Plasma fractionation - Variety of Products

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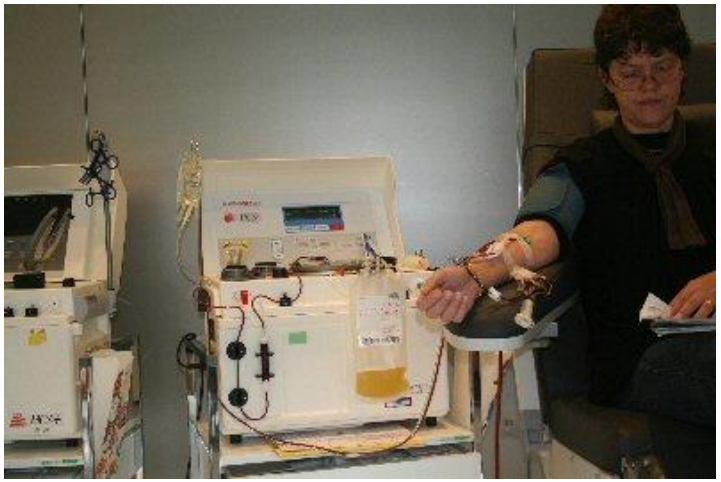
IPFA / BCA Global Symposium on “The Future for Blood and Plasma Donations, Fort Worth
September 28, 2015

Blood and Beyond

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From donor ….









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…. manufacturing of plasma products…..









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…. to patients.















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Plasma fractionation - Variety of Products

- Production process of plasma products
- Variety of products and clinical application

Blood components and plasma products

Red blood cells
Platelets
Fresh Frozen Plasma

Blood components



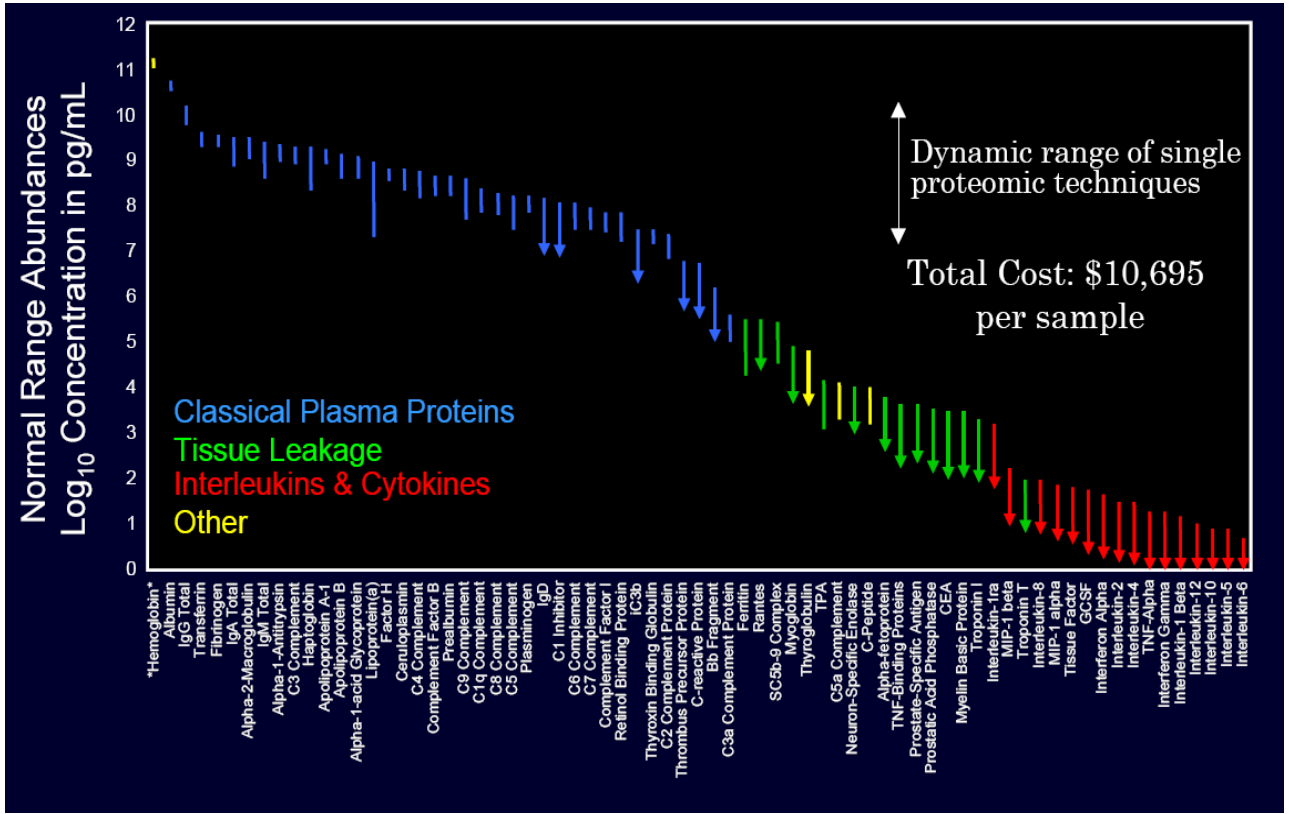
Albumin
Immunoglobulins
Coagulation factors
C1-inhibitor concentrate
Other proteins

Plasma products / medicines

Pooling and production

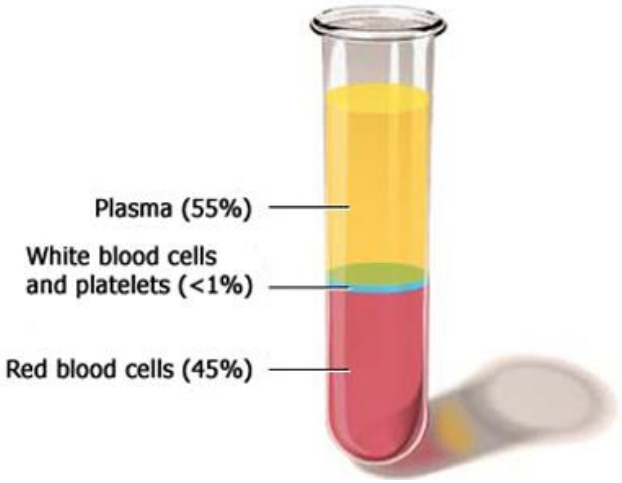
Blood plasma

- > 1,000 proteins
- about 250 proteins identified
- 117 proteins FDA licensed assays
- ~ 20 proteins commercially used as therapeutics



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Plasma fractionation



- Purification of therapeutic plasma proteins

- Somewhat comparable with dairy industry:
  * Protein solution as source
  * One source material contributes to multiple products
  * Hygienic importance

- Important differences with dairy industry:
  * Tight measures on transmission of blood borne infections
  * Specific regulations
  * Pharmaceutical production process

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Cohn fractionation

•Differences in solubility of proteins influenced by e.g.:

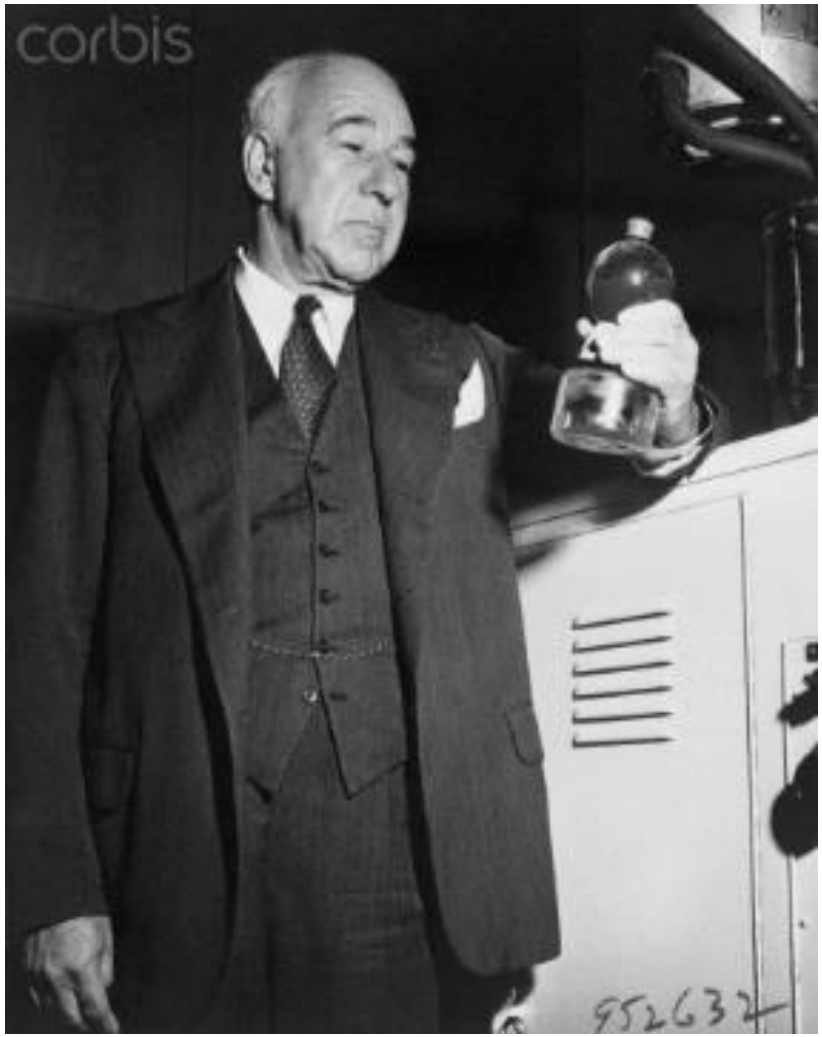
Alcohol concentration

Temperature

pH

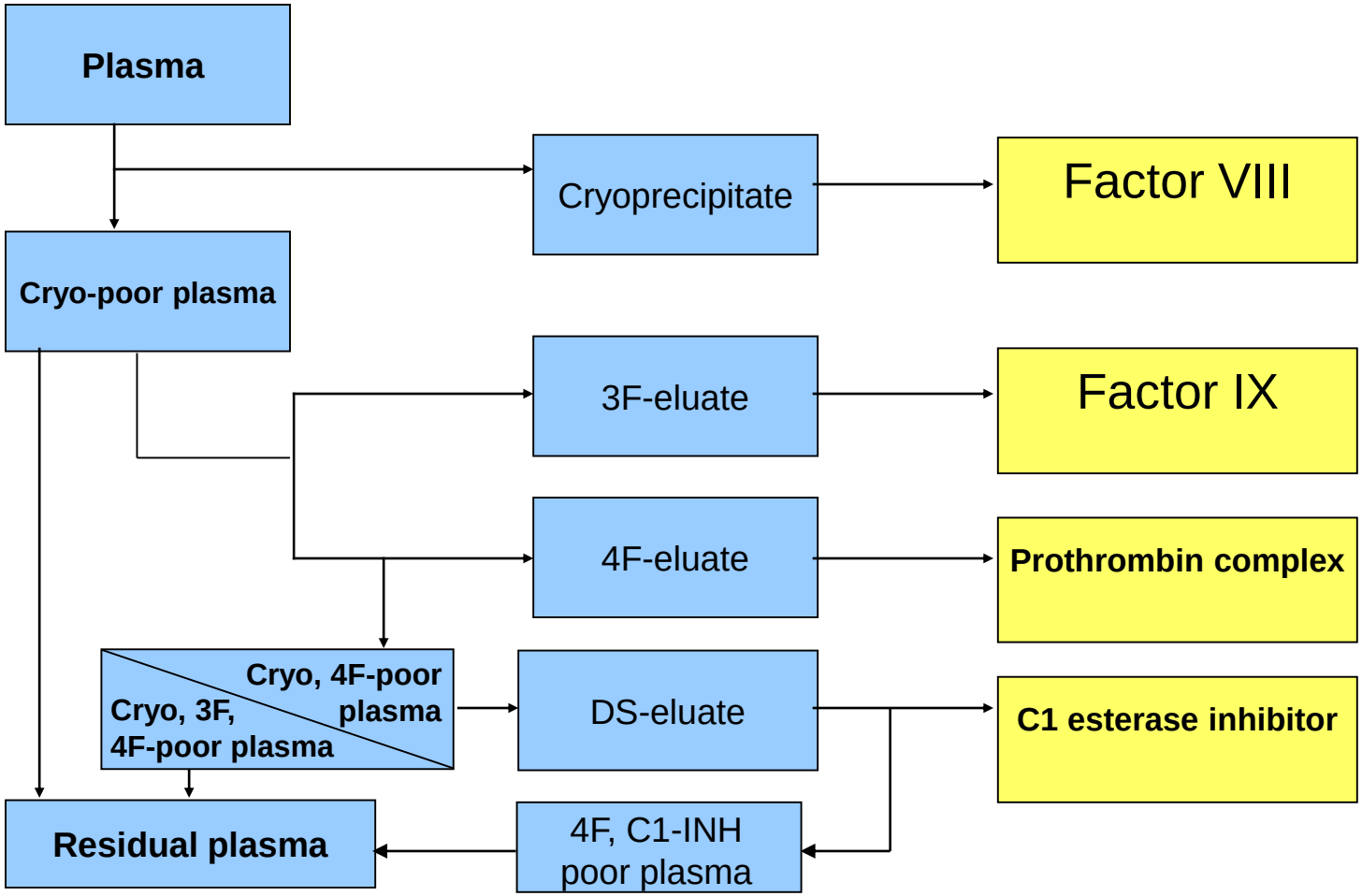
Ionic strenght

=> Variations in process conditions lead to separation of proteins

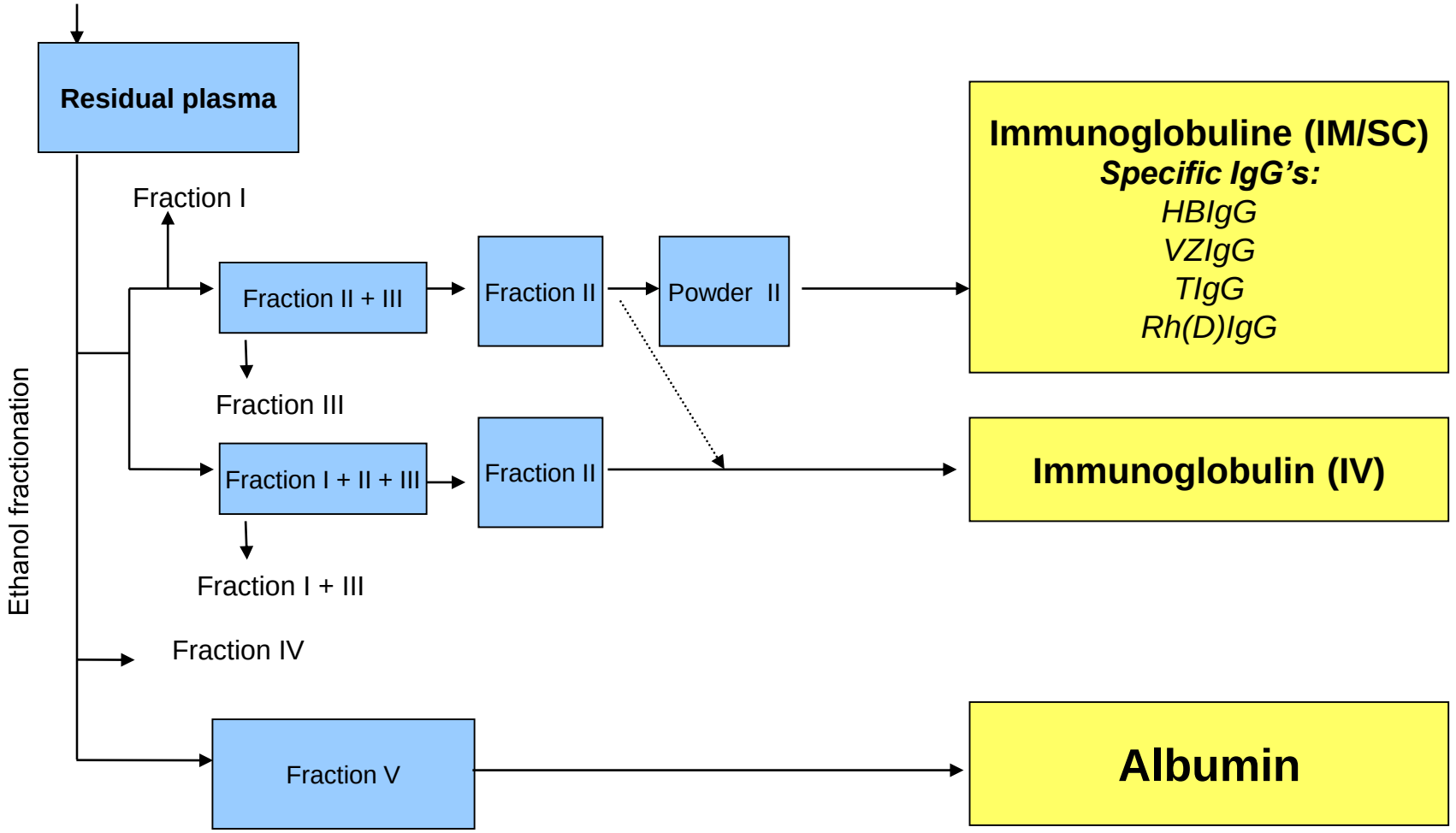


Edwin Joseph Cohn1892-1953

Plasma fractionation scheme (1)



Plasma fractionation scheme (2)



Source material



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The plasma arrives…..

1250 - 1600 Kg plasma per batch = ± 5000 - 6000 donaties







Cryoprecipitate is used for factor VIII



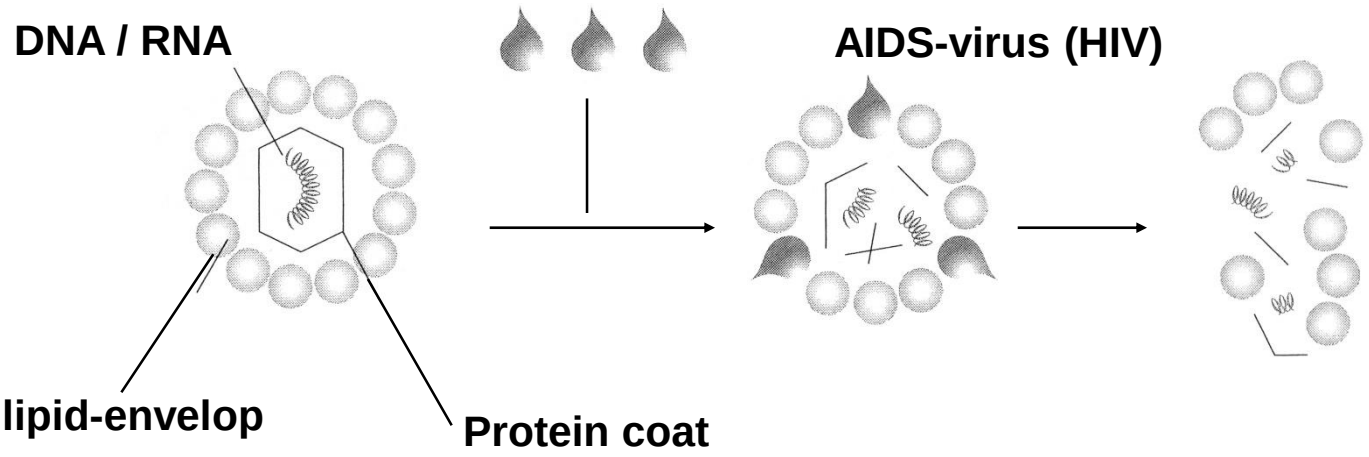
Cold precipitation

Frozen for storage

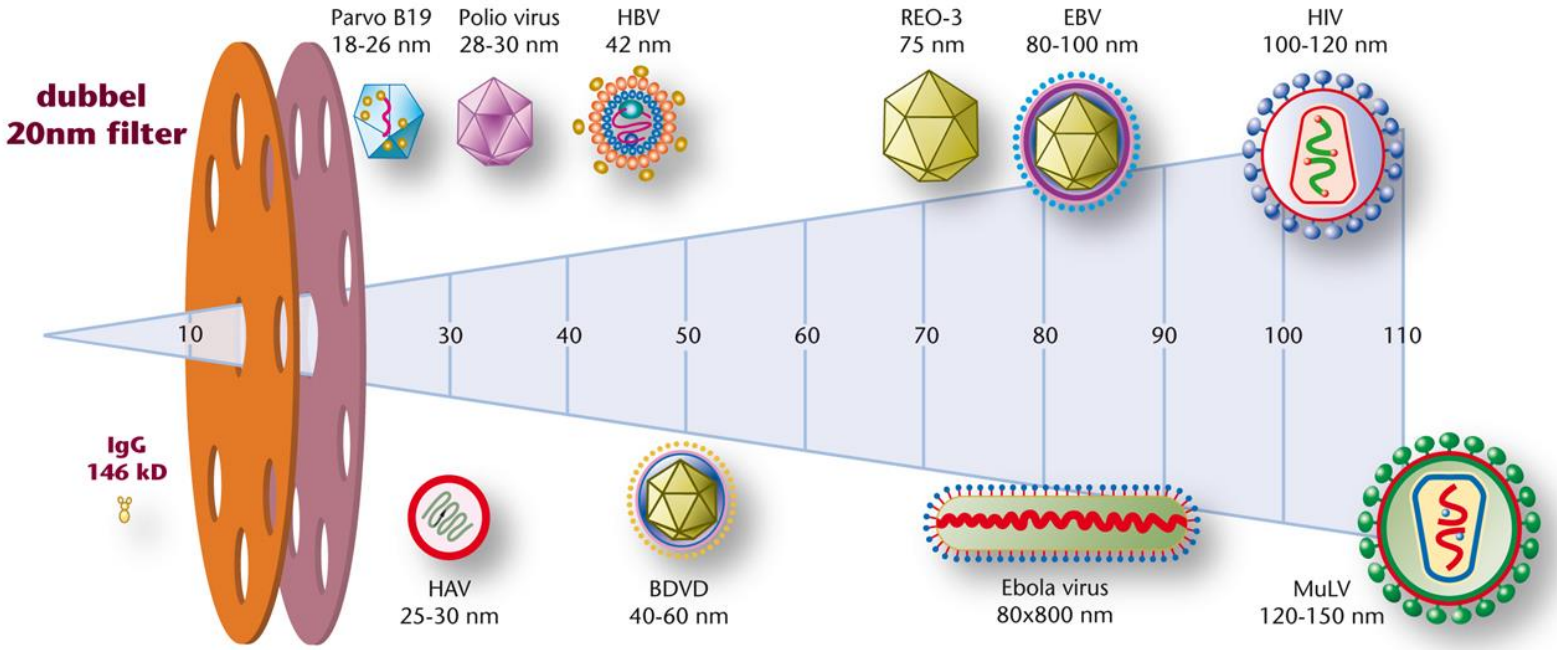


SD treatment

solvens-detergens,
bijv. TNBP and Tween



Virus-removing treatments



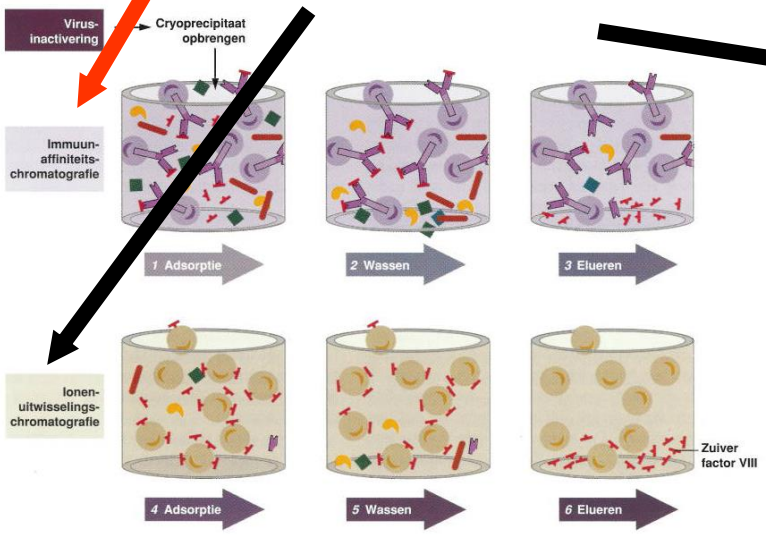
- **4 $\log_{10}$ => reduction factor 10,000 (99,99% reduction)**

Immunopurification of factor VIII

Semi-automated purification of factor VIII:

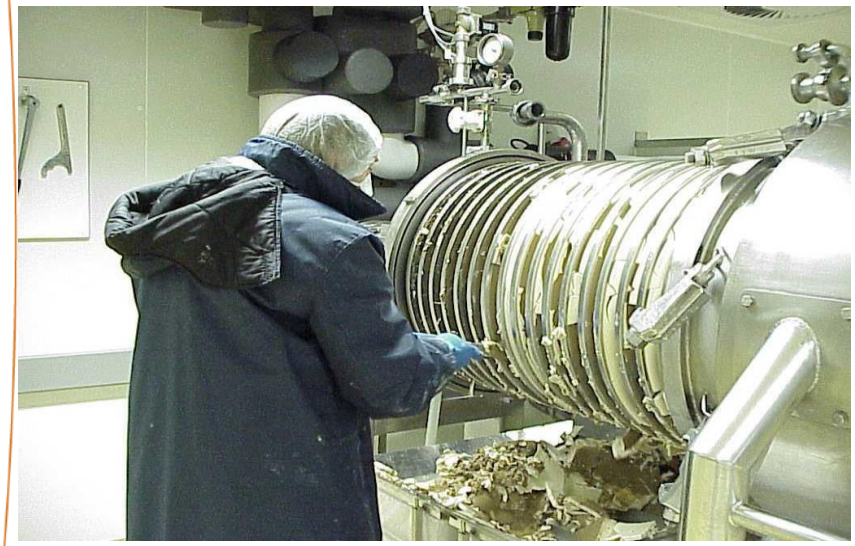
immuno-affinity chromatography

ion exchange chromatography





Paste II is the source for immunoglobulins











High-quality technologies for further manufacturing, purification, and virus-inactivation or virus-removing treatments….

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Plasma fractionation – Variety of Products

- Production process plasma products
- Variety of products and clinical application
    - Clotting factors and coagulation
    - Albumin
    - Alpha-1 proteinase inhibitor
    - C1-esterase inhibitor concentrate
    - Immunoglobulins
    - Hyper-immune globulins or specific globulins
    - C1 esterase inhibitor

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Variety of Products

Clotting factors and clinical usage

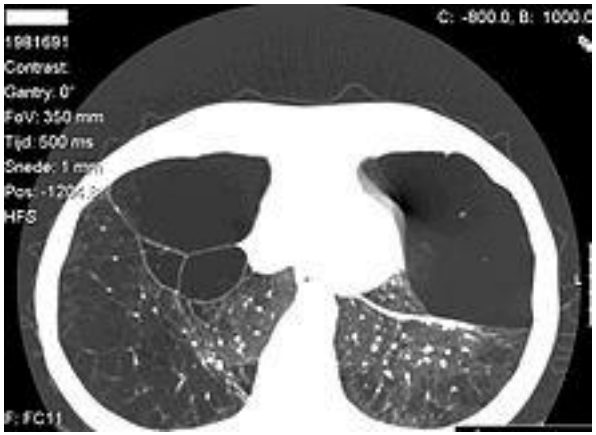
- **Factor VIII**
  - Hemophilia A
- **Factor IX**
  - Hemophilia B
- **Activated prothrombin complex concentrate (Anti-Inhibitor Coagulant Complex)**
  - Factor VIII inhibitor bypassing agent
  - Control of spontaneous bleeding episodes and use in surgery in hemophilia A and B patients with inhibitors
- **Prothrombin complex concentrate**
  - Factor II, VII, IX and X, or without VII
  - Reversal VKA treatment or congenital deficiency of factor
- **Antithrombin III**
  - Inherited deficiency of anti-thrombin III

Variety of Products

Clotting factors and coagulation

- **Protein C**
  - Severe congenital Protein C deficiency, for the prevention and treatment of venous thrombosis, and purpura fulminans
- **Factor XIII**
  - Congenital deficiency of Factor XIII and resultant haemorrhagic diathesis, haemorrhages and disturbances in wound healing.
- **Factor VII, factor XI, factor XIII**
  - These plasma derived clotting factor concentrates are used to treat patients with deficiency of the relevant clotting factor
- **von Willebrand factor (VWF)**
  - Von Willebrand's disease
- **Fibrinogen** (**Factor I**)
  - Congenital fibrinogen deficiency (eg, afibrinogenemia, hypofibrinogenemia)
- **Fibrin Sealant**
  - Creating fibrin clot

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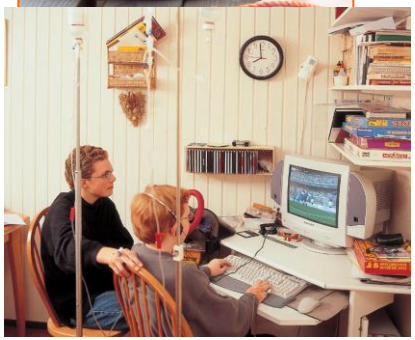


Variety of Products

- **Albumin**
  - Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated
- **Alpha-1 proteinase inhibitor**
  - Alpha-1 antitrypsin deficiency
- **C1-esterase inhibitor concentrate**
  - hereditary angioedema
- **Immunoglobulins**
  - Multiple indications
- **Hyper- immunoglobulins or specific immunoglobulins**
  - Passive immunization

Indications of immunoglobulins







Substitution

- Primary immune deficiency
- Secondary immune deficiency

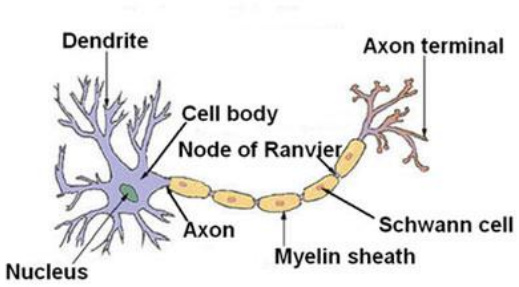


Immune modulation

- Idiopathic Thrombocytopenic Purpura (ITP)
- Guillain-Barré syndrome
- Kawasaki's disease







Off-label indications of IVIG

- Abortion (spontaneous)
- M. Alzheimer
- Asthma
- Autism
- Chron. Inflam. Demyel. Poly-neuropathy (CIDP)
- Critical Illness polyneuropathy (CIP)
- M. Crohn
- Dermatomyositis / polymyositis
- Diabetes mellitus
- Hematological coagulation disorders
- Hematological, immunological cellular disorders
- Infections in neonates
- Multiple Sclerosis (MS)
- Multifocal Motor Neuropathy(MMN)
- Myasthenia Gravis
- Parvo-B19 associated anemia
- Post-transfusion Purpura
- Rheumatoid arthritis
- Sepsis
- Stiff Person Syndrome
- SLE
- Therapy resist. epilepsy in children
- Etc. Etc.

Hyper-immune globulins

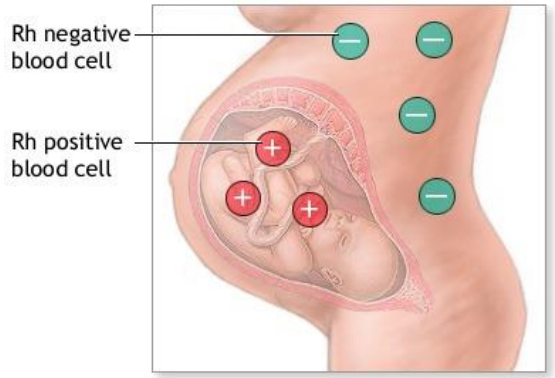
- **Plasma from immunized and/or reconvalescent donors**

- **Post-exposure prophylaxis**
  - Hepatitis B immunoglobulin
  - Varicella zoster immunoglobulin
  - Tetanus immunoglobulin
  - Rabies immunoglobulin
  - Pertussis immunoglobulin
  - Cytomegalovirus immunoglobulin
  - Rhesus (D) immunoglobulin
  - (anti- Ebola, anti- Echo virus, anti-diphteria, anti-measles, anti-pneumococcus, anti-rubella, anti-polio, anti-respiratory syncytium virus, anti-vaccinia, etc.)





Rh(D) immunoglobulin

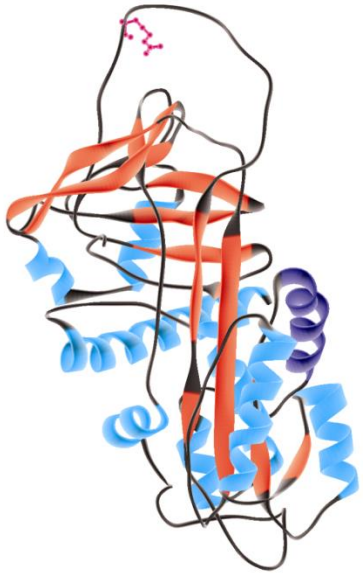


- Rh(D) negative woman and Rh(D) positive infant
  - Anaemia and fetal hydrops
  - Severe haemolytic disease of the newborn (HDN)
    - Oedema, hepatosplenomegaly, severe anaemia severe jaundice and/or death
- Rh(D) immunoglobulin at 30 weeks and at birth (within 48 hours)



C1-esterase inhibitor concentrate

- Since 1972 available in Europe
- Since 2008 available in the USA
- Treatment and/or prophylactic use in HAE
- Increased usage in Europe and USA
- Home treatment



C1-esterase inhibitor concentrate for hereditary angioedema

- The disease is congenital
- Unexpected swellings
- Painful and sometimes very dangerous





Novel Plasma Proteins under Development

Protein	Isolation (Cohn Fractionation)	Disease 1	Disease 1 incidence	Disease 2	Disease 2 incidence	Disease 3	Disease 3 incidence
Transferrin/Apotransferrin	Fraction IV-4	Congenital deficiency	Worldwide - 10-20 patients	ß Thalassemia	US Prevalence is 1,000 patients	Sickle Cell Anemia	US Prevalence is 70,000-90,000 patients
Ceruloplasmin	Fraction IV-1	Congenital deficiency (aceruloplasminemia)	US Prevalence is 315 patients , or 1:1M population	Wilson Disease	US Incidence is 3,000-12,000 patients, or 1-4:100k population.	Menke Disease	US prevalence is 1,200 - 2,700 patients.
Factor H	Fraction II+III	aHUS (atypical Hemolytic-uremic syndrome)	US Incidence is 15,000-60,000 patients	Dry Age-Related Macular Degeneration	US Prevalence is 12,700,000 patients	Wet Age-Related Macular Degeneration	US Prevalence is 1,600,000 patients
Factor V	None - new process	Congenital Factor V Deficiency	US Prevalence is 163 patients.	Congenital Factor V/Factor VIII Deficiency	US Prevalence is ~100-300 patients		
Fibronectin	Cryoprecipitate	Wound Healing		Cancer (leukemia)	US Incidence is 44,600 (ACS 2011 data)		
Haptoglobin	Fraction IV-1, IV-4	Diabetic Neuropathy		Coronary artery disease in type 1 diabetes	US Incidence is 25,000-50,000 patients for Type 1 Diabetes	Crohn's disease	North America prevalence is 400,000-600,000 patients
High Density Lipoproteins (A	Fraction IV-1	Acute coronary syndrome (ACS)	US Incidence (2008) is 1.255M new or recurrent coronary attacks annually, and 450,000 deaths.	Congenital HDL deficiency (Tangier disease)	Worldwide - about 50 patients		
IgA	Fraction II+III	Selective IgA deficiency	US Prevalence is 500,000-1,000,000 patients	Celiac disease with IgA deficiency	US Prevalence is 4,000 patients		
Plasmin	Fraction II+III	acute peripheral arterial occlusion (aPAO)	US Incidence is 100,000 patients	Ischemic stroke	US Incidence is 360,000 patients		
Plasminogen	Fraction II+III	Ligneous Conjunctivitis	US Prevalence is 210 patients, or about 1.5:1M population.				
Protein S	Fraction IV-1	Congenital Protein S Deficiency	US Prevalence about 100,000 patients	Acquired Protein S Deficiency	US Incidence is 3,600-7,200 patients with Ischemic Stroke & DVT		

Summary

- One blood- or plasma-donation may contribute to many plasma-derived medicinal products
- Plasma products have an important place in the treatment of many patients
- Plasma products have multiple functions in clinical therapy and these functions will be further developed
- Care will become more patient-driven (e.g. more concentrated products, patient friendly ways of administrations)
- New plasma products will be developed for ‘niche markets’

- The need for sufficient supply of plasma will equally row