Dipartimento gravi insufficienze
d'organo e dei Trapianti

Policlinico S.Orsola-Malpighi

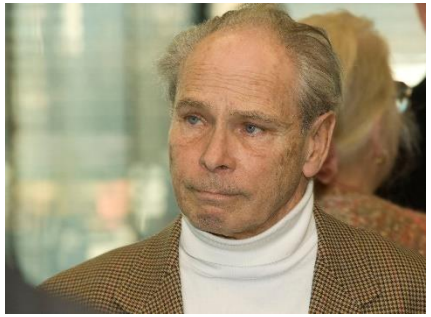
Azienda Ospedaliero-Universitaria

Bologna - ITALY

Aferesi : presente e futuro

Antonio Santoro, MD,FERA

The nephrologist



- *The ultimate goal of a nephrologist is to maintain renal function and to treat kidney diseases,manage associated metabolic changes and prolong time till dialysis.*
- *Nephrologist perform hemodialysis,PD, and* ***other extracorporeal depuration techniques (apheresis).***
- *Nephrologists manage Acute Renal Failure and provide lifesaving Continuous and intermittent Renal Replacement Therapy (CRRT) or other extracorporeal therapies.*
- *Nephrologists are specialists in electrolyte, fluid balance, acid/base, anemia associated to renal diseases, metabolic bone disease, hypertension management and renal trasplantation.*

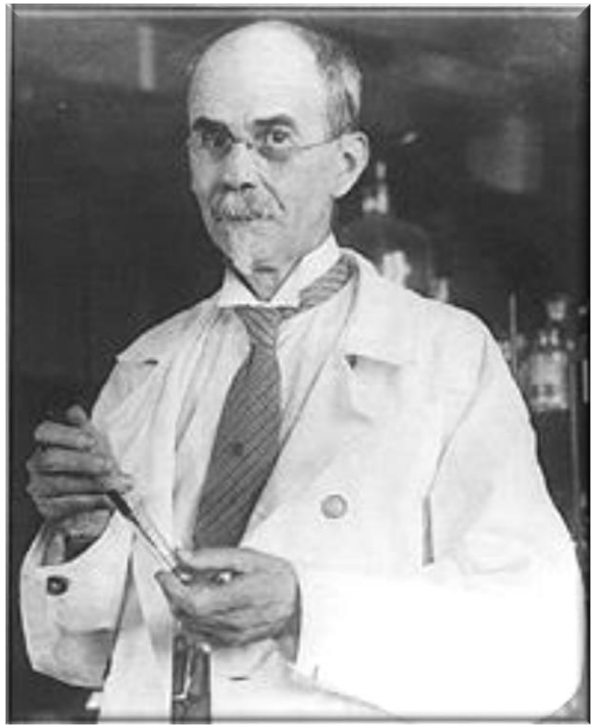
. Stewart Cameron, ERA-EDTA Rimini 1998

Vadim Yurevich

Russki Vratch (Russian Physician) Journal no. 18 (1914)

“ On the Question Regarding Washing of Blood Outside of the Body and the Vitality of Red Blood Cells".

1913: A First "Artificial Kidney"



John J.Abel

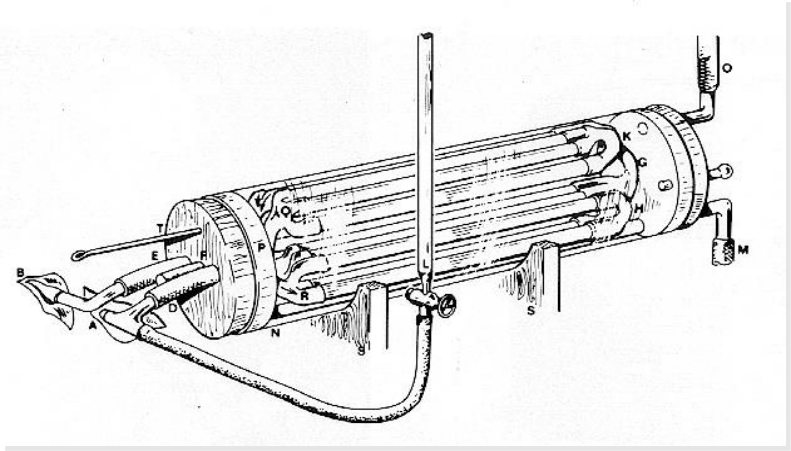
The Times.

LONDON, MONDAY, AUGUST 11, 1913. PRICE, WITH RUSSIA

AN ARTIFICIAL KIDNEY.

At University College the demonstration which excited the most interest was without doubt that of Professor Abel, of Baltimore.

PROFESSOR ABEL presented a new and ingenious method of removing substances from the circulating blood, which can hardly fail to be of benefit in the study of some of the most complex problems. By means of a glass tube tied into a main artery of an anæsthetized animal the blood is conducted through numerous celloidin tubes before being returned to the veins through a second glass tube. The celloidin tubes are immersed in saline solution. All diffusible substances circulating in the blood pass through the intervening layer of celloidin, and can be found in the saline solution, where they can be subjected to fractional analysis. In this way Professor Abel has constructed what is practically an artificial kidney. In many instances the working of the added excretory organ is more rapid than that of the actual kidney of the animal; 3 per cent. per hour of salicylic acid can be removed from the blood. Although primarily the apparatus is of use in the estimation and analysis of the diffusible contents of the blood, it is possible that the principle may ultimately be adopted in the treatment of disease. At the close of the demonstration, which excited the liveliest interest and discussion, Professor Abel was accorded round after round of applause.



PLASMA REMOVAL WITH RETURN OF CORPUSCLES

(PLASMAPHAERESIS)

FIRST PAPER

JOHN J. ABEL, L. G. ROWNTREE AND B. B. TURNER

From the Pharmacological Laboratory of the Johns Hopkins University

1914: prima plasmaferesi su un modello animale (Abel)
per trattare la "toxiemia", provocata sperimentalmente, in cani sottoposti a nefrectomia bilaterale. Il trattamento consisteva essenzialmente in una successione di salassi di sangue in toto, da cui il plasma veniva scartato, sostituito da una soluzione di Locke e successivamente reinfuso

Apheresis *(ἀφαίρεσις (aphairesis, "a taking away")) is a medical technology in which the blood of a person is passed through an apparatus that separates out one particular constituent and returns the remainder to the circulation. It is thus an extracorporeal therapy.*

Hemodialysis versus Apheresis

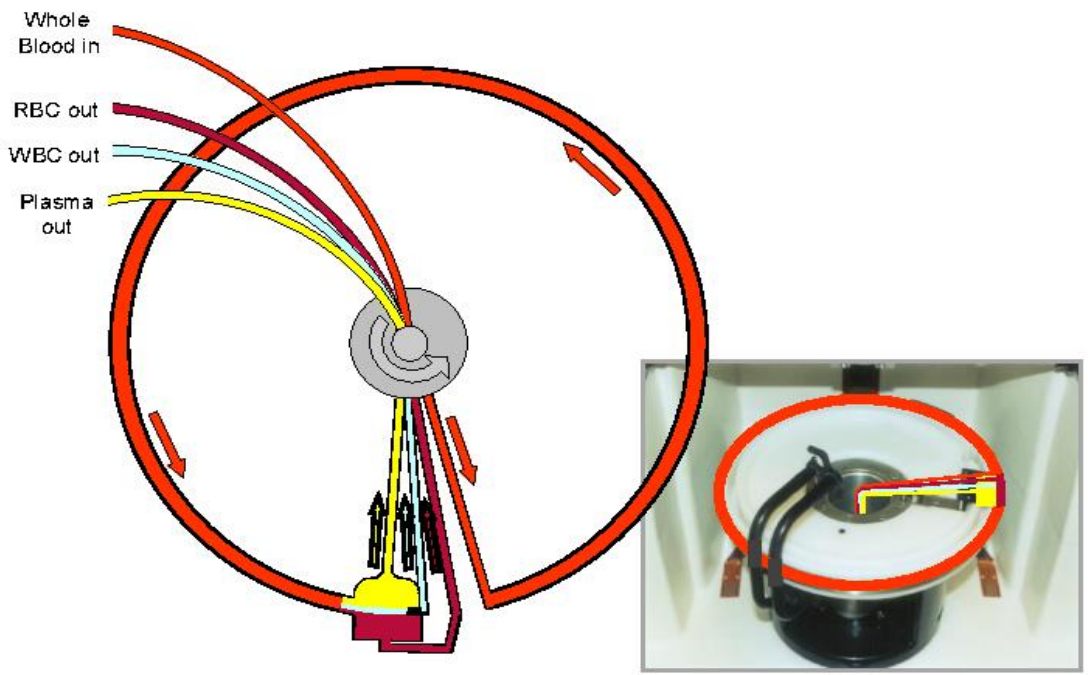
HEMODIALYSIS

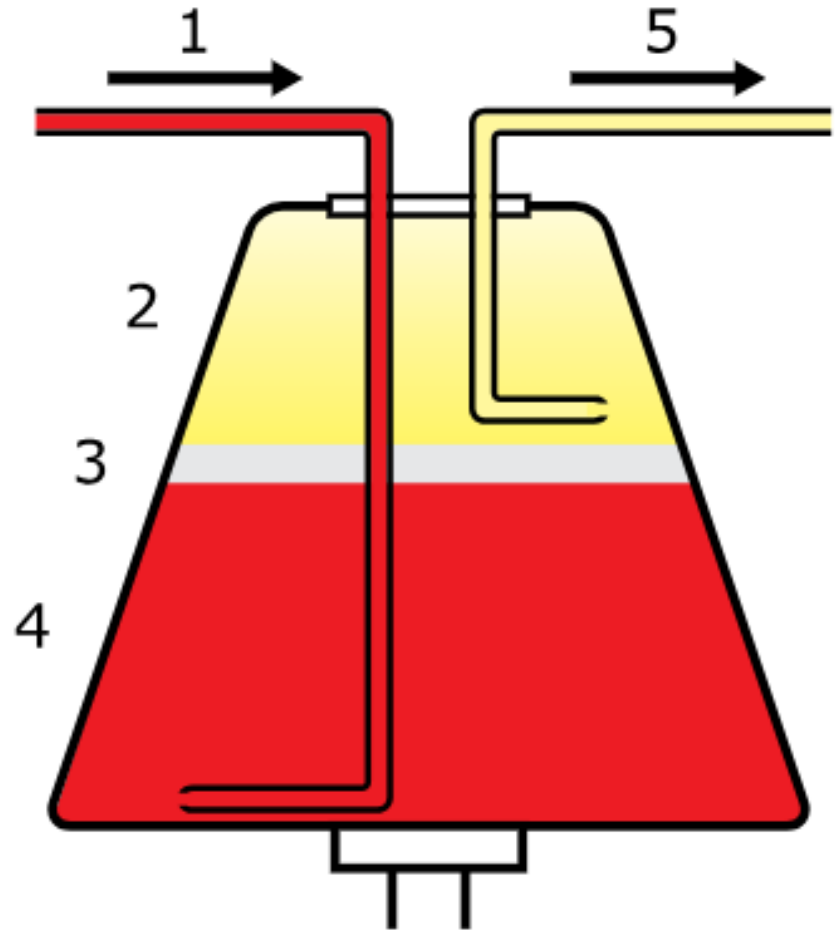
- Diffusion , convection, adsorption
- Kidney model
- Salt & water removal and BP control
- Retains large mol wt (e.g. proteins, antibodies, protein bounds solutes or drugs)
- Mainly meant to remove metabolic waste

APHERESIS

- Blood component separation removal and replacement
- No ideal model
- No very effective in salt, water removal and BP control
- Removes protein and proteins boun substances
- Mainly remove useful substances (clotting factors, antibodies)

Separation by centrifugation





Separation by centrifugation

Stoke's Law:

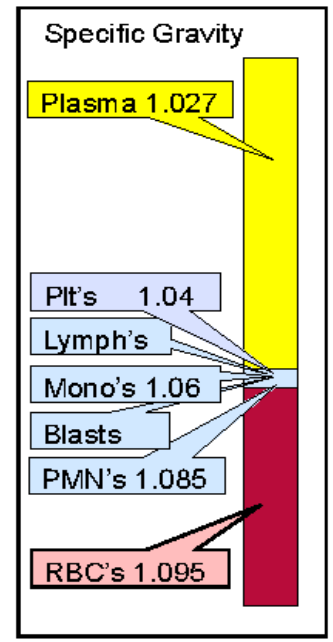
$$S_V = \frac{2\,\omega^2 R\, r^2\,(\rho_{cell} - \rho_{plasma})}{9\mu}$$

Stoke's law says that the cellular velocity of sedimentation (S_V) is proportional to:

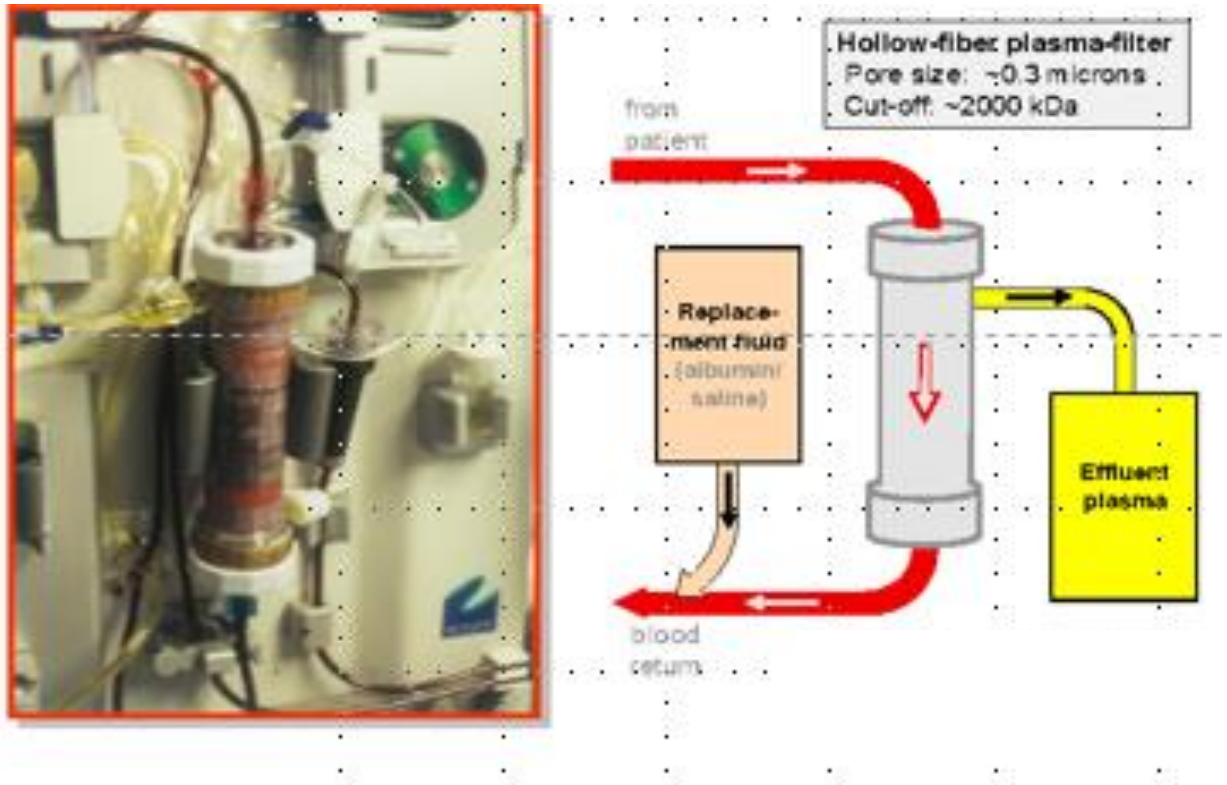
- Centrifugal acceleration ($\omega^2 R$) or g
- Square of the cell radius (r^2)
- Difference between the density of cell and plasma ($\rho_{cell} - \rho_{plasma}$)
- Inverse of the fluid viscosity (μ)

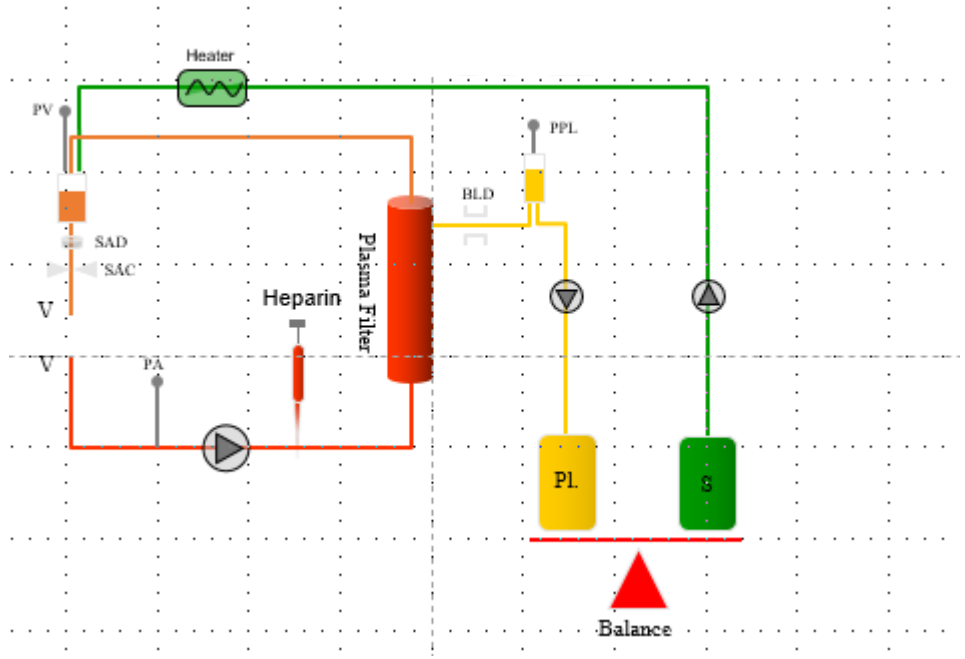
Centrifugal separation is a function of:

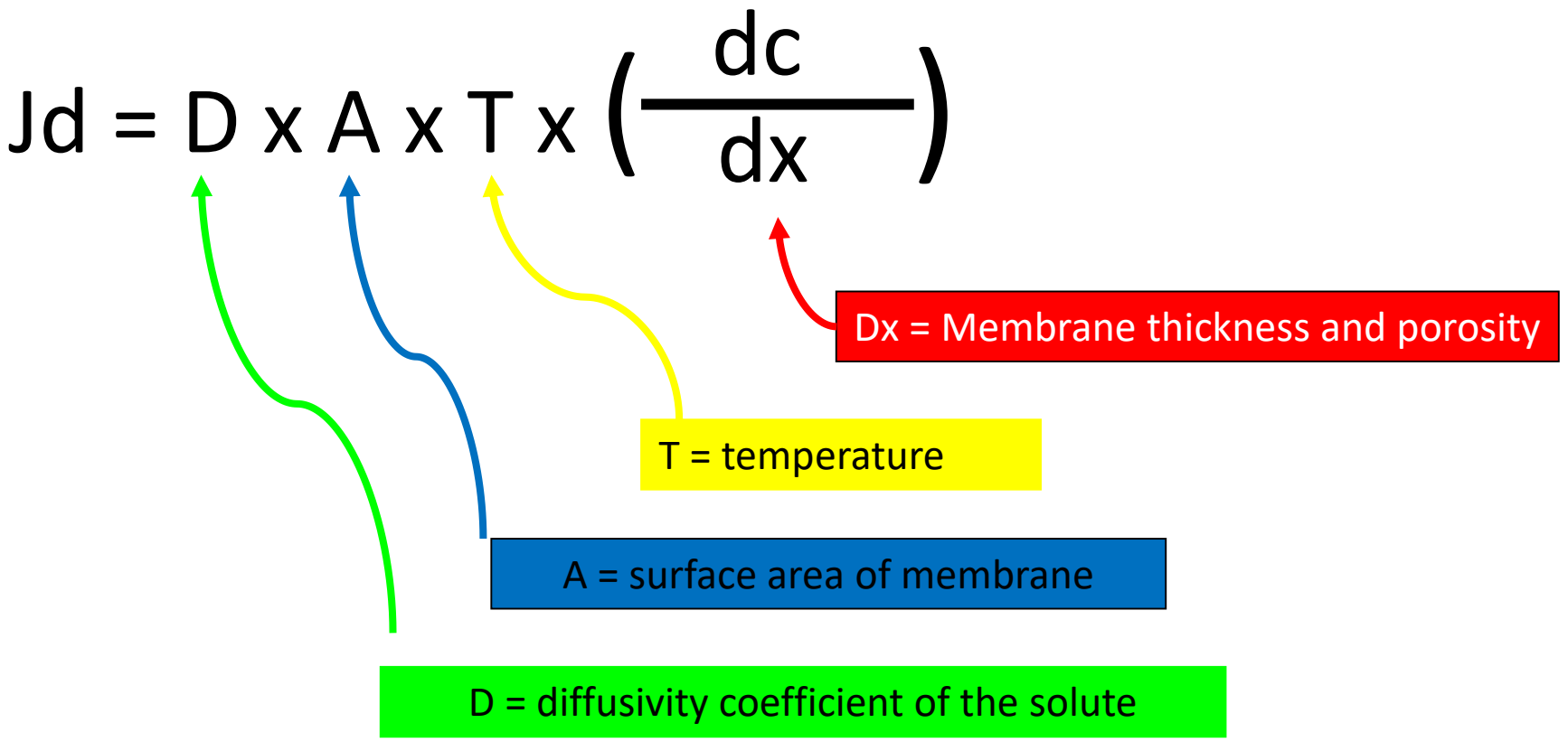
- **S_V** and
- **Dwell time** (inverse of inlet blood flow rate)



Separation by membrane filtration



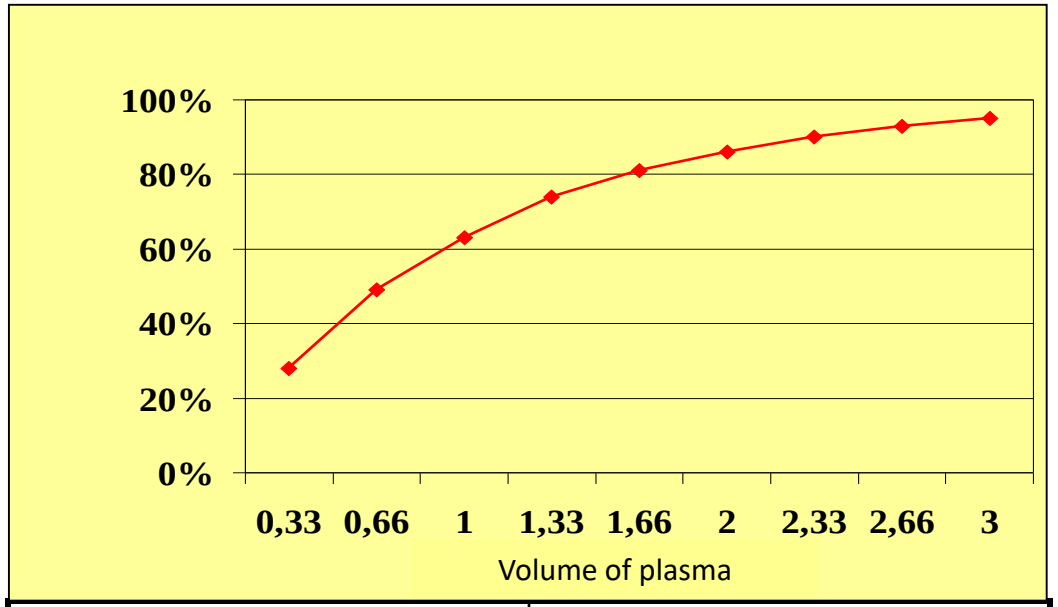



Jd = D x A x T x (dc/dx)
Dx = Membrane thickness and porosity
T = temperature
A = surface area of membrane
D = diffusivity coefficient of the solute

Factors that influence the efficacy of apheretic therap

- Concentration of the substance to be removed and severity of the disease
- Distribution of the substance between intravascular and extravascular space (eg 80% intravascular IgM, only 40% IgG) and speed of rebalancing between the two compartments
- Synthesis and degradation of the substance to be eliminated (IgM half-life 5 days, IgG 23 days)
- Volume of plasma exchanged and blood mass of the patient

Reduction of pathological substances: volume of treatment



Volume of plasma	Percentage of removed substance
1 volume	63%
2 volumes	86%
3 volumes	95%

P.V.(liters)= 0.065 x (peso Kg) x (1-Hct)

Operational contrast between centrifuge and membrane apheresis procedure

	Centrifuge	Membrane
• Mechanism	centrifugal force	Capillary membrane forces
• Blood flow ml/min	10-150 ml/min	150 ml/min
• Plasma extraction	80%	30 %
• Plasma removal	Variable	30 ml/min
• Anticoagulation	citrate	Heparin/citrate
• Separation	Specific gravity	Size
• Blood volume in circuit	180 ml	120 ml
• Molecular weight cutoff	N/A	3 milion daltons
• Fluid replacement	alb,fresh frozen plasma	alb, gresh frozen plasma

Membrane plasma filtration requires higher processing volumes (3 blood volumes compared to 1.5 volume) to extract the equivalent of 1-1.5 plasma volumes.

Choice of replacement solution

Fresh frozen plasma (FFP)

- To replace deficient or defective plasma costituents (example TTP)
- To prevent exacerbating active lung hemorrhage (all or part of replacement fluid)
- Example: Goodpasture or ANCA vasculitis

Albumin or other colloid

- Used for most applications
- Either 5% albumin for whole replacement volume
- Or ¼ saline and 3/4 albumin
- Or other colloidal solution
- If needed for clotting factors depletion: give 2 units of FFP at the end of session

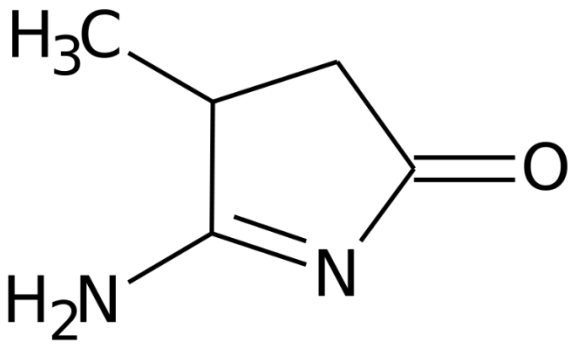
Choice of replacement fluid

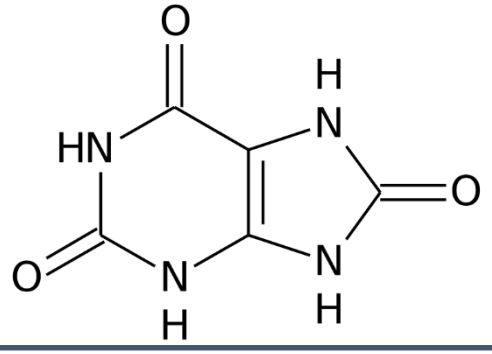
Ideal target molecule characteristics for therapeutic PE

- Identified etiologic agent or substance
- High molecular mass > 15.000 daltons
- Slow rate of formation
- Low turnover
- Low volume of distribution

Plasmapheresis - Which molecules do we remove?

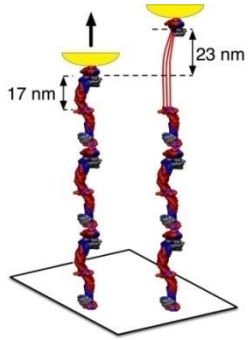
With dialysis we remove substances with low / medium molecular weigh

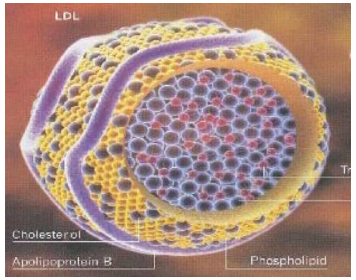




Urea= 60 Da
Creatinin = 113 Da
Uric acid = 168 Da
Beta 2 microglobulin = 11,6 KDa

With the therapeutic apheresis we aim to generally remove substances with a high molecular weight (lipoproteins, fibrinogen, immunoglobulins, etc.)





IgG= 150 KDa
IgM= 900 KDa
Fibrinogen = 341 Kda
LDL-col. = 2500 KDa

Kinetics of plasma constituents

Costituent	Half life (days)
IgG (1,2,3)	22
IgG 3	7
IgM	5
IgA	6
IgD	2.8
IgE	2.5
Albumin	17
C_3	2
C_4	2
Fibrinogen	4.2
TNF	6-20 minutes
Cytokines	minutes

Dose of plasma exchange

Prescribed volume of each plasma Exchange procedure

X

Number and frequency of procedures

= DOSE

Depends of patient size (plasma volume)

Depends on
- Pathogenic molecule
- Volume of distribution
- Disease characteristics

Example :
Patient of 70 Kg
Volume of exchange
3.5 liters

Example :
Anti GBM GN
Rx daily x 5
then reassess

Mechanisms of action of TPE

- Removal of causative molecules : antibody (Ab) , etc.
- Sensitization of Ab-producing cells to medications
- Unblocking of systemic phagocytic clearance
- Removal of cytokines and adesion molecules
- Replacement of missing plasma components
- Alteration in immune cell balance:
  - Increase in regulatory T-cells
  - Increase in suppressor T-cells
  - Decrease B cells
  - Tipping Th1:Th2 ratio in favor of Th1
  - Changes in NK cell numbers and activity

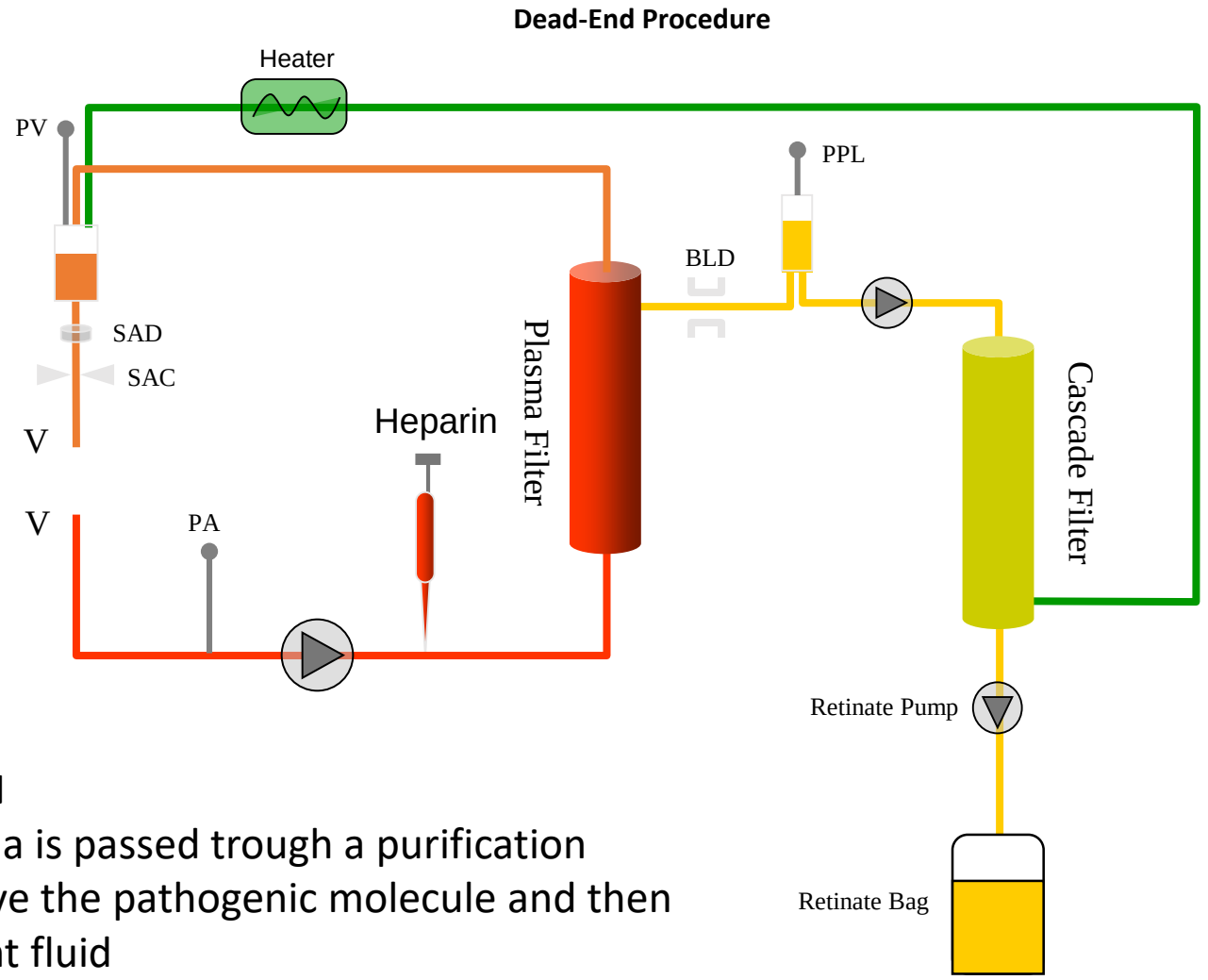
Revees HM, Winters JL. Brit J Hematol 164:342-351; 2014

Examples of pathogenic target molecules for TPE in Kidney Disease

Kidney disease	Target molecules
• Anti GBM disease	• Autoantibody reactive with type IV collagen
• TTP	• Aquired autoantibody reactive with ADAMST13 enzyme
• Pauci immune rapidly progressive GN	• Autoantibodies reacting against component of cytoplasma of neutrophil sequential ANCA
• Multiple mieloma	• Removal K and lambda free light chains
• Cryoglobulinemia	• IgM anti IgG antibody, immuno complexes
• Recurrent FSGS	• Circulating glomerular permeability factor, suPAR
• Atypical HUS	• Complement regulatory component
• Kidney transplantation	• Alloantibodies reactive with HLA antigens

DFPP

Rheopheresis



PLASMA REGENERATION

The patient's own plasma is passed trough a purification system on- line to remove the pathogenic molecule and then reinfused as replacement fluid

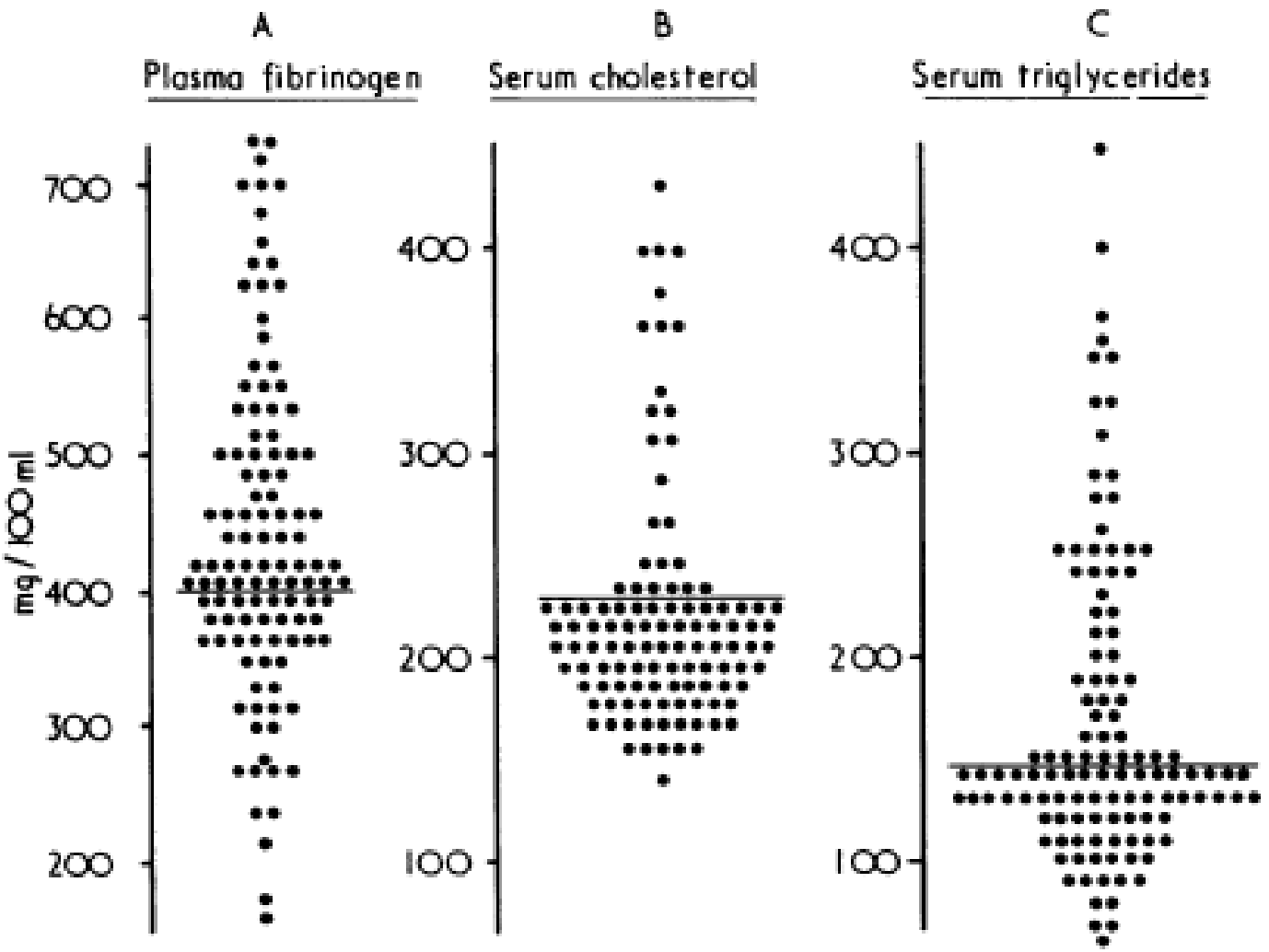


FIG. 5—Distribution of (A) plasma fibrinogen, (B) serum cholesterol, and (C) serum triglyceride concentrations. Upper limits of our normal ranges (normal mean +2 S.D.) in a non-aged-matched population are indicated.

Dormandy JA, BMJ, 1973

Main mechanisms of action of selective adsorption

They are part of the technology:

1.NOT SOLUBLE MATIRX → **CARRIER**

2.LIGANDO (Active Substance) → **FIXED TO CARRIER BY AFFINITY**

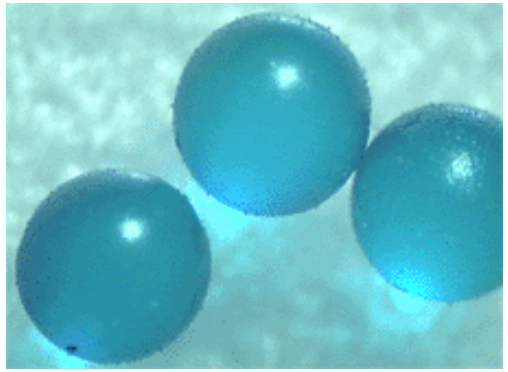
→

1- CHEMICAL-PHYSICAL BOND

2-I MMUNOLOGICAL-BIOLOGICAL BOND

Selective Adsorption: Carrier

Carrier	Origin:
Sepharose	Semi-sinthetic
Agarose	Natural (seaweed)
Polivinil-alcool gel	Synthetic
Cellulose microspheres	Natural (cotton)
Glass or silica balls	Natural
Carrier properties:	
Inert bubstance	
High biocompatibility	



The ligands

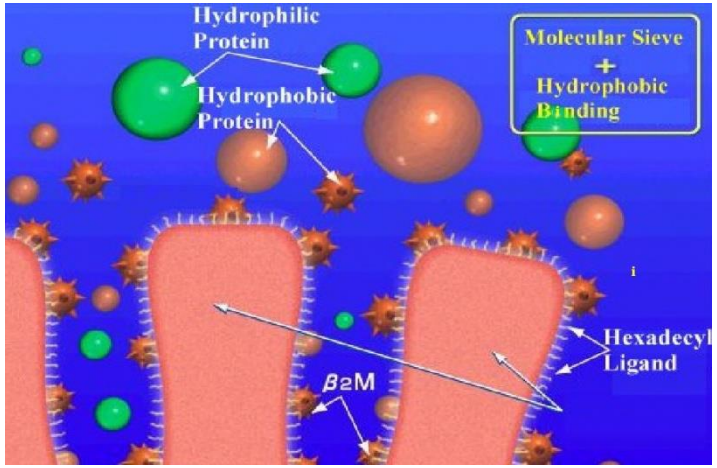
- The chemical-physical ligands are represented by different substances such as ion exchange resins, styrene divinyl benzene and activated carbon on bilirubin, destran sulfate and polyacrylate for LDL / Lpa cholesterol; pentapeptides for fibrinogen.

- Immunological ligands are commonly antibodies (of animal or monoclonal origin) anti-immunoglobulins of IgG, IgM, IgA, IgE, immune complexes or free light chains, or, specific antibodies to molecular antigens (such as anti-apoB antibodies).

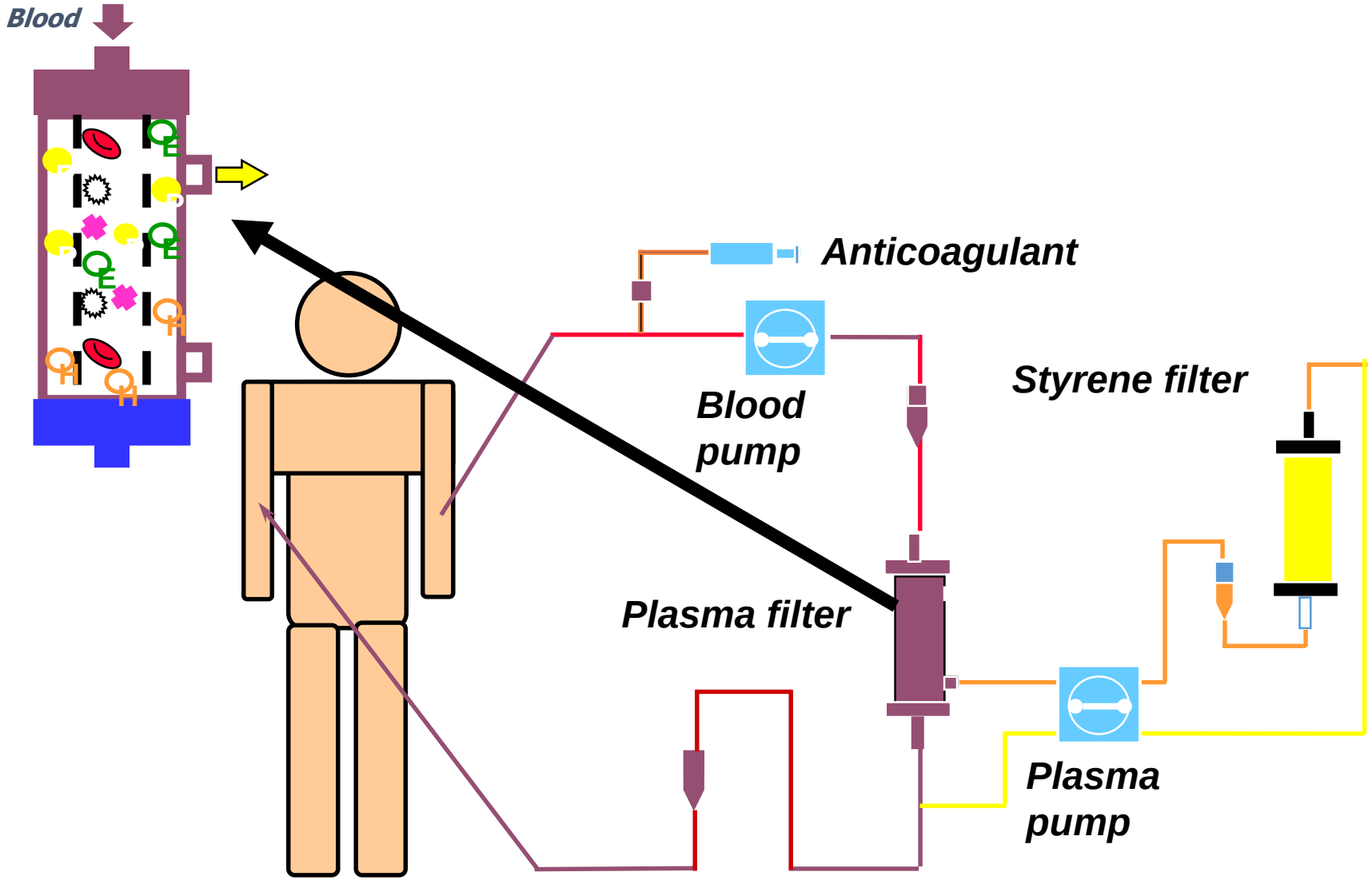
- Biological ligands are substances such as tryptophan, phenylalanine, Staphylococcal protein A, or coagulation factors VIII and IX and C1q, that bind immunoglobulins and immunocomplexes with hydrophobic type bonds. Among the biological ligands are those with biologically active carbohydrates (terminal trisaccharides of the A / B / AB blood groups) that selectively remove the anti-A / B / AB isoagglutinins, or the heparin that in the acidic environment precipitates the LDL and Lp(a).

Selective Adsorption: Chemical-physical Ligand

Ligando	Molecola adsorbita
Ion exchange resins: -Polianions (styrene divinylbenzene) Destran sulfate	Bilirubin Colesterol-LDL
Heparin	Colesterol-LDL
Active charcoal	Bilirubin, Drugs, Poisons
Poliacrylate	Colesterol-LDL

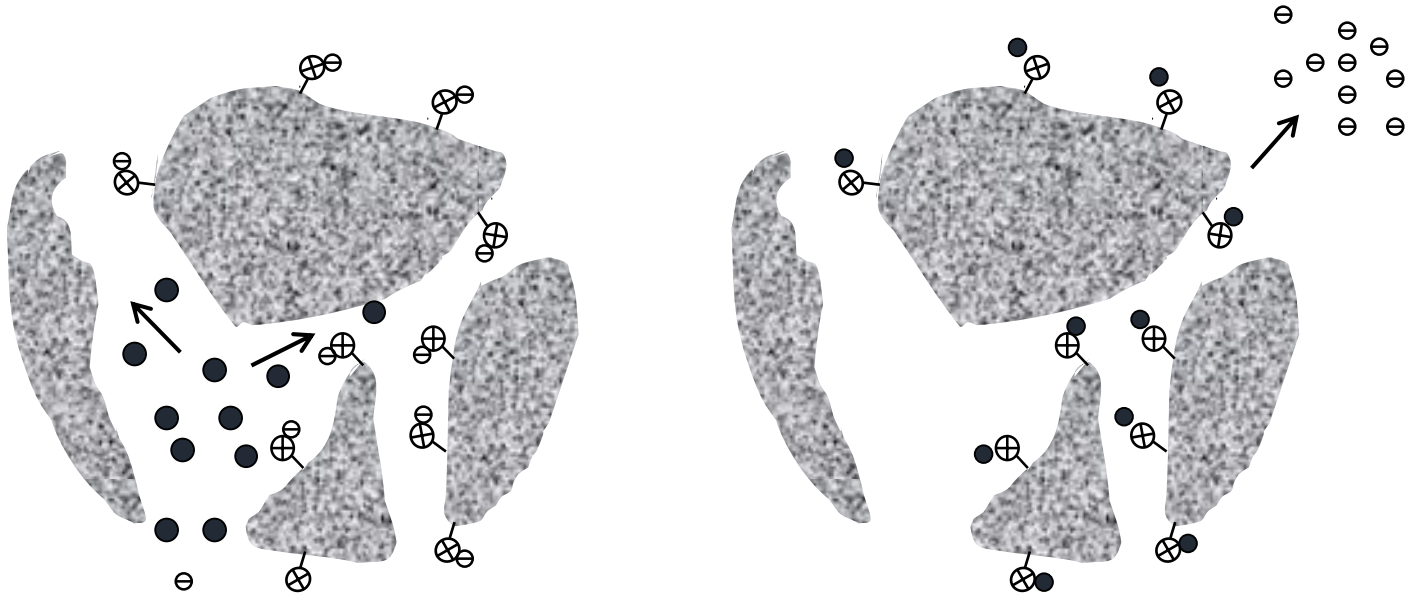


E.Mancini ,A.Santoro . G Ital Nefrol 2012


Blood
Anticoagulant
Blood pump
Styrene filter
Plasma filter
Plasma pump

Processo adsorbitivo sul plasma della bilirubina

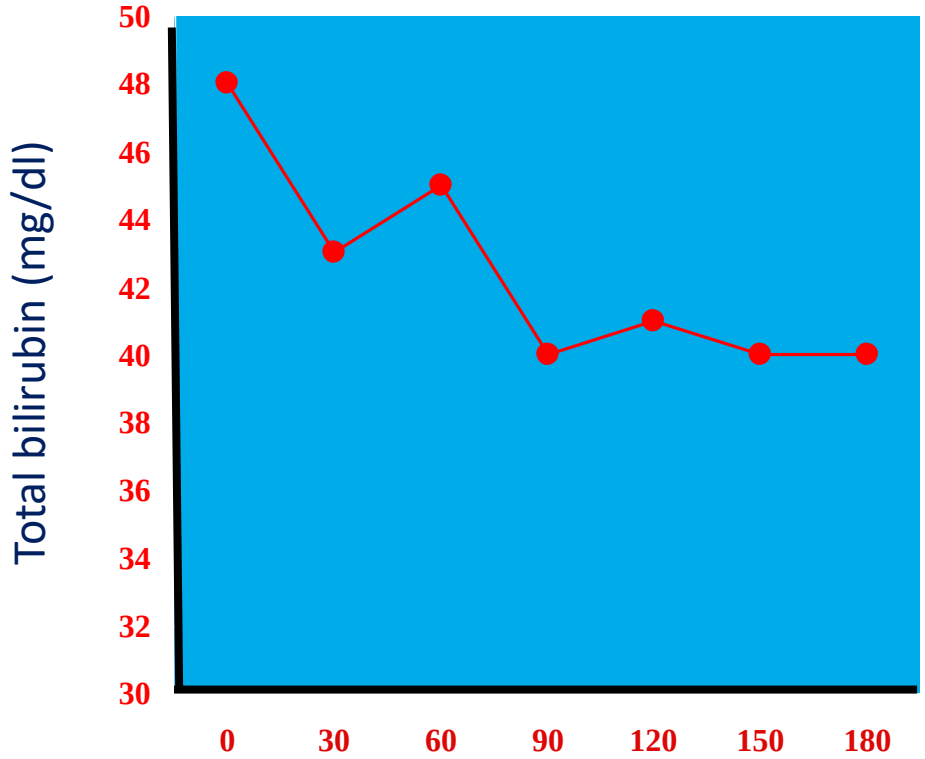
Schematic illustration of bilirubin adsorption to the ionic resin of BR-350(L)



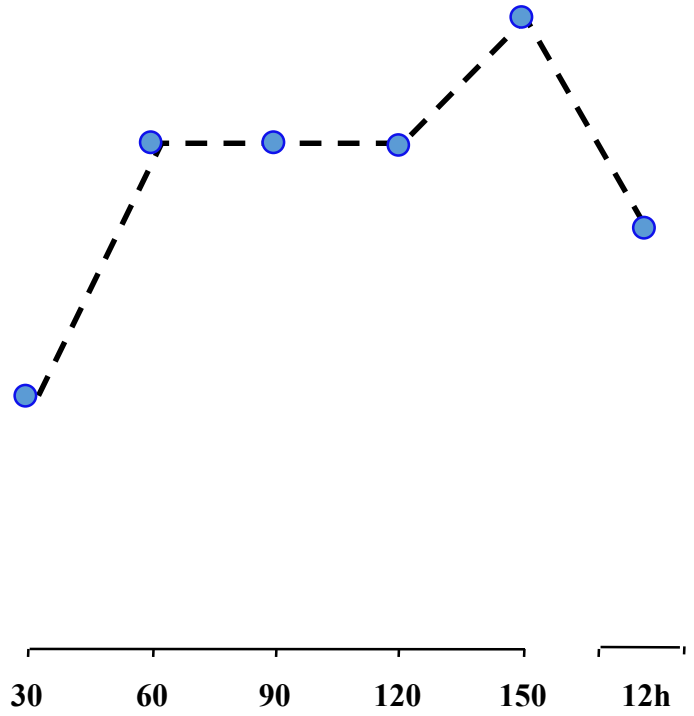
- ● bilirubin (negatively charged)
- ⊖ chloride ion (anion)
- ⊕⊖ ammonium chloride (ligand)
- ⊕● bilirubin-ammonium ionic complex formed by ion exchange

Bilirubin removal

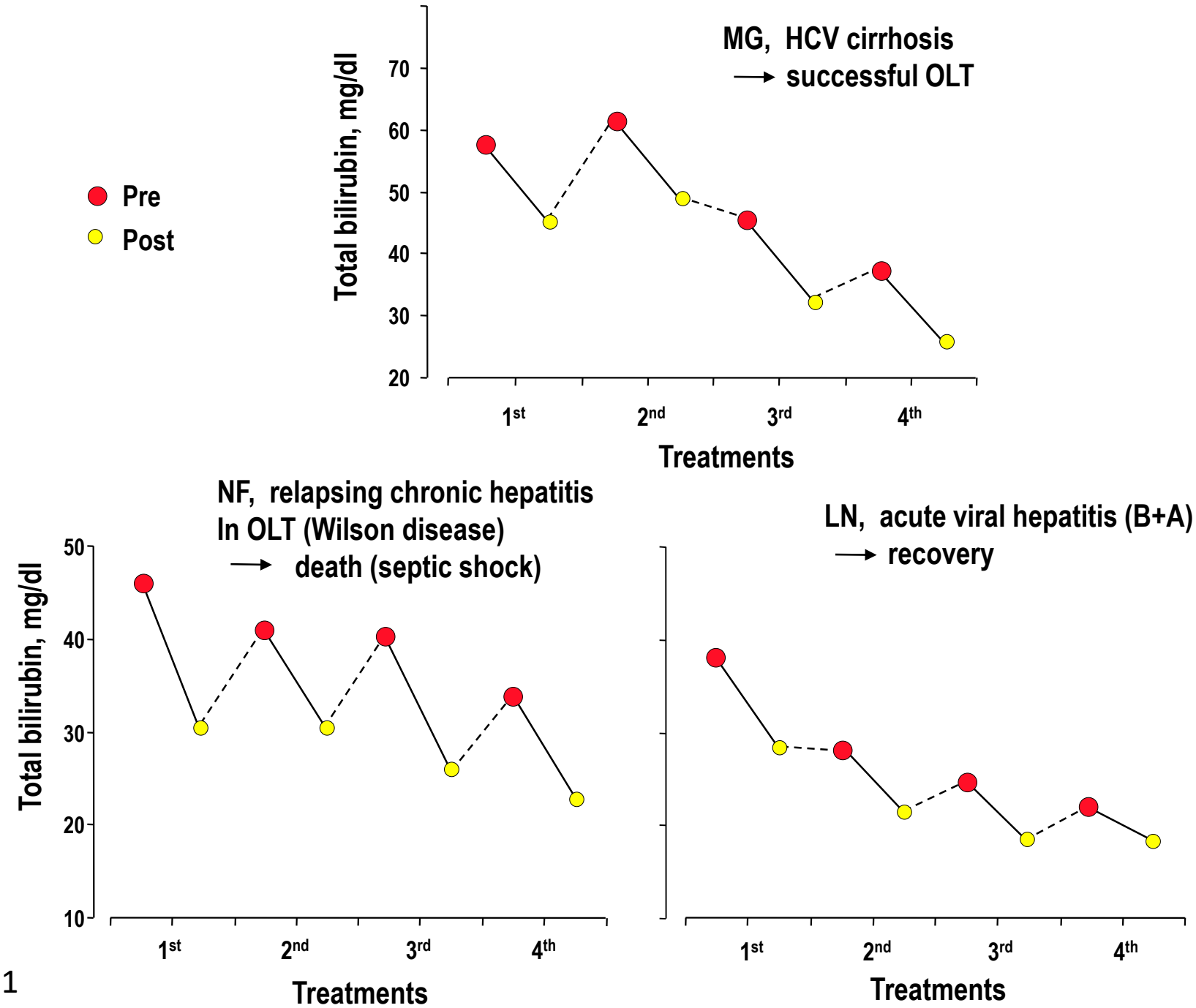
Cascade plasma exchange



REBOUND POST-PE

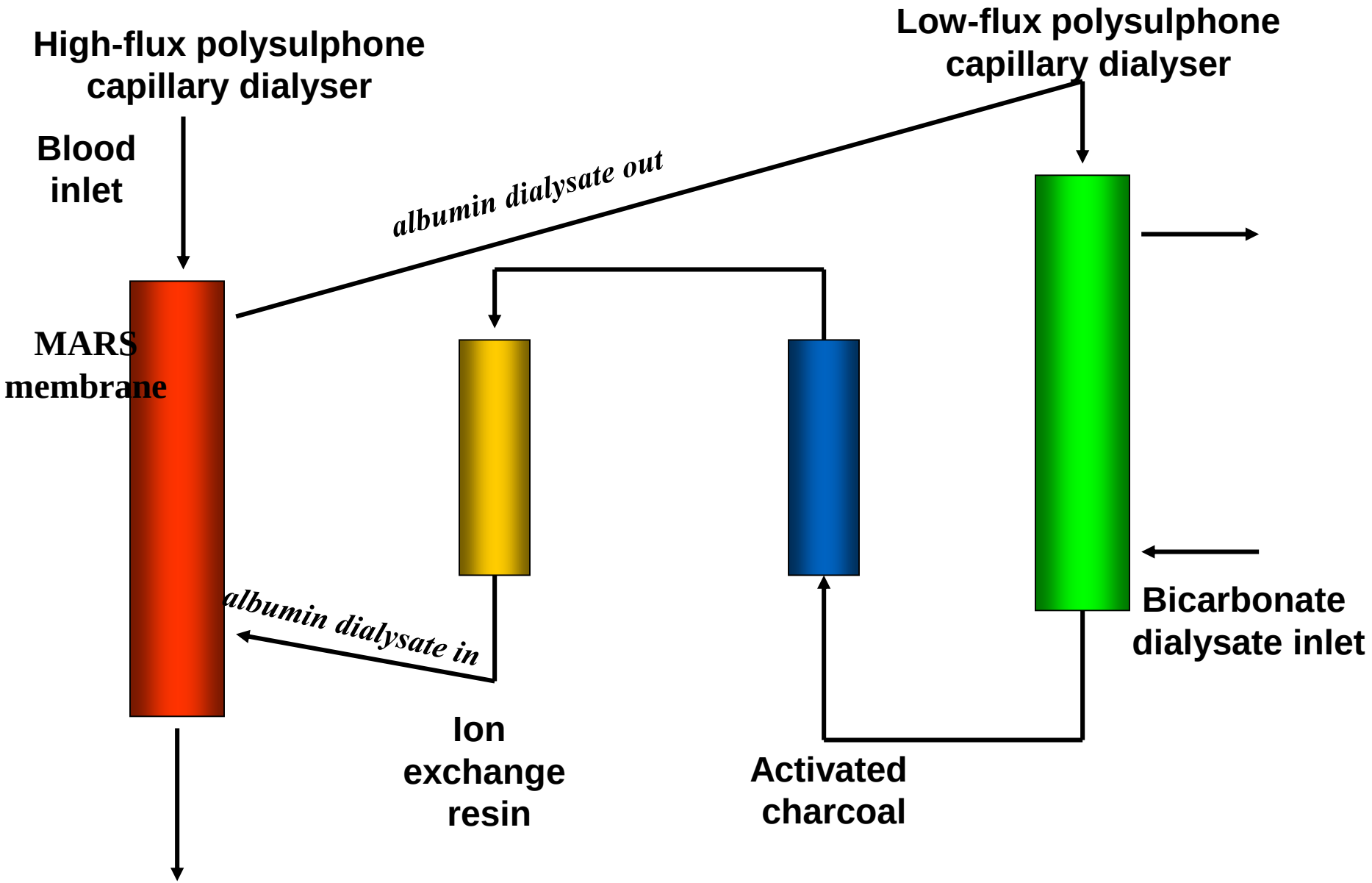


Santoro A. The International Journal of Artificial Organs 2004



Santoro A. ASN 2011

MARS CIRCUIT



Prometheus system: *fractionated plasma-separation adsorption (FPSA)*

2004 →  → 2011

First clinical use in Italy

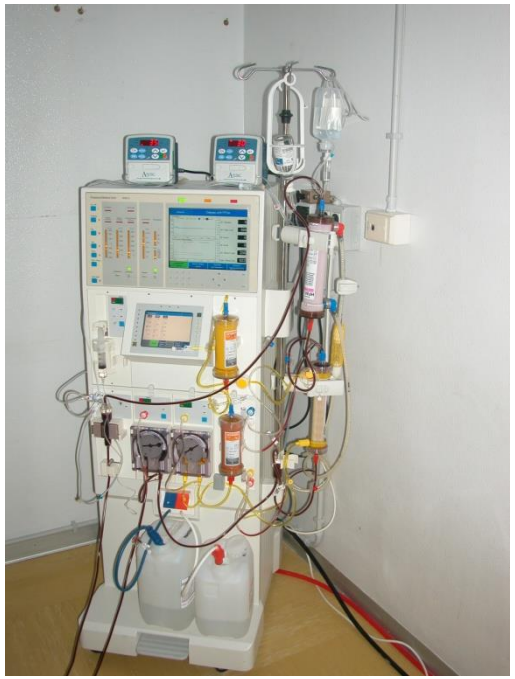
Malpighi Nephrology, Bologna

Patients treated: 24

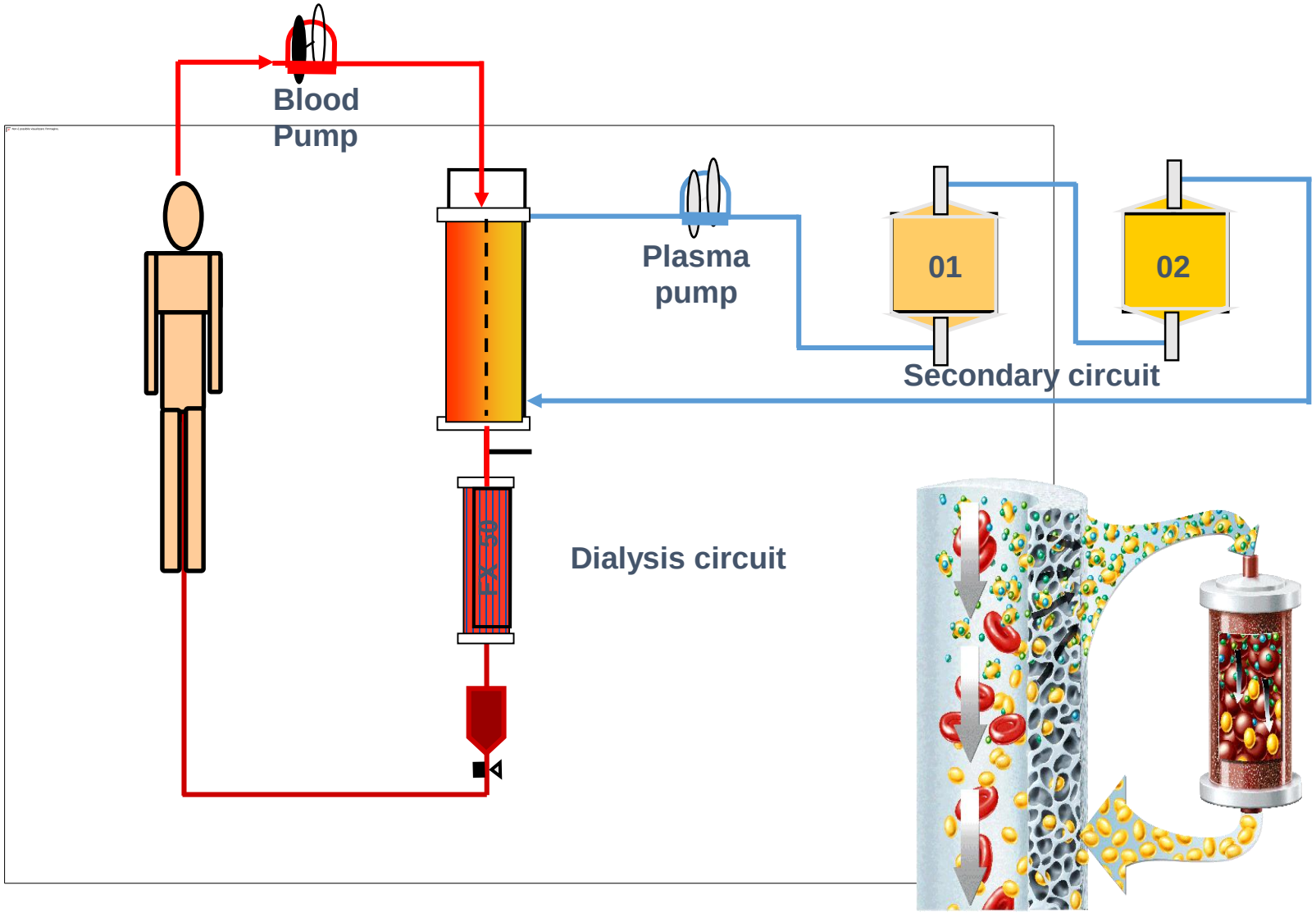
Treatments : 104

On waiting list for OLT: 10

Received OLTs: 8



Fractionated Plasma Separation Adsorption and Dialysis : the system



Prometheus – Adsorbers

prometh® 01

Neutral, highly porous resin

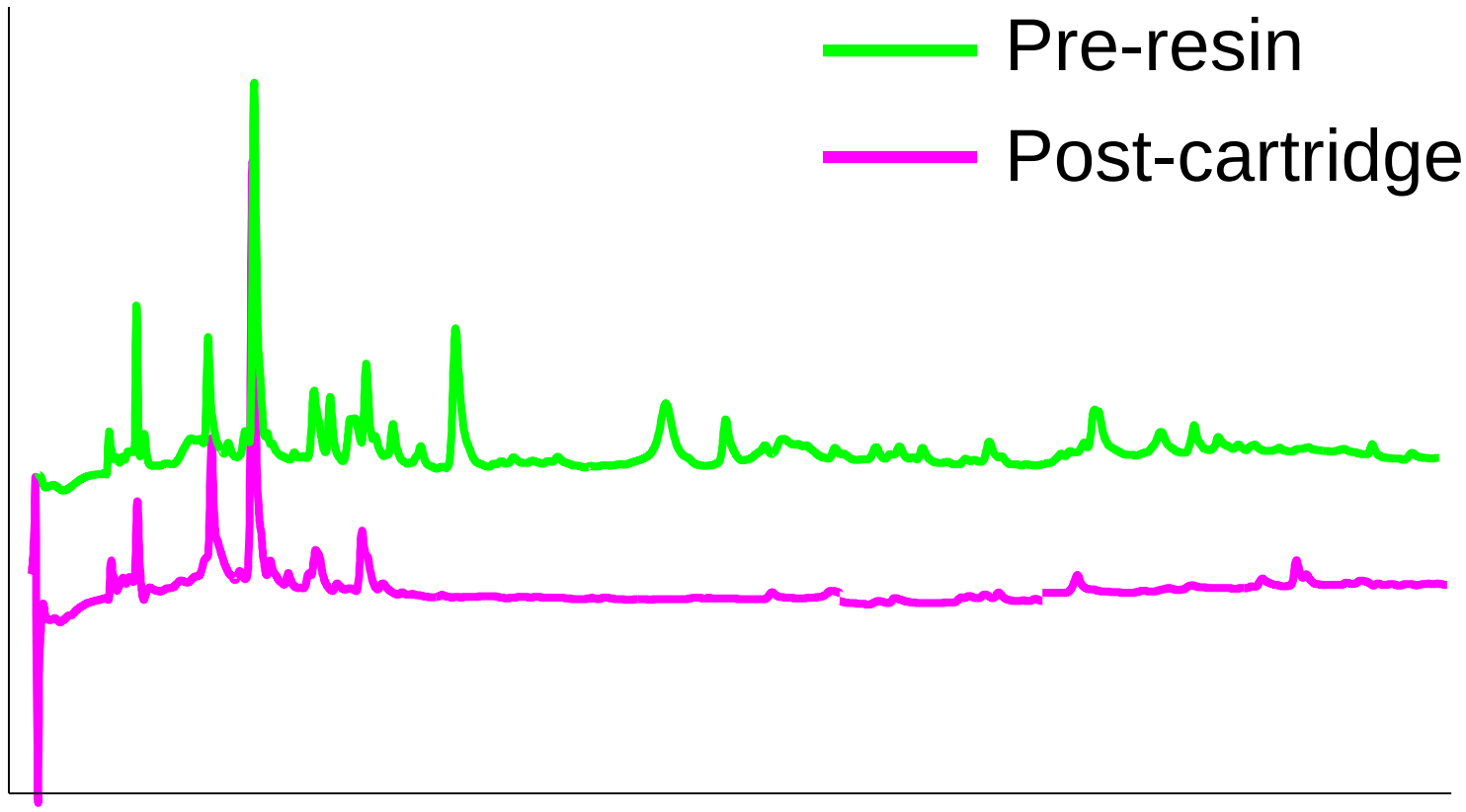
- *Specific surface: 1,050 m^2/g*
- *Grain diameter: 0.3 - 1.0 mm*
- ***Adsorber (phenols, triptophane, biliary acids)***
- *Priming volume (plasma): 91 ml*
- *Sterilisation: steam*

prometh® 02

Ionic alkaline exchange resin

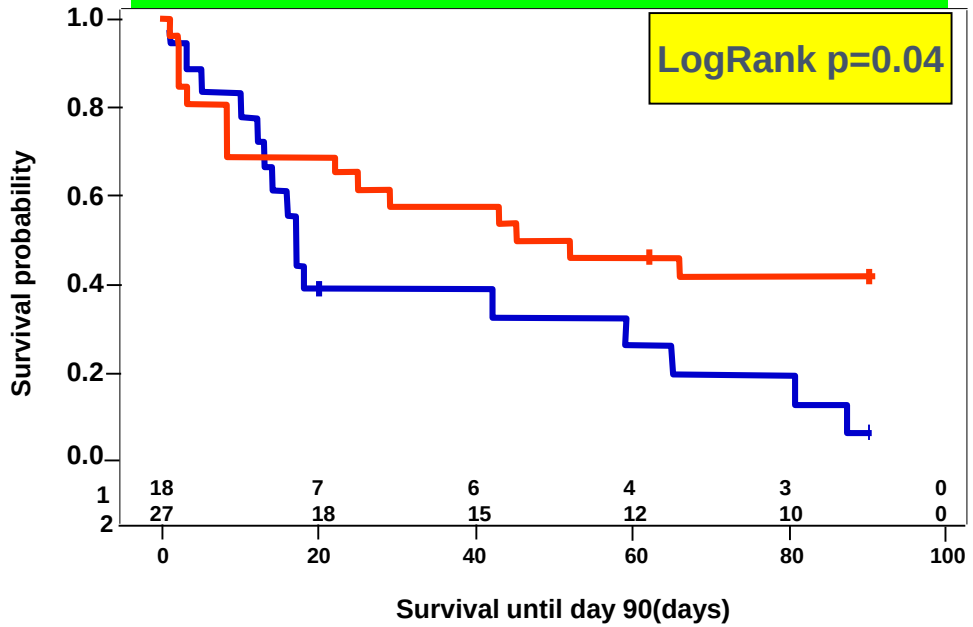
- *Chloride ion charged*
- *Specific surface: 23 m^2/g*
- *Grain diameter: 0.3 - 1.0 mm*
- ***Adsorber (bilirubin-unconjugated, uric acid)***
- *Priming volume (plasma): 91 ml*
- *Sterilisation: steam*

Reverse phase HPLC



HELIOS study (Prometheus European Liver Disease Outcome Study)

Survival benefit for pts with Hepatorenal Syndrome type I



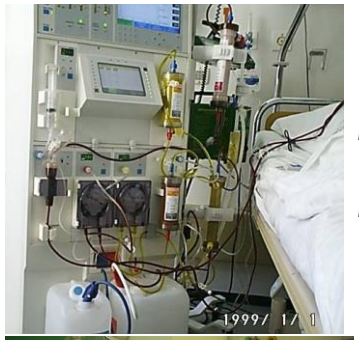
Survival benefit for pts with MELD score >30:

LogRank p= 0.02

A Kribben, ….. E Mancini, P Caraceni…..K Rifai and the HELIOS Study group *Gastroenterology, 2012*

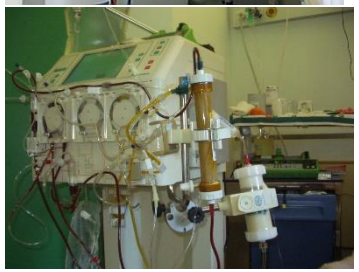
Special treatments, special devices

For End Stage Liver Failure



Prometheus System

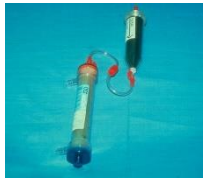
Mars system



Selective plasmapheresis

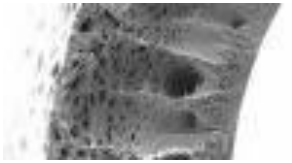
Bilirubin removal

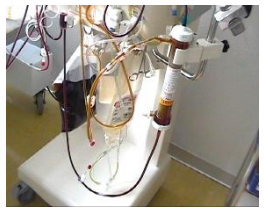
For toxic states, poisoning



Hemoperfusion, Charcoal resins

For hematological disorders, Light Chain removal, Hemolysis

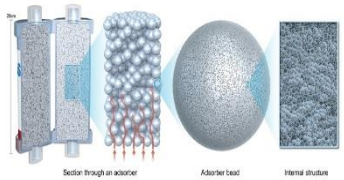




High cut-off superflux treatments, membrane adsorption, CPFA

For Sepsis

CPFA, Hemo/ Plasmadsorbtion

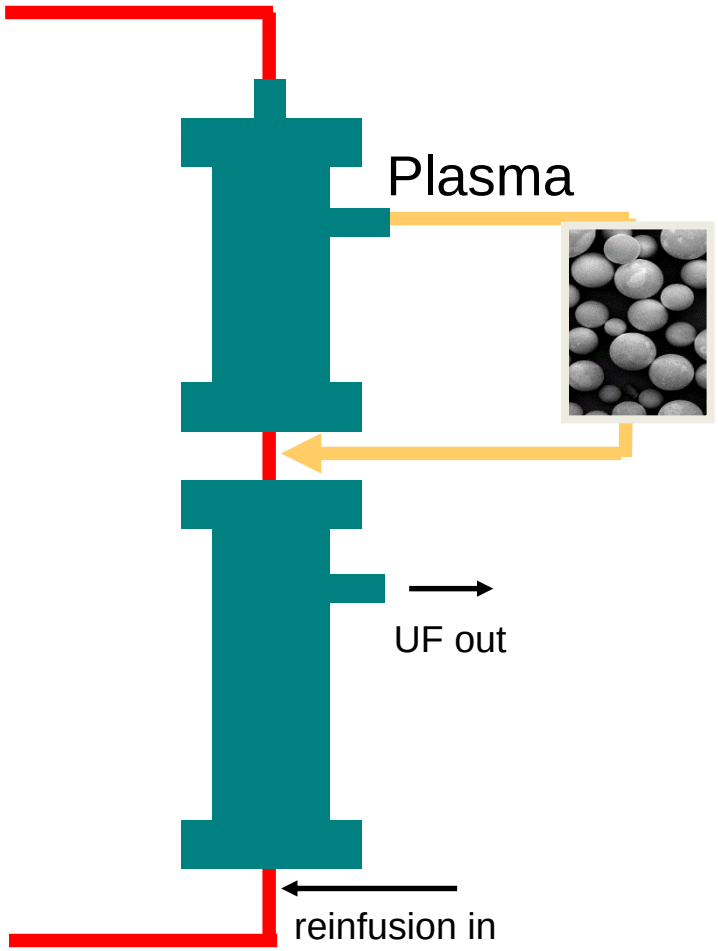


For Lipid disorders

LDL-aferesis

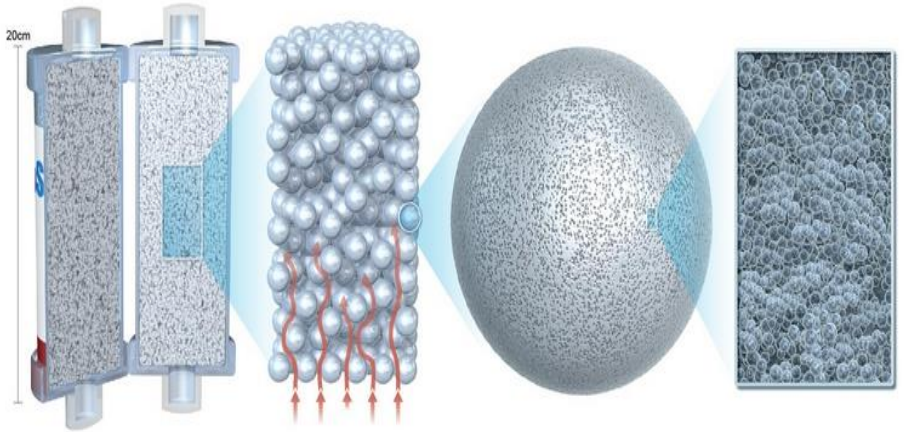
Rheoapheresis

Coupled Plasma Filtration-Adsorption



Selective removal of cytokines and inflammatory mediators

- Highly biocompatible, porous polymer beads
- Removal of hydrophobic substances due to
  - physicochemical properties
  - pore size



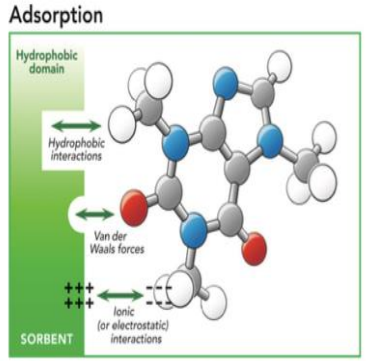
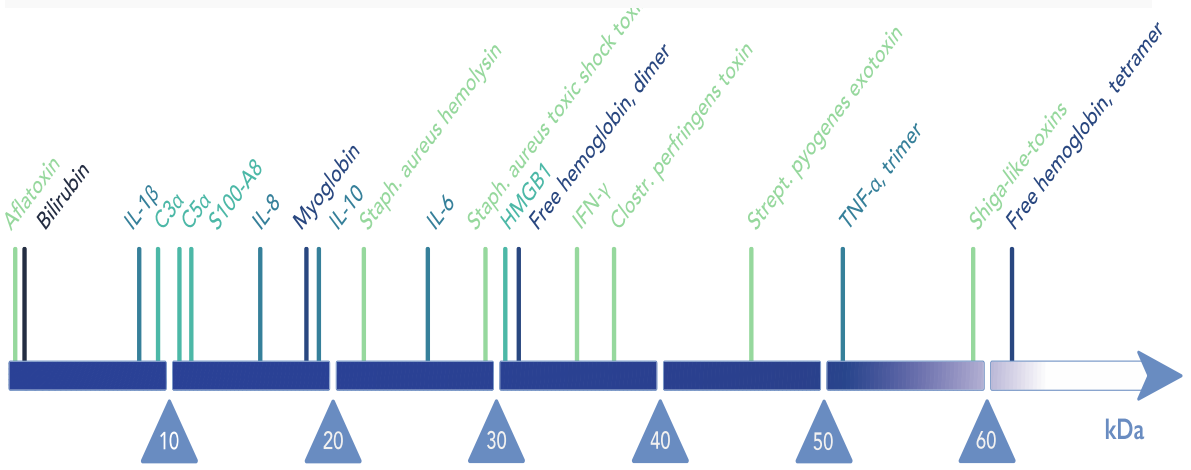


Fig. 3. Adsorption corresponds to the saturable fixation of some molecules directly on a sorbent or a membrane along an affinity gradient depending on ionic, hydrophobic, and van der Waals interactions.

Size-selective removal

Controlled and effective adsorption of numerous substances

- PAMPS (Pathogen Associated Molecular Patterns) e.g. enterotoxins [12]
- DAMPS (Damage Associated Molecular Patterns) [12,13]
- Cytokines [1,2,3,4,5]
- Myoglobin [4,11]
- Metabolites (e.g. Bilirubin, Bile acids, Ammonia) [9,10]



FC/Reopheresis– clinical indications

IgM,crioglobuline, lipidi

- Waldenstrom's macroglobulinemia
- Crioglobulin
- Poluyneuropathy anti-MAG
- Polyarteritis
- Hyper-triglicerideremia (familiar and acute)
- Hyercolesterolemia
- Hyperlipoproteinemia (a)
- Reduction in viral load

IgG, IgA

- Mieloma IgA or IgG
- Vasculitis (Goodpasture and Wegener)
- GSF
- AB0 transplant incompatible
- Humoral rejection after renal transplantation
- Multiple sclerosis

Fibrinogen, lipids

- Degenerative maculopathy
- Acute hearing loss
- Diabetic food
- Peripheral arteriopathy

Journal of Clinical Apheresis 31:149–162 (2016)

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue

Joseph Schwartz,[1] Anand Padmanabhan,[2] Nicole Aqui,[3] Rasheed A. Balogun,[4] Laura Connelly-Smith,[5] Meghan Delaney,[6] Nancy M. Dunbar,[7] Volker Witt,[8] Yanyun Wu,[9] and Beth H. Shaz[1,10,11]*

Category Definition for Therapeutic Apheresis

Category	Description
I	Disorders for which apheresis is acccepted as first-line therapy, either as primary standalone treatment or in conjunction with other modes of treatment
II	Didorders for which apheresis is acccepted as second line therapy either as a standalone treatment or in conjunction with other modes of treatment
III	Optimum role of apheresis therapy is not established. Decision making should be individualized
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful

Journal of Clinical Apheresis 22:270–276 (2007)

Complications of Therapeutic Plasma Exchange: A Prospective Study of 1,727 Procedures

Douglas Shemin,* Doris Briggs, and Melanie Greenan

Division of Renal Diseases, Rhode Island Hospital, Department of Medicine, Brown University School of Medicine, Providence, Rhode Island

The type and number of complications was prospectively examined in 1,727 successive TPE treatments in 174 patients over 66 months at a single center. Most treatments were prescribed for thrombotic thrombocytopenic purpura (TTP; 42%), recurrent focal segmental glomerulosclerosis (FSGS; 22%), or myasthenia gravis (MG; 13%). About 57% of treatments used albumin–saline as the replacement solution and 43% used fresh-frozen plasma (FFP), almost all for TTP. There were 889 complications; 614 treatments (36% of the total) involved a complication. Most complications were minor; there were no deaths. Three treatments (0.2%) were discontinued due to a complication, and 2 (0.1%) required transfer to a higher acuity hospital bed. The most common complications were fever (7.7% of treatments), urticaria (7.4%), and hypocalcemic symptoms (7.3%). 42% of treatments with FFP involved a complication, compared to 30% of treatments using albumin–saline ($P < 0.0001$). The most common complications with FFP were urticaria (17%) and pruritis (13%); these occured more commonly than in patients receiving albumin–saline. The most common complications with albumin–saline replacement were hypocalcemic symptoms (8.2%) and mild hypotension (8.1%). Mild and severe hypotension was significantly ($P < 0.0001$) more common with albumin–saline replacement. TPE is associated with a number of minor complications. Complications occur more commonly with FFP replacement compared to albumin–saline replacement. Pruritis and urticaria occur more commonly with FFP, and hypotension occurs more commonly with albumin–saline. J. Clin. Apheresis 22:270–276, 2007.

Key words: therapeutic apheresis; complications

INTRODUCTION

Therapeutic plasma exchange (TPE) involves the separation of blood into its component parts by a centrifugation or a filtration method, and the subsequent removal of plasma and its replacement by an equal volume of fresh-frozen plasma (FFP) or some combination of serum albumin and isotonic sodium chloride. TPE is thought to be clinically effective for two reasons: it may decrease the concentration of a pathogeneic plasma protein and allow the administration plasma proteins in diseases associated with deficiencies of or inhibitors to proteins without the risk of volume overload. A large number of disparate diseases have been shown to respond to TPE: thrombotic thrombocytopenic purpura (TTP) [1], Guillain-Barré syndrome (GBS) [2] myasthenia gravis (MG) [3], antiglomerular basement membrane disease [4], chronic inflammatory demyelinating polyradiculoneuropathy [5], recurrent focal and segmental glomerulosclerosis (FSGS) [6], Waldenstrom macroglobuminemia, and cryoglobulinemia [7]. In addition, a large number of diseases have been reported, usually in published case reports or anecdotes, to respond dramatically to TPE; in general, criteria describing improvement tend to be subjective and not uniform. It is probably accurate to say that the number of conditions for which plasmapheresis may have a role is much greater than the number of conditions in which plasmapheresis clearly has a role. Many patients receive therapeutic plasmapheresis when their diagnosis is unclear and their condition is deteriorating, in an attempt to improve a desperate situation [8].

TPE has been used at least since 1960, when it was shown to be beneficial in Waldenstrom macroglobulinemia [9]. The frequency of its use is not completely known. In Sweden, 41.5 treatments per 100,000 population were done in 1995, and 24.0 per 100,000 population in 2002 [10]. The largest and most complete TPE registry, in Canada, reports a stable number of 8,500 treatments per year [11], assuming similar practice patterns in the United States, which has over 10 times the Canadian population, it is likely that almost 100,000 TPE treatments are done annually in this country.

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DOI: 10.1002/jca.20143

Total treatments with complications	614 (36%)
Fever	133 (7.7%)
Urticaria	128 (7.4%)
Hypocalcemic symptoms	126 (7.3%)
Pruritis	101 (5.8%)
Tachycardia	96 (5.6%)
Mild hypotension (SBP < 95 mmHg)	96 (5.6%)
Nausea	56 (3.2%)
Vomiting	47 (2.7%)
Dizziness	23 (1.3%)
Severe hypotension (SBP < 85 mmHg)	22 (1.3%)
Exit site bleeding	21 (1.2%)
Exit site infection	9 (0.5%)
Headache	6 (0.3%)
Chest pain	6 (0.3%)
Dyspnea	4 (0.2%)
Back pain	3 (0.2%)
Abdominal pain	2 (0.1%)
Anxiety	2 (0.1%)
Arrhythmia	2 (0.1%)
Leg cramps	2 (0.1%)
Pharyngitis	2 (0.1%)


WHAT'S NEXT

Therapeutic Apheresis in the 21st Century:

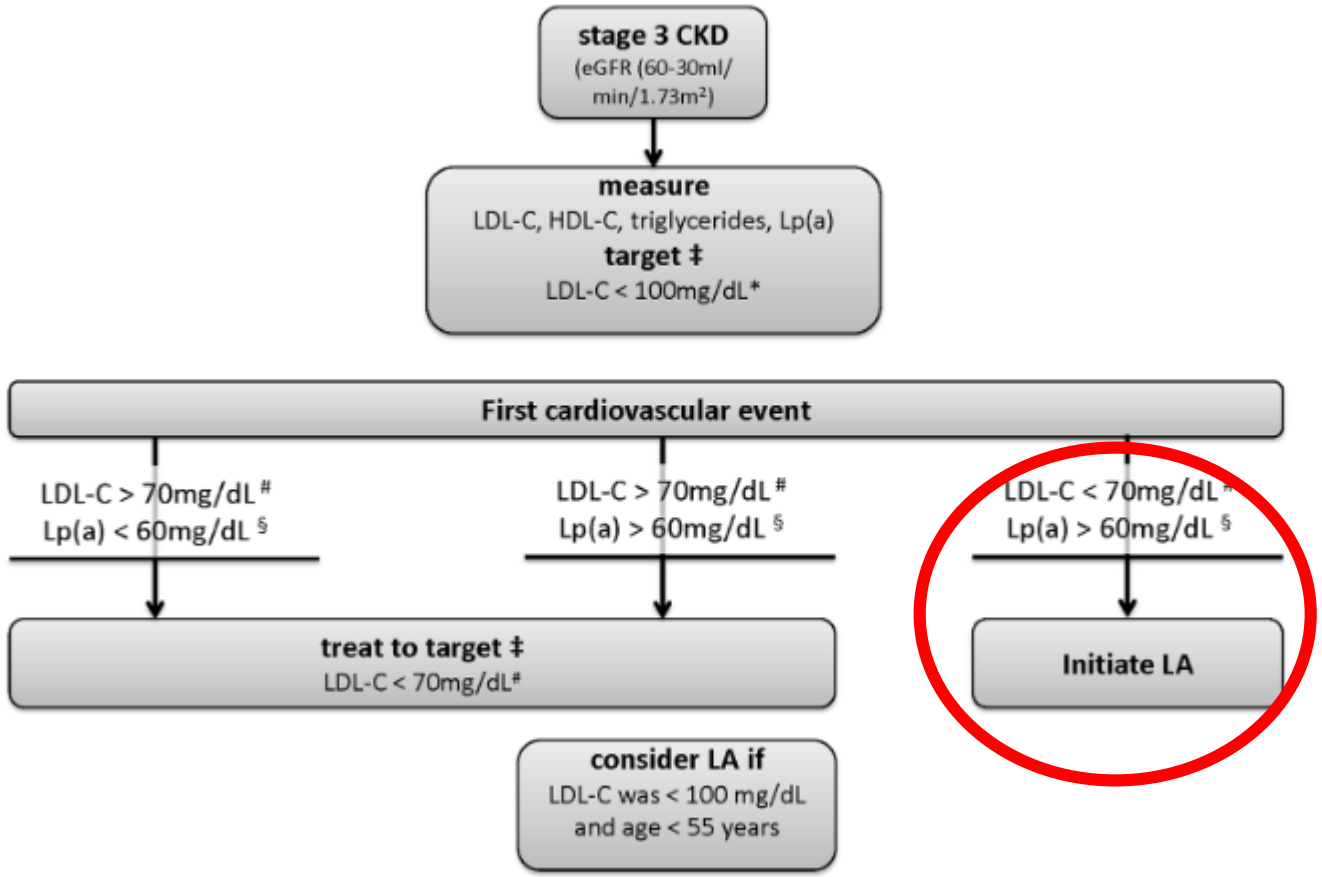
1) Therapeutic plasma exchange or absorption

2) Cythoapheresis

Clin Res Cardiol Suppl (2017) (Suppl) 12:27–30
DOI 10.1007/s11789-017-0086-z

Lipoprotein(a) in nephrological patients

Bernd Hohenstein[1,2]



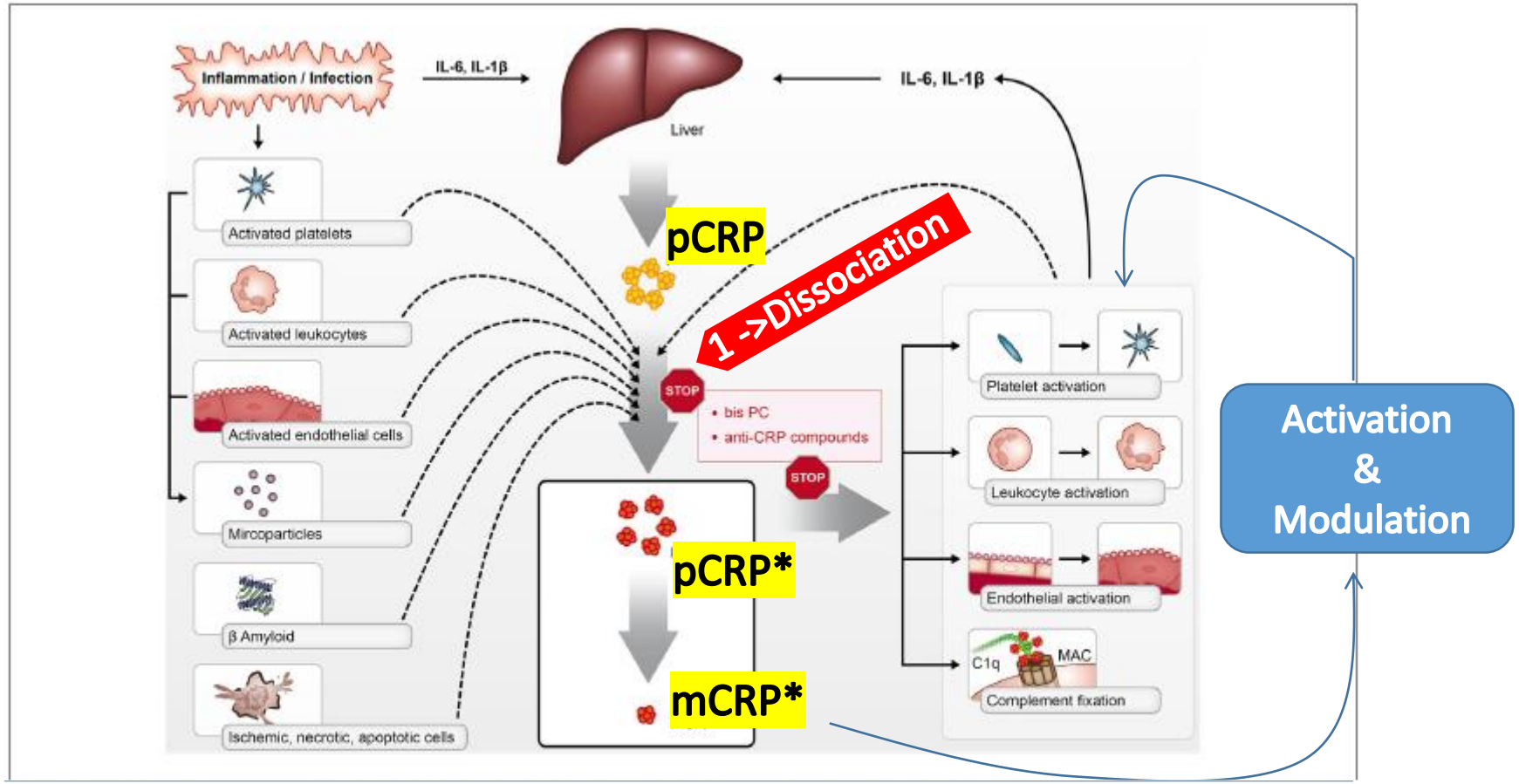
Role of C-reactive protein in Acute Myocardial Infarction

1. CRP: well known and widely recognized as a marker of inflammatory reactions [1].
2. CRP concentration increases in AMI [2].
3. Its level predicts the AMI outcome [2].

Growing body of data aimed to show its role as direct mediator of inflammatory reactions and the innate immune response [3].

1. Abernethy TJ, Avery OT., J Exp Med (1941) 73:173–82Clinical
2. Ridcker P, Clinical Chemistry (2009) 55:2 209–215.
3. McFadyen JD, et al, Front. Immunol. (2018) 9:1351.

Direct Biological Role of C-Reactive Protein and its Conformational Changes



McFadyen JD, et al, Front. Immunol. (2018) 9:1351.

Selective apheresis of C-reactive protein: A new therapeutic option in myocardial infarction?

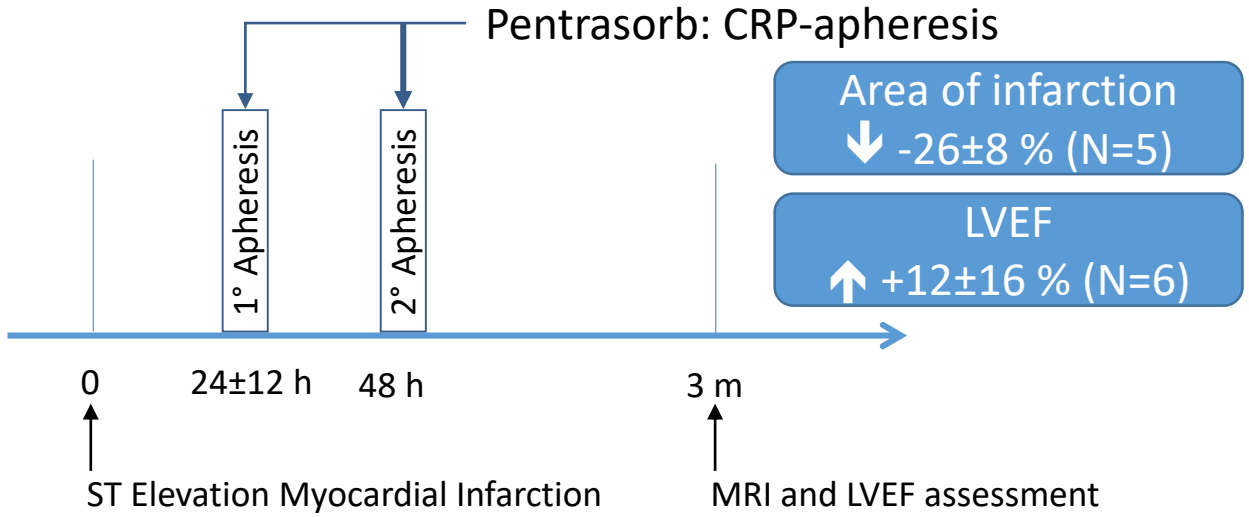
Hypothesis

Limiting Myocardial Damage during Acute Myocardial Infarction by inhibiting C-Reactive Protein, Richard Kitsis, N Engl J Med 2006; 355:513-515:
1,6-bis(phosphocholine)-hexane inhibits increased myocardial damage

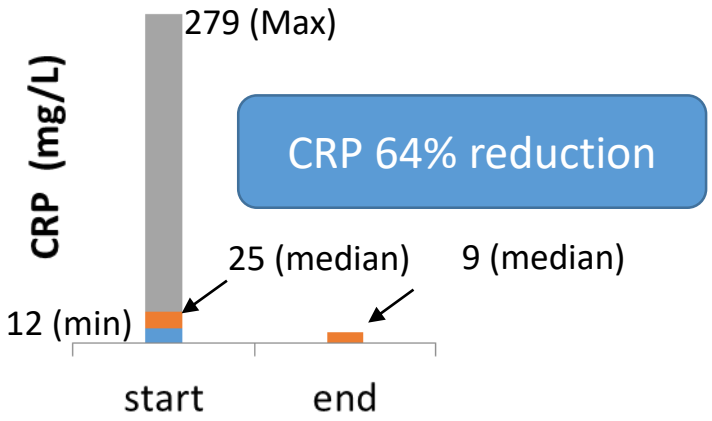
Removal

Selective removal of CRP by apheresis:
Mechanism: removal by plasma Phosphocholine derivative in agarose beads

First clinical results of CRP-apheresis after AMI in humans

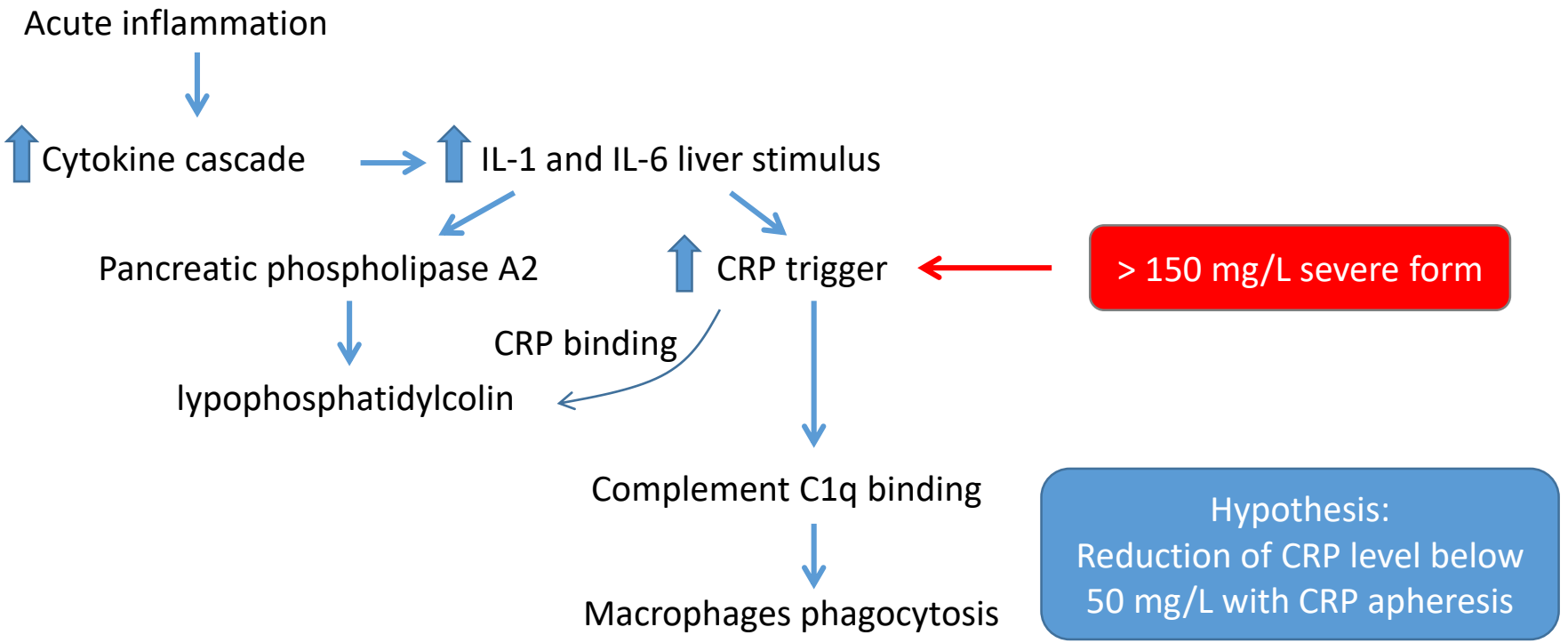


Apheresis: 2 treatments lasting 4-5 h each 6L plasma treated



Ries W. et al, Ther Apher Dial, 2018, 21, 5, 532-533

Further application of CRP apheresis: severe acute pancreatitis

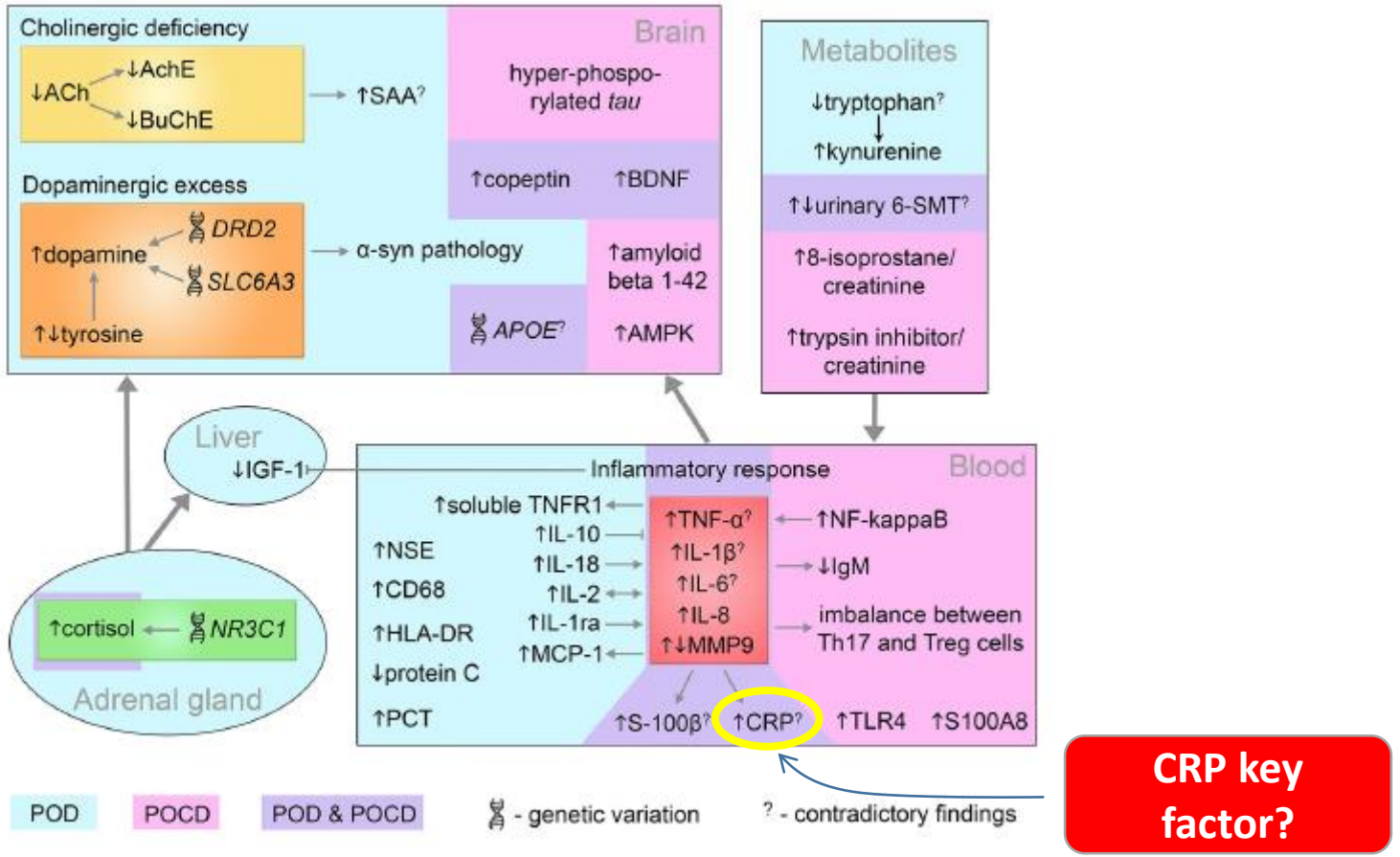


Sheriff A et al, Ther Apher Dial, 2018, 21, 5, 532

Further potential application of CRP apheresis: post-operative delirium

- Delirium affects 15–53% of older surgical patients
- Associated with several poor outcomes, including: longer hospital stay,
  - greater postoperative complications,
  - higher rates of discharge to nursing homes

Mechanism of PO delirium and related biomarkers

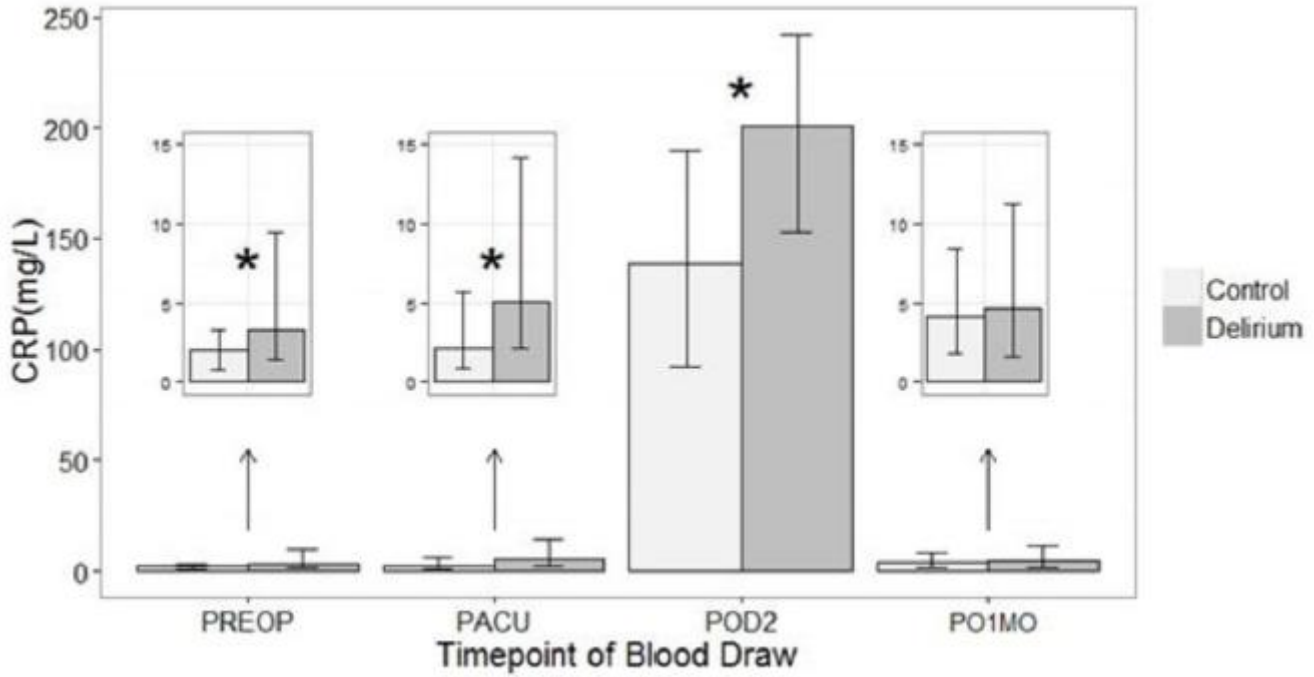


CRP key factor?

Androsova G, 2015, Front. Aging Neurosci. 7:112

CRP postoperative level

- POCD patients have elevated levels of CRP following
  - coronary artery by pass grafting (Hudetz etal., 2011),
  - liver transplantation (Li etal., 2013b)
  - lumbar discectomy (Zhang et al., 2014a)

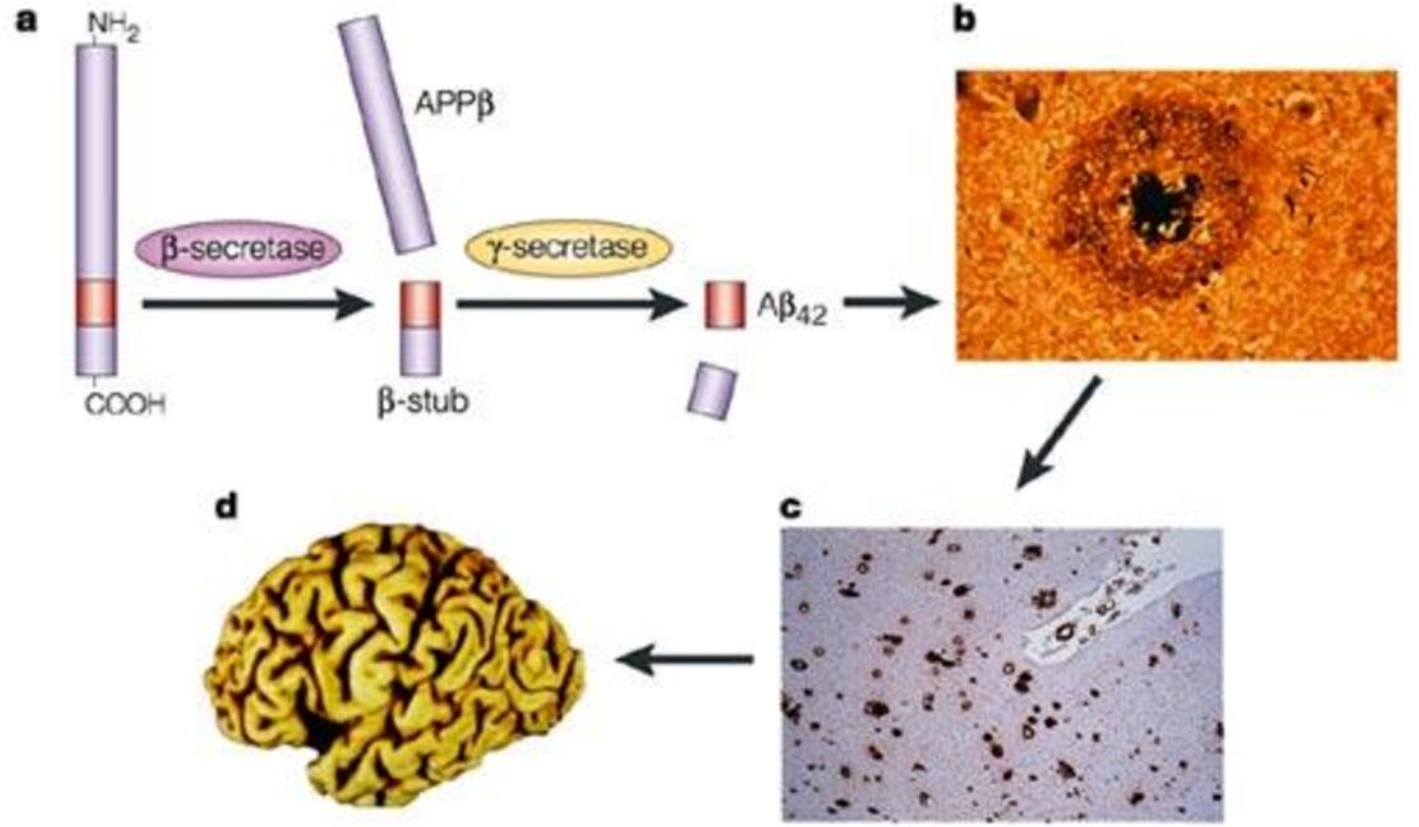


Therapeutic Apheresis in the 21st Century: Therapeutic plasma exchange plus or absorption

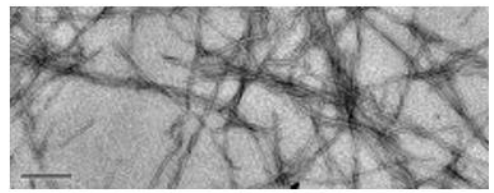
- Atopic (neuro) dermatitis (atopic eczema) recalcitrant
- Cardiac neonatal lupus
- Complex regional pain syndrome
- Erythropoietic porphyria, liver disease
- Hashimoto's encephalopathy
- HELLP syndrome
- Hemophagocitic lynphohistiocytosis
- N-methyl D-aspartate receptor antibody encephalitis
- Prevention of RhD alloimmunization after RBC exposure
- Progressive multifocal leukoencephalopathy associated with nataluziamab
- Dementia, Alzheimer's disease

One in three elderly have dementia when they die
Janice Lloyd, USA TODAY12:23a.m. EDT March 19, 2013

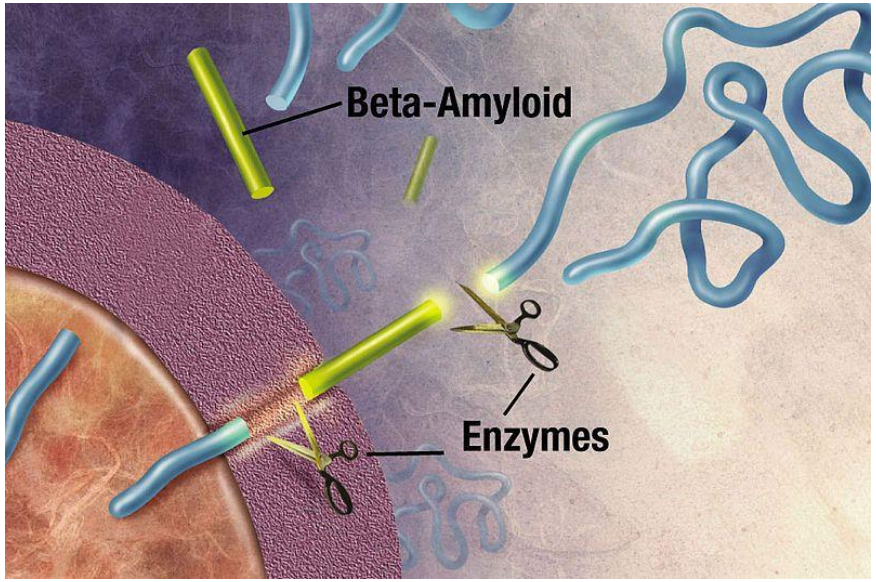
- The number of people with Alzheimer's disease is expected to rise from 5.2 million to 13.8 million by 2050
- Payments for health care, long-term care, and hospice care are expected to increase from $203 billion to $1.2 trillion by 2050 for patients ages 65 and older.
- Medicare costs for an older person with Alzheimer's or other forms of dementia are nearly three times higher than for seniors without dementia. Medicaid payments are 19 times higher.
- The stress on caregivers is estimated to result in the more than $9 billion in increased health care costs.

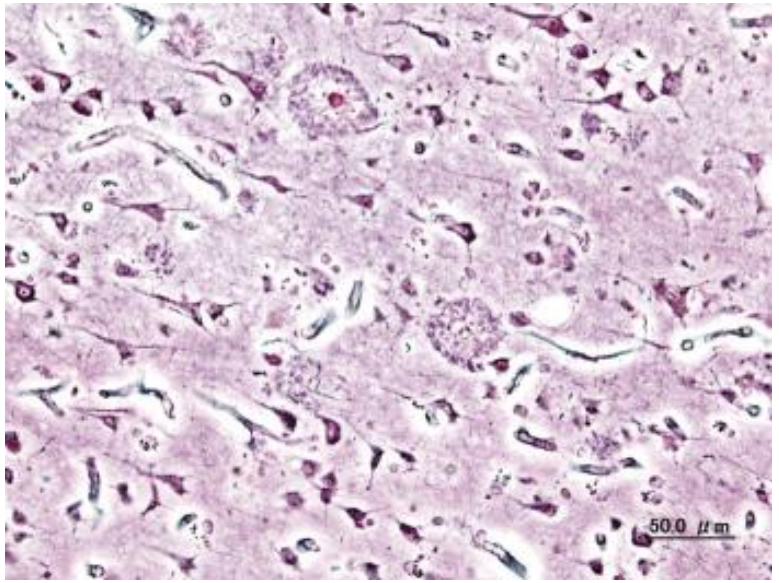


Nature Reviews | Neuroscience



Amyloid in Brain





People who have Alzheimer's disease have higher concentrations of plaques in areas of the brain responsible for memory, like the hippocampus.

Lifelong Management of Amyloid-Beta Metabolism to Prevent Alzheimer's Disease

Sam Gandy, M.D., Ph.D.

N Engl J Med 2012; 367:864-866August 30, 2012DOI: 10.1056/NEJMe1207995

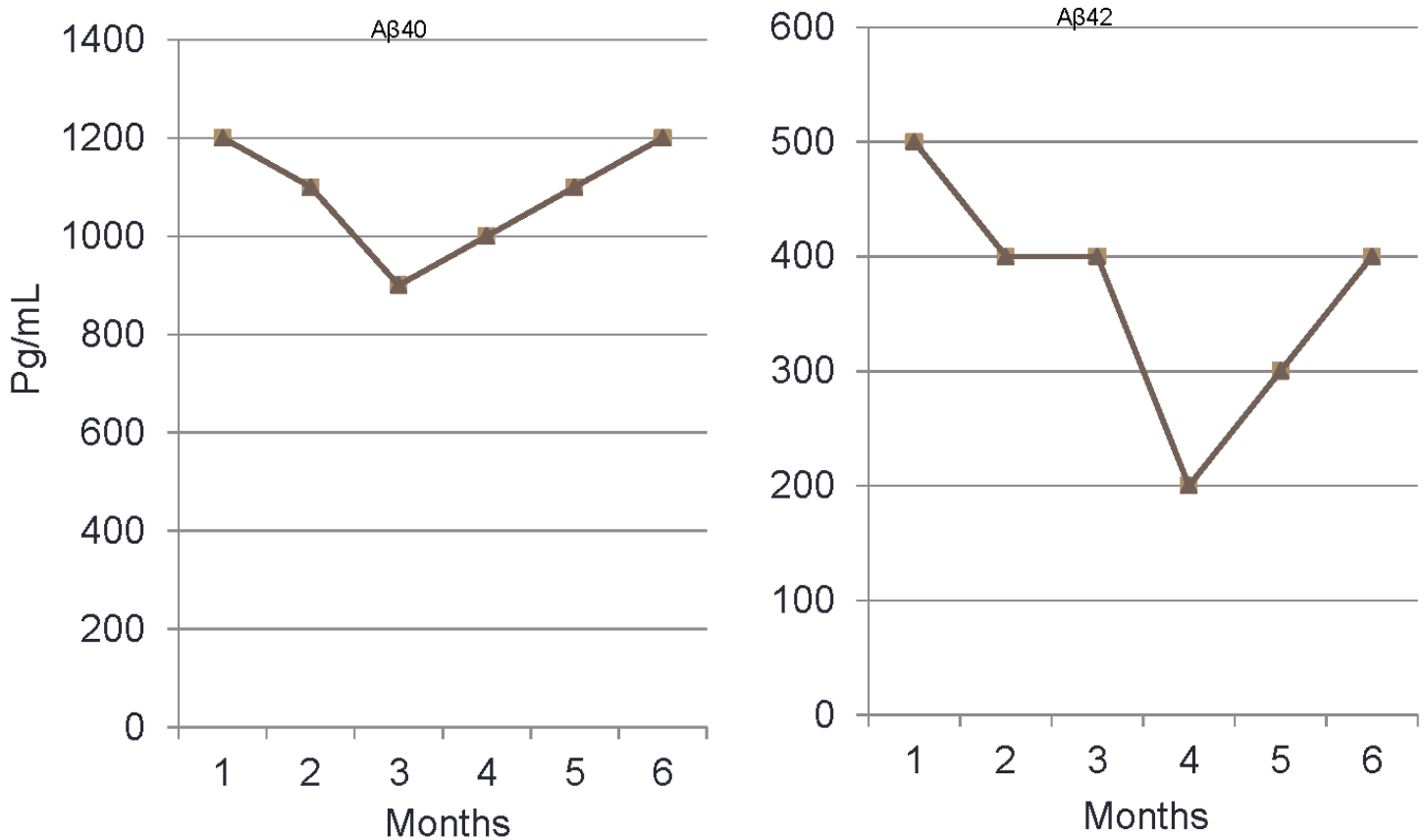
- There is growing interest in Aβ-lowering therapies for presymptomatic disease.
- What is also clear — regardless of whether, in light of the protective APP mutation, one considers the “amyloid hypothesis of Alzheimer's disease” as proven or not — is that any comprehensive strategy aimed at reduction of late-life dementia risk will almost certainly include monitoring and immunopharmacologic or neuropharmacologic control of Aβ metabolism.

Neurologia. 2016 Sep;31(7):473-81. doi: 10.1016/j.nrl.2014.02.003. Epub 2014 Jul 9.

Treatment of Alzheimer disease using combination therapy with plasma exchange and haemapheresis with albumin and intravenous immunoglobulin: Rationale and treatment approach of the AMBAR (Alzheimer Management By Albumin Replacement) study.

[Article in English, Spanish]

Boada M[1], Ramos-Fernández E[2], Guivernau B[2], Muñoz FJ[2], Costa M[3], Ortiz AM[3], Jorquera JI[3], Núñez L[4], Torres M[4], Páez A[4].



Champagne Improves Memory

- *Giulia Corona, David Vauzour, Justine Hercelin, Claire M Williams, Jeremy P.E. SpencerAntioxidants & Redox Signaling. March 2013,*

Autoantibodies to Adrenergic Receptors in Dementia

- agAAB directed against G protein-coupled receptors (GPCR) seems to modulate several cardio- and cerebrovascular diseases as dilated cardiomyopathy and dementia.
- The pathogenic effect of agAAB has been demonstrated in rat models for the α1-adrenergic receptor in the context of cerebrovascular impairment.

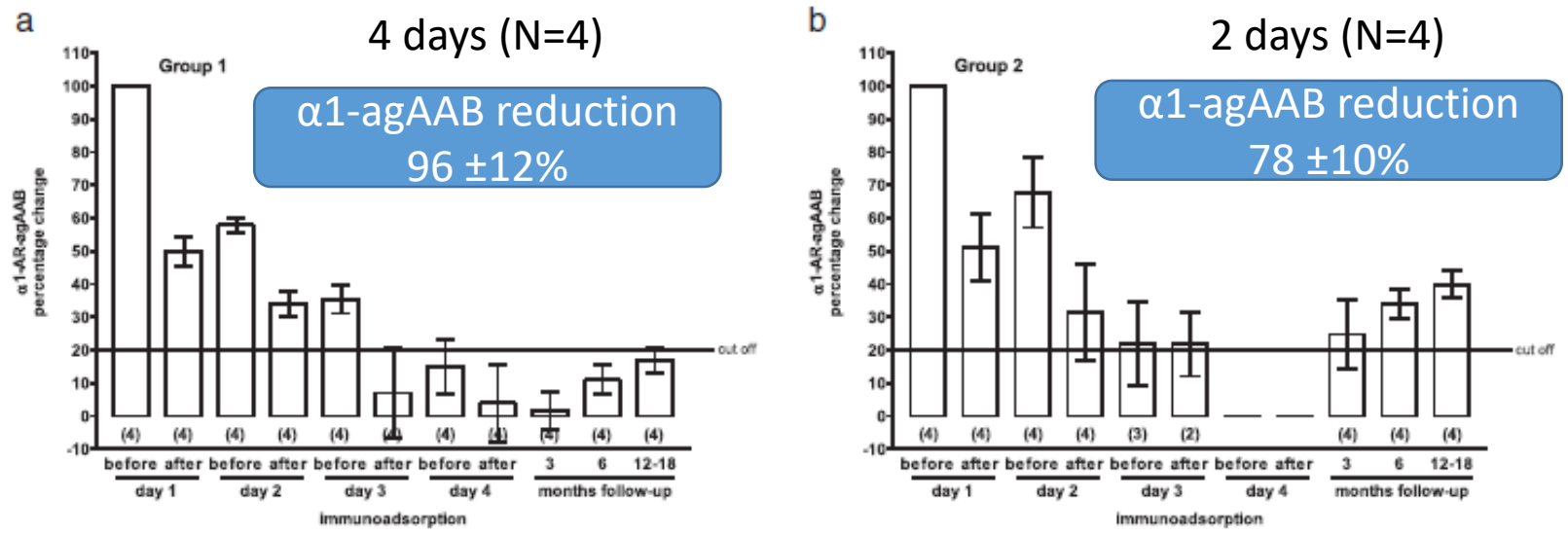
	Number	Age (mean ± SD)	MMSE[a] (mean ± SD)	agAAB positive for AR		
				α_1	β_2	$\alpha_1 + \beta_2$
Dementia	54	77 ± 10	23 ± 5	8	3	21
Controls[b]	12	83 ± 10	n.d.	1	0	1

[a]Mini-mental state examination.

P. Karczewski et al, Scandinavian Journal of Immunology, 2012, 75, 524–5

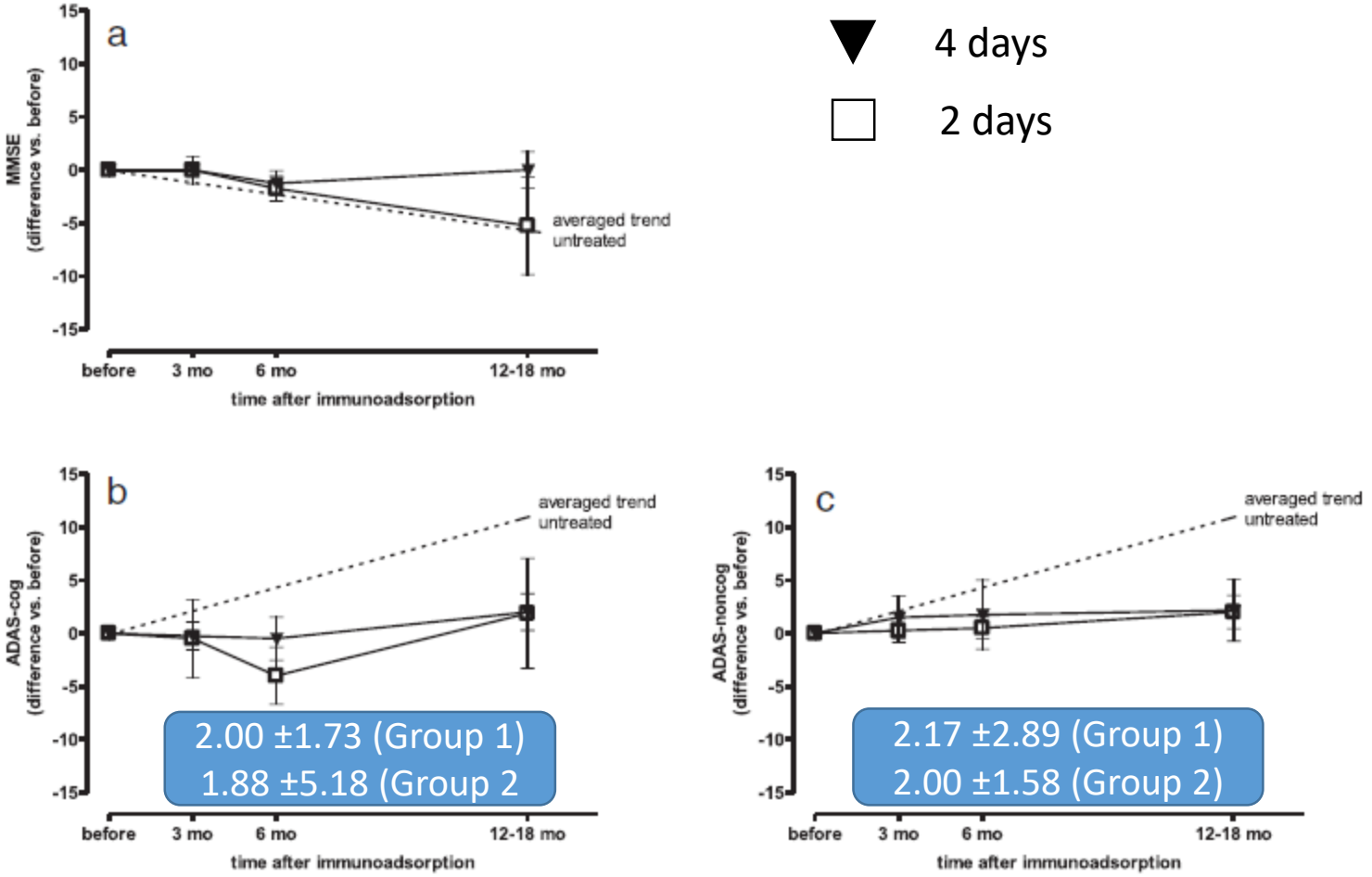
Immunosadsorption in Alzheimer disease

- Elimination of IgG by immunoadsorption is highly effective in removing agAAB
- Immunoadsorption period of 2 - 4 consecutive days with Protein-A Immunosorba, for 2.0 – 2.5 plasma volume treatment



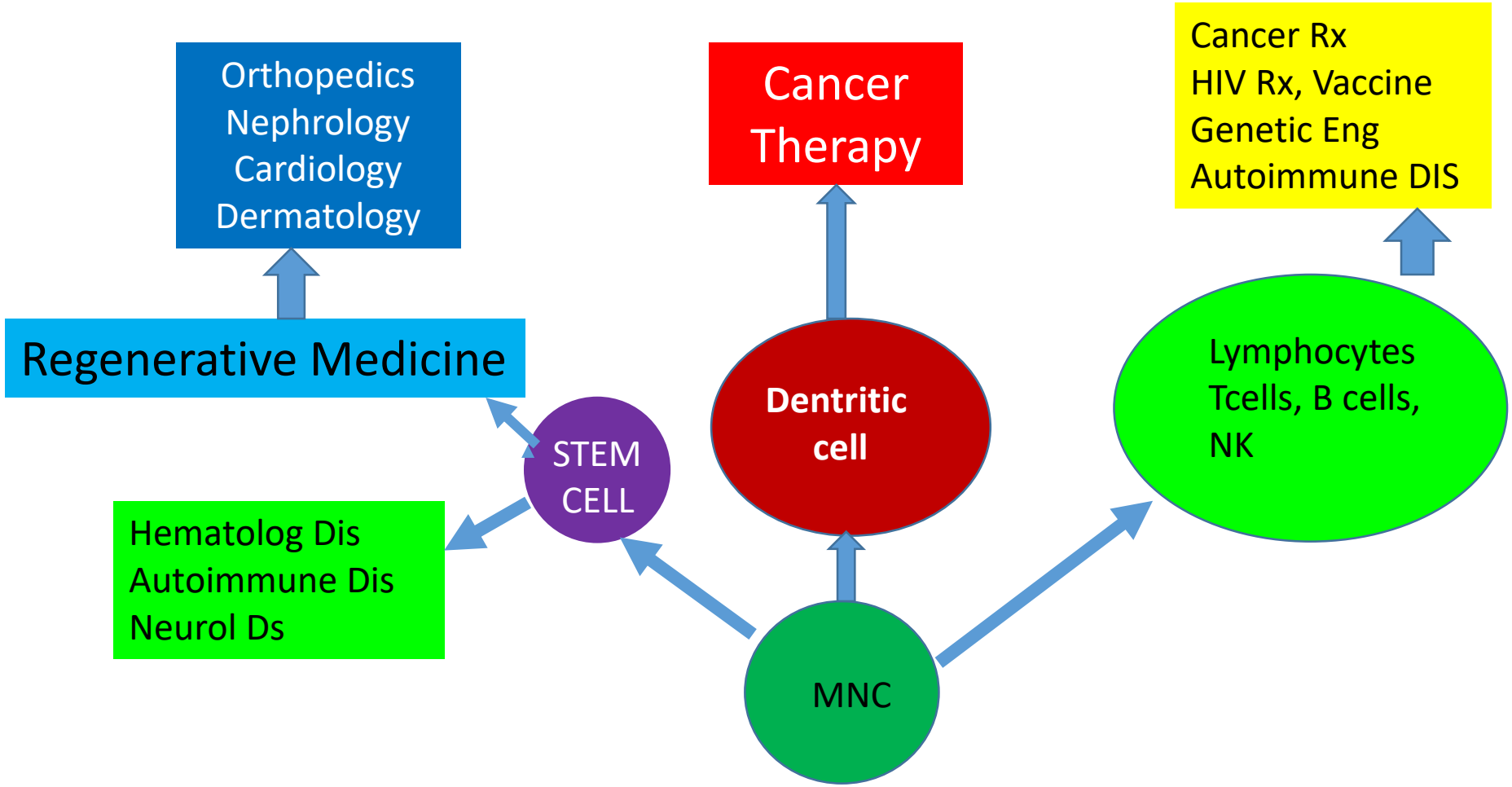
Hampel P et al, Ther Apher Dial, Vol. 20, No. 5, 2016

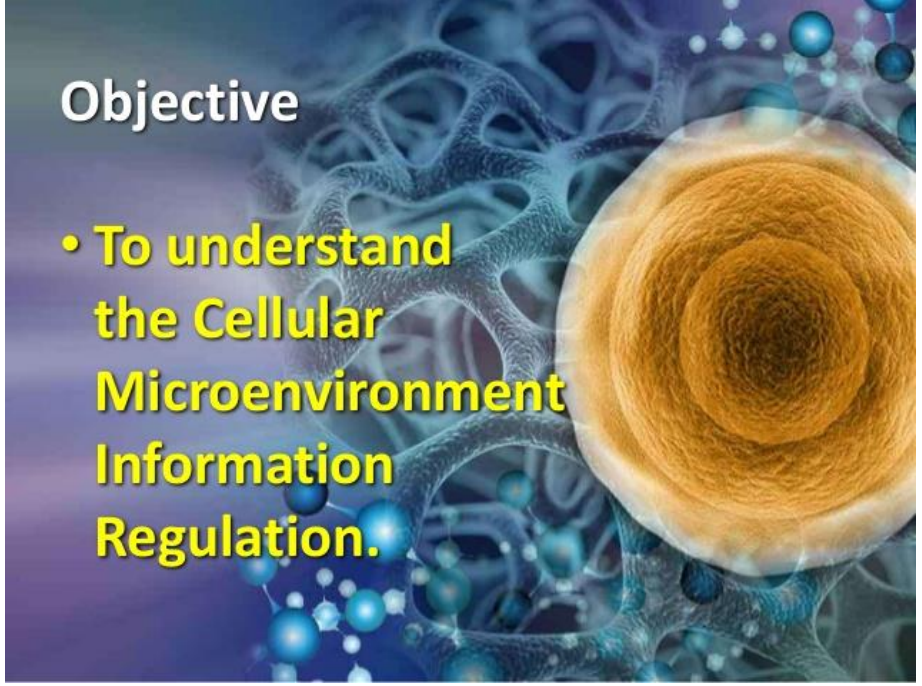
Mini Mentale State Examination and Alzheimer's Disease Assessment Scale

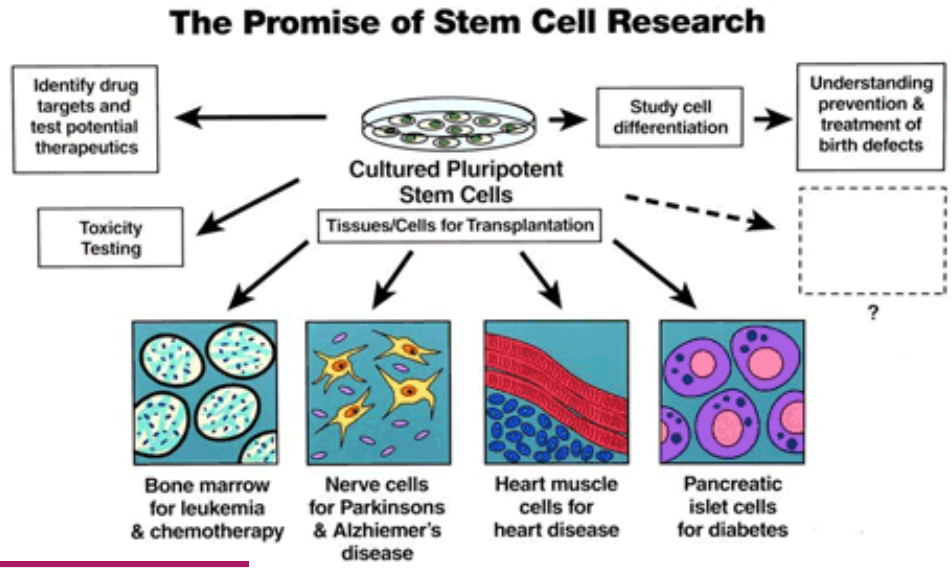


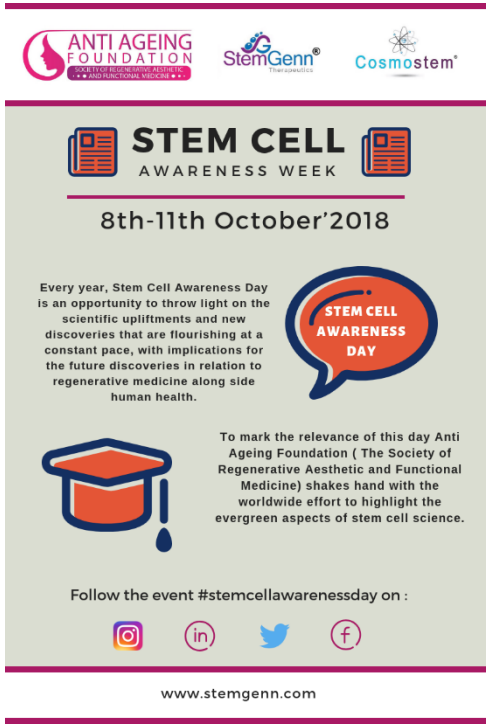
Hampel P et al, Ther Apher Dial, Vol. 20, No. 5, 2016

Therapeutic Apheresis in the 21st Century: Cytoapheresis with mononuclear cells collection




Objective
• To understand the Cellular Microenvironment Information Regulation.


The Promise of Stem Cell Research
Identify drug targets and test potential therapeutics
Study cell differentiation
Understanding prevention & treatment of birth defects
Cultured Pluripotent Stem Cells
Toxicity Testing
Tissues/Cells for Transplantation
?
Bone marrow for leukemia & chemotherapy
Nerve cells for Parkinsons & Alzhiemer's disease
Heart muscle cells for heart disease
Pancreatic islet cells for diabetes


ANTI AGEING FOUNDATION
StemGenn
Cosmostem
STEM CELL
AWARENESS WEEK
8th-11th October'2018
Every year, Stem Cell Awareness Day is an opportunity to throw light on the scientific upliftments and new discoveries that are flourishing at a constant pace, with implications for the future discoveries in relation to regenerative medicine along side human health.
STEM CELL AWARENESS DAY
To mark the relevance of this day Anti Ageing Foundation (The Society of Regenerative Aesthetic and Functional Medicine) shakes hand with the worldwide effort to highlight the evergreen aspects of stem cell science.
Follow the event #stemcellawarenessday on :
www.stemgenn.com

Opportunities in Apheresis

Stem cell and cancer vaccines

New Technology

Cell reinfusion

Very expensive
Time consuming
Inefficient
Infections
Travel
Cell viability

Primary System

Membran Filter → Separation

Centrifuge

Throw away

TPE

Secundary System

Plasma Modulation

Cryo-Filtration
Heparin Precipitation

Plasma Filtration

Cascade Filtration

Plasma -Hemo Perrfusion

Dextran sulfate Adsorption
Immuno-Adsorption

Polymer beads

Conclusion

- Apheresis is a useful treatment modality used in a variety of life-threatining conditions
- Usually a temporary measure until definitive therapy
- Evidence in many conditions is lacking
- Must be used carefully also for possible complications
- The future in many new diseases is a combination of plasma absorption and cytoapheresis