transfusion medicine in XXIst century

- Component therapy (give only what is needed)
- A global challenge: the desire to donate decreases, clinic requirements are unchanged for blood products
- Blood-Saving Patient Care - PBM (Patient Blood Management Program: How to avoid transfusion? How to reduce blood product use?
- Stricter / restrictive indication areas, thresholds, and lower doses.
- Responsible blood use - it (also) depends on us!


Thank you for your attention!
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