Extracorporeal Blood Therapies
Membrane Plasma Treatment

Paul S. Malchesky, D.Eng.

The International Center for Artificial Organs and Transplantation

Painesville, OH, USA

Outline of Presentation

- Rationale for Extracorporeal Therapies
- Selection of Apheresis Technology
- Why Membrane Plasma Filtration?
- Sorbent Applications
- Temperature Regulated Membrane Plasma Filtration
- Limitations to Achieving Potential

Rationale for Extracorporeal Therapies

- Abnormal chemistries in disease states
- Excess solutes may be detrimental
- Removal of excesses will improve symptomology and possibly effect a cure
- Define removal means

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Example of Renal Failure

- Abnormal chemistries
  - Toxins, electrolytes, water
- Removal means
  - Forced diuresis, sauna bath treatment, edible sorbents, microorganisms, blood exchange, dialysis (GI, peritoneal, hemo)
- Dialysis “most practical”

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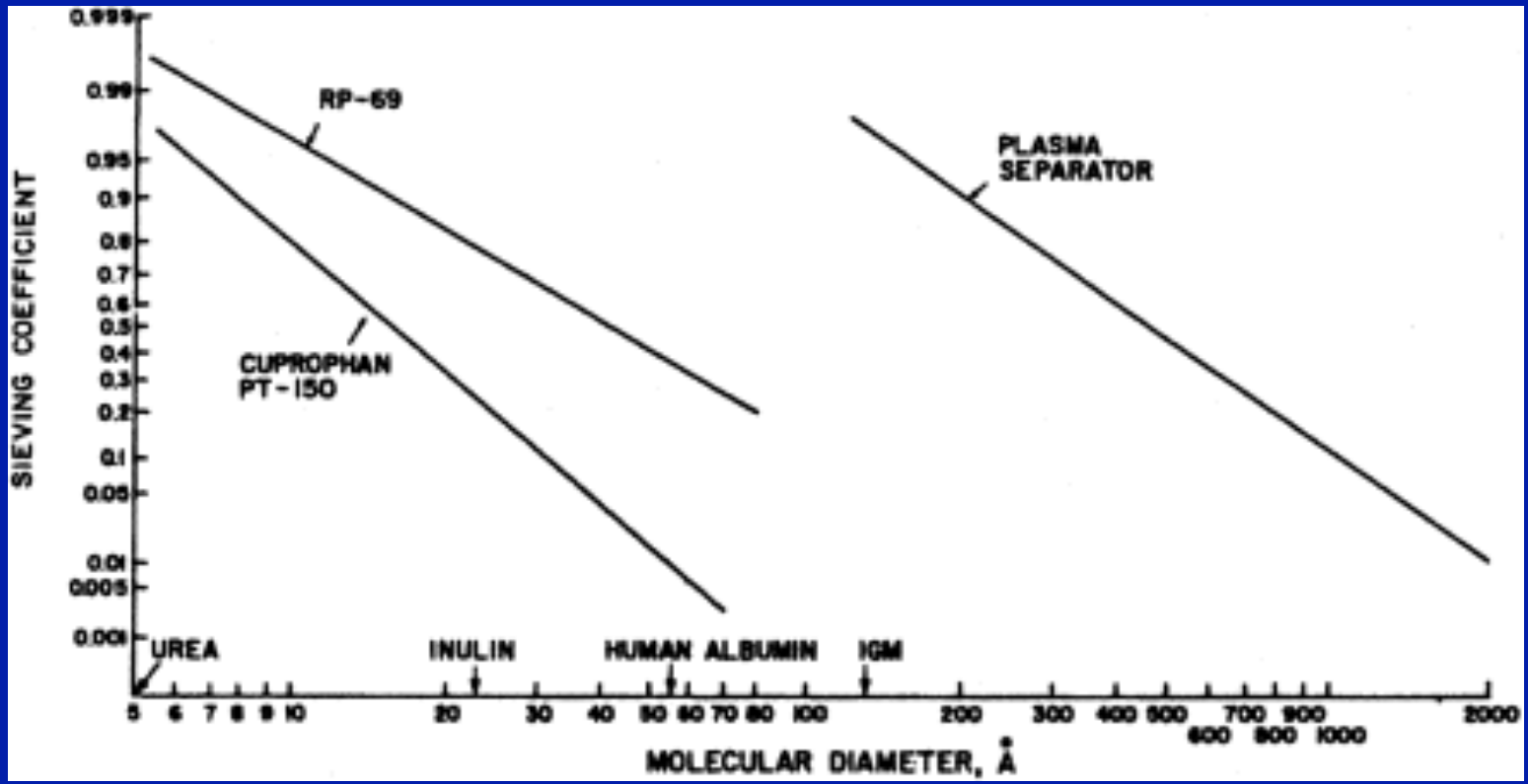
Extrapolation to Other Diseases

- Standard dialysis has molecular size removal limits
- Many disease states (metabolic, immunologic) exhibit abnormalities of higher molecular weight solutes or protein-bound solutes
- Identification of appropriate separation/removal means (i.e. sorption, plasma exchange, blood/plasma treatment)

Sieving as a Function of Molecular Diameter

For membranes used in plasma separation, hemofiltration (RP-69) and dialysis (Cuprophan PT-150)



Malchesky, PS et al. *Ther Apher* 2000; 4:47-53.

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Immunological Disorders

Disease	Increased factor(s) or abnormality
Myasthenia gravis	Antibody specific for acetylcholine receptor
Renal transplant rejection Goodpasture's syndrome	Antibody to glomerular and lung basement membranes
Rhesus incompatibility	Anti-D-antibody
Systemic lupus erythematosus	DNA antibodies and immune complexes of DNA
Glomerulonephritis	Immune complexes or autoantibodies, fibrinogen, complement
Macroglobulinemia (Waldenstrom's syndrome)	Increased IgM and hyperviscosity
Pemphigus vulgaris	Increased IgG antibodies
Asthma bronchitis	Increased IgE
Myeloma	Increased myeloma globulin
Raynaud's disease	Increased macroglobulin, increased viscosity
Thrombocytopenic purpura	Increased immune complex
Cancer	α-1, α-2 globulins, β-globulins, α1-antitrypsin, ceruloplasmin, orosomucoid, haptoglobin, IgA
Breast cancer	Increased circulating immune complex
Polyneuropathy	Increased antibodies to myelin
Rheumatoid arthritis	Immune complexes, rheumatoid factor
Diabetes	Autoantibodies to insulin receptor
Autoimmune hemolytic anemia	Antibody to RBC

Malchesky PS et al. *Trans Am Soc Artif Intern Organs* 1981:27:439-43.

Metabolic Disorders

Disease	Increased factor(s) or abnormality
Hypercholesterolemia	Cholesterol forms including LDL, VLDL
Hypertriglyceridemia,	Triglycerides and hyperviscosity
Hypercoagulability Hyperviscosity Syndrome	Fibrinogen, fibronectin
Macroglobulinemia (Waldenstrom's syndrome)	Increased IgM and hyperviscosity
Chylomicronemia	Chylomicrons
Hepatic coma and insufficiency	Metabolic factors
Refsum's Disease	Phytabuc acid (bound to lipoproteins)
Poisonings	Protein-bound drug
Dialysis dementia	Protein-bound aluminum
Amyotrophic lateral sclerosis (?)	Cytotoxic factors, immune complexes suspected

Malchesky PS et al. *Trans Am Soc Artif Intern Organs* 1981:27:439-43.

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Apheresis Technology

- Cell separation
  - Leukocytes
    - Subfractions
- Plasma separation
  - Exchange
  - Treatment
    - Sorbent
    - Membrane
    - Other physio-chemical means

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Why Plasma Exchange for Macromolecule Removal?

- Historical – largest database
- Procedural – simple
- Disease requirement – not known for most disease states

Various Disease States Treated by PE

Myasthenia gravis	Hepatic coma and insufficiency	Diabetic hypertriglyceridemia
Glomerulonephritis	Raynaud's disease	Hypercholesterolemia
Goodpasture's syndrome	Renal transplantation	Cancer
Skin diseases Pemphigus Herpes gestationis	Removal of protein-bound toxins Poisons Hormones Metals	Hypertension
Severe asthma	Rhesus incompatibility	Motor neuron diseases
Immune complex diseases Crescentic nephritis Systemic lupus erythematosus Wegner's polyarteritis Subacute bacterial endocarditis Cryoglobulinemia Cutaneous vasculitis	Hematological diseases Hemolytic anemia Red cell agglutinins Auto-antibody lymphocytes TTP Immune thrombocytopenia Factor VIII inhibitor or antibodies	Macroglobulinemia Waldenström's syndrome Hyperviscosity syndrome Paraproteinemias, myeloma
Insulin resistant diseases	Refsum's disease	Arthritis
Sezary syndrome	Guillain-Barré syndrome	Idiopathic pulmonary hemosiderosis

Malchesky PS et al. *Trans Am Soc Artif Intern Organs* 1981:27:439-43.

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Disincentives of Plasma Exchange
(Centrifugal or Membrane)

- Requirement for plasma products for infusion (availability an issue)
- Possible contamination of infusion solution or reactions thereof (viruses, prions)
- Loss of plasma solutes and cells (minimal by membrane technologies)
- Potential loss of essential plasma constituents

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Selection of Solute(s) Removal Means

- Safe
  - Biocompatible, releases no detrimental agent, requires no biological infusion products
- Effective
- Not too selective (broad selectivity)
- Versatile
- Cost effective

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Renal Failure: Lesson Learned

Non-selective (dialysis) approach although imperfect proves to be life sustaining

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Severe Sepsis: Lessons Learned

- Major cause of mortality
- Leads to multiorgan failure
- Causes homeostasis imbalance
- Shows increase in pro- and anti-inflammatory mediators
  - Single causative mediator unlikely
- Non-selective extracorporeal removal methods perform better
- Continuous methods perform better
- Treatment dose may be important
- Early intervention is beneficial

Malchesky PS. Plasma Solute Removal in Critical Care. Presented at the 5th World Congress of the ISFA. May 5-8, 2005 in Rostock, Germany.

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Nonbiologic Semiselective Plasma Treatment

- Eliminates requirement for plasma replacement products
- Spares normal plasma constituents
- Treatment modules are safe
- General applicability

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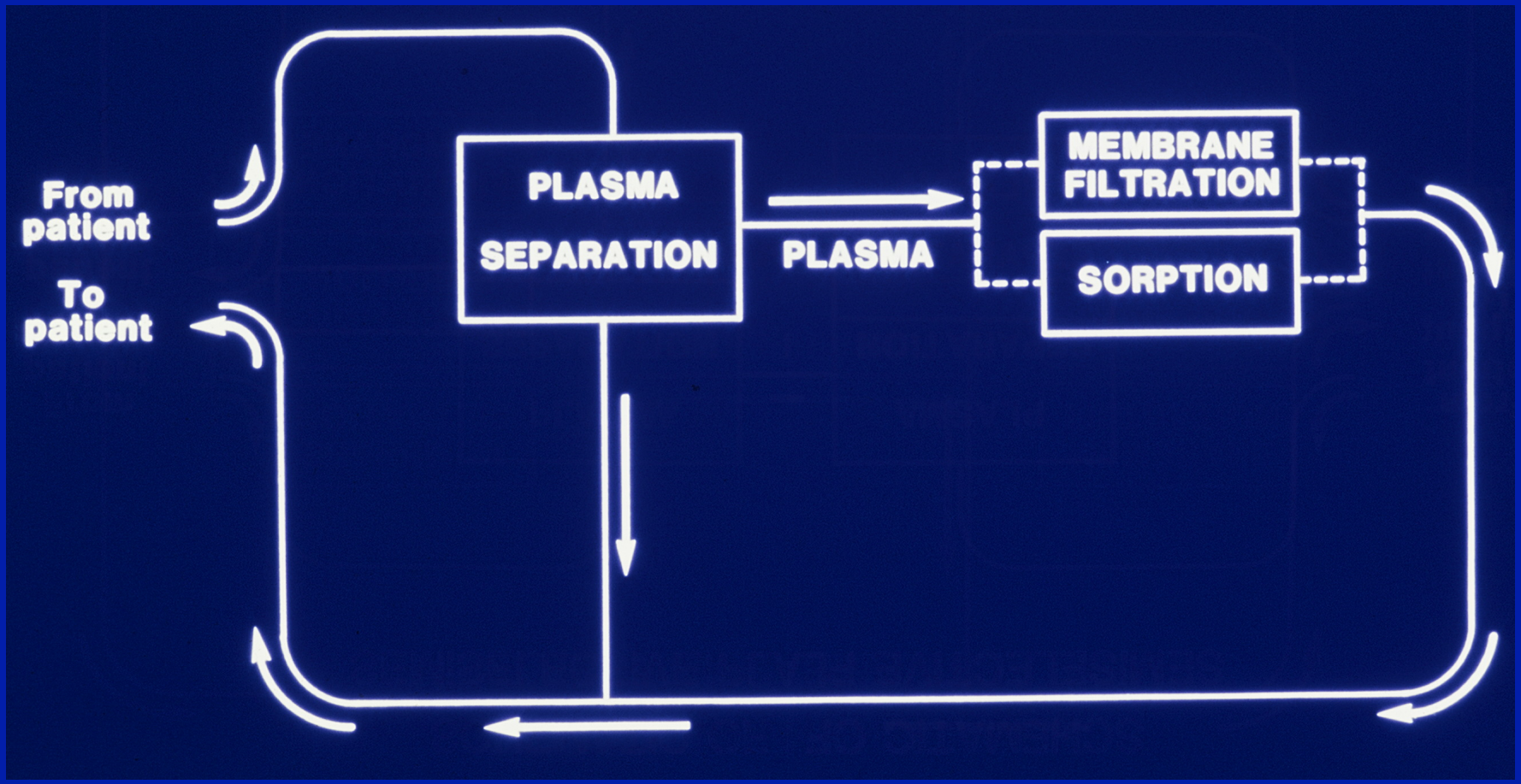
Schematic of Circuitry for Nonbiologic Plasma Treatment



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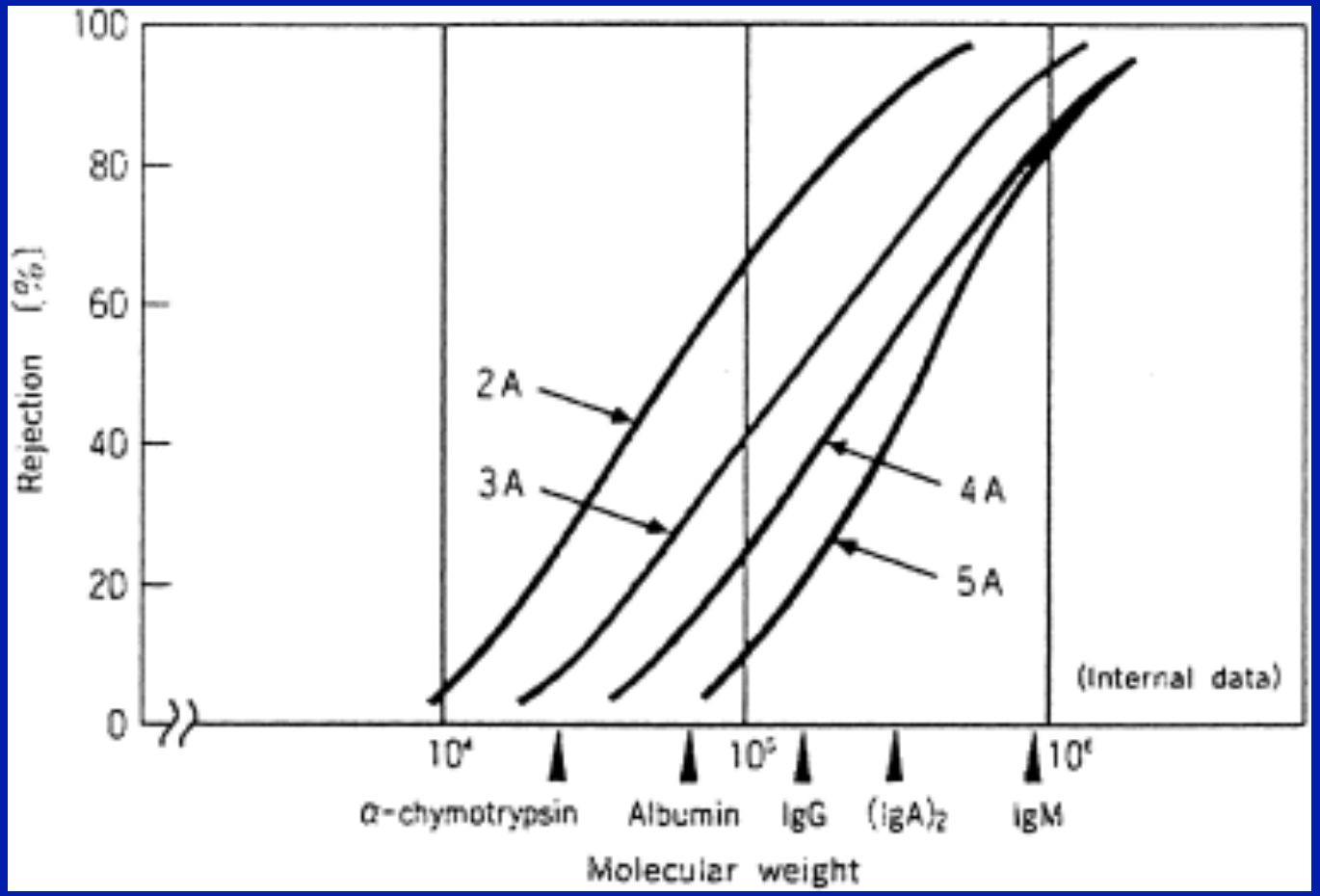
Why Membrane Plasma Filtration?

- For disease states treated by plasma exchange the marker solutes are of a molecular weight greater than that of albumin and generally greater than 100,000 daltons
- Molecular cut offs of membranes not very selective (circa 1981)
- Improve selectivity by augmenting molecular separation (i.e. temperature)
  - Cryofiltration for removal of cold aggregating solutes
  - Thermofiltration for removal of lipid and higher molecular with solutes

Membrane Plasma Filtration

- Based on size differential
- More selective than plasma exchange
- Cost effective compared to other on-line treatments
- Temperature dependency
- Unique membranes
- Novel module designs

Rejection Curves of 4 Types of Evaflux Membranes



Nakaji S, Yamamoto, T. *Ther Apher* 2002; 6:267-270.

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Clinical Applications of Evaflux for Various Diseases

	Disease	Target substances to remove	Membrane
Collagen	Malignant rheumatoid arthritis	Immune complex, Rh factor, anti-RANA Ab macroglobulin, cryoglobulin	3A, 4A
	Systemic lupus erythematosus	Anti-DNA Ab, anti-nuclear Ab, immune complex, macroglobulin, cryoglobulin	2A, 3A
Neurological	Myasthenia Gravis	Anti-Ach R Ab, anti-skeletal muscle Ab	2A, 3A
	Guillain-Barré syndrome	Anti-myelin Ab, anti-skeletal muscle Ab, ganglioside Ab	2A, 3A
	Multiple Sclerosis	Anti-myelin Ab, anti-skeletal muscle Ab	2A, 3A
Hematological	Thrombotic thrombocytopenic purpura	Anti-platelet Ab	2A, 3A
	Hyperglobulinemia	Macroglobulin, IgM	3A, 4A
	Red cell isoimmunization	Anti-Rh Ab	2A, 3A
Renal	Focal glomerular sclerosis	LDL, IgM, C3	2A, 3A
	ABO-incompatible kidney transplantation	Anti-A or B Ab, anti-lymphocyte Ab	2A, 3A
Other	Multiple myeloma	M protein	2A, 3A
	Pemphigus (Pemphigoid)	Anti-epidermal cell membrane glycoprotein Ab	2A, 3A
	Familial hypercholesterolemia	LDL, VLDL	5A
	Arteriosclerosis	LDL, VLDL	5A

RANA: rheumatoid-associated nuclear antigen

Sueoka A. *Ther Apher* 2000; 4:, 211-212.

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Characteristics and Specifications of Secondary Membrane Plasma Fractionators

Secondary Filter	Membrane type	Agent removed
Evalfux 2A (Kuraray, Osaka, Japan)	Ethylene vinyl alcohol	IgG, IgA
Evaflux 3A (Kuraray)	Ethylene vinyl alcohol	Cytokines
Evaflux 4A (Kuraray)	Ethylene vinyl alcohol	IgM, LDL
Evaflux 5A (Kuraray)	Ethylene vinyl alcohol	LDL-C
Cryoglobulin filter (Pall Gelman, Ann Arbor, MI, U.S.A.)	Versapor acrylic copolymer	Cryoproteins
Plasmaflo-AP06M (Asahi, Tokyo, Japan)	Cellulose diacetate	Cryoproteins

Ig: immunoglobulin, LDL: low-density lipoprotein, LDL-C: low-density lipoprotein cholesterol.

Siami GA, Siami FS. *Ther Apher* 2001; 5: 315-320.

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Specifications of Commercialized Membrane Plasma Fractionators

Manufacturer	Filter	Membrane Material	Surface area (m^2)	Pore Size (μm)
Asahi Medical	Cascadeflo-1730	DA (HF)	1.7	0.013
	Cascadeflo-1740	CDA (HF)	1.7	0.018
	Cascadeflo-1760	CDA (HF)	1.7	0.025
	Cascadeflo-1770	CDA (HF)	1.7	0.037
	Plasmaflo-AP-06	CDA (HF)	0.65	0.2
Dideco SpA	Albusave BT 902	CDA (HF)	0.8	0.02
Kuraray	Evaflux 2A	EVAL (HF)	1.0, 2.0	0.01
	Evaflux 3A	EVAL (HF)	1.0	0.02
	Evaflux 4A	EVAL (HF)	1.0, 2.0	0.03
	Evaflux 5A	EVAL (HF)	2.0	0.03
Senko	MPF	PP (HF)	0.3-1.5	0.025
Teijin	TA-100	CDA (HF)	0.8	--
	TA-200		0.8	--
Terumo	CF-01	CA (PL)	1.0	--
Toray	Plasmax AC-08	PMMA	0.8	--
	Plasmax ASC-08	PMMA	0.8	--

Sueoka A. *Ther Apher* 1997; 1:138

Membrane Plasma Filtration

Disease	Solute
Cryoglobulinemia	Cryoglobulins
Rheumatoid arthritis	Immune complexes, cryoglobulins, rheumatoid factor, fibrinogen, others
Rheumatoid vasculitis	Immune complexes, cryoglobulins
Sjögren's syndrome	Cryoglobulins
Macroglobulinemia	IgM
Hypercholesterolemia	LDL, VLDL, Lp(a)
Hypertriglyceridemia	VLDL
Systemic lupus erythematosus	Anti-DNA antibody, immune complexes
Macular degeneration	Fibrinogen, cholesterol, von Willebrand factor, α2-macroglobulin

Medicare Approved Devices for Apheresis

As of May 1986, and As of July 2001

Disease	Methodology
Myasthenia gravis, acquired	Plasma exchange
Leukemia	Leukopheresis
Macroglobulinemia, primary	Plasmapheresis
Hyperglobulinemia	Apheresis
TTP, life threatening	Plasmapheresis, PE
Rheumatoid vasculitis, life threatening	Plasmapheresis, PE
Pruritis	Plasma perfusion (charcoal)
Good-Pasture's syndrome	PE
Glomerulonephritis, advanced	PE
Polyneuropathy, chronic relapsing	Plasmapheresis
Scleroderma, life threatening	Plasmapheresis
Polymyositis, life threatening	Plasmapheresis
Guillain-Barré	Apheresis
Systemic lupus erythematosus, life threatening	Apheresis

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Macromolecule Removal in Immunological Disorders Approved by Medicare for Treatment

Disease	Macromolecule
Myasthenia gravis	Acetylcholine receptor antibody
Hyperproteinemia Macroglobulinemia Globulinemia Cryoglobulinemia	IgM paraprotein, Ig monoclonals, elevated protein concentrations, cryoglobulins
Thrombocytopenia	Antibodies?, aggregating factor?
Rheumatoid vasculitis	Immune complexes
Goodpasture's syndrome	Anti-GBM antibody, fibrinogen
Glomerulonephritis	Antibodies
Polyneuropathies	Antibodies, immune complexes
Scleroderma	Antibodies
Polymyositis	Antibodies?, paraproteins
Systemic lupus erythematosus	Anti-DNA antibodies, immune complexes

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Influences in US Therapeutic Apheresis

- Technical developments
- Clinical applications / efficacy studies
- Food and Drug Administration (FDA)
- Centers for Medicare and Medicaid Services (CMS)
- Third party payors (Insurance companies)

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Approved Diseases for Therapeutic Apheresis in Japan

- Multiple myeloma
- Macroglobulinemia
- Fulminant hepatitis
- Post-op severe hepatic failure
- Acute hepatic failure
- Drug intoxication
- Myasthenia gravis
- Malignant rheumatoid arthritis
- Systemic lupus erythematosus
- Thrombotic thrombocytopenic purpura
- Hemolytic uremic syndrome
- Severe blood incompatible pregnancy
- Multiple sclerosis
- Chronic inflammatory demyelinating neuropathy
- Guillain-Barré syndrome
- Pemphigus vulgaris
- Pemphoid
- Focal glomerulosclerosis
- Familial hypercholesterolemia
- Arteriosclerosis obliterans
- Blood type incompatible or anti-T lymphocyte antibody positive renal transplantation
- Ulcerative colitis

Akizawa, T. *Ther Apher* 2001; 5:1.

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Medical Costs of Therapeutic Apheresis in Japan (US$)

	Technical Fee	Column	Others	Total
Adsorption	417	725 + 275	10	1427
LDL				1427
PE	417	275	FFP 2295	2987
Cryofiltration	417	230 + 275	292	1214
Endotoxin	167	3042	10	3219
Hemodialysis				188 (per month: 2445)
Hemofiltration				183

FFP, fresh frozen plasma

Kawamura A. *Ther Apher 2003; 7*:497.

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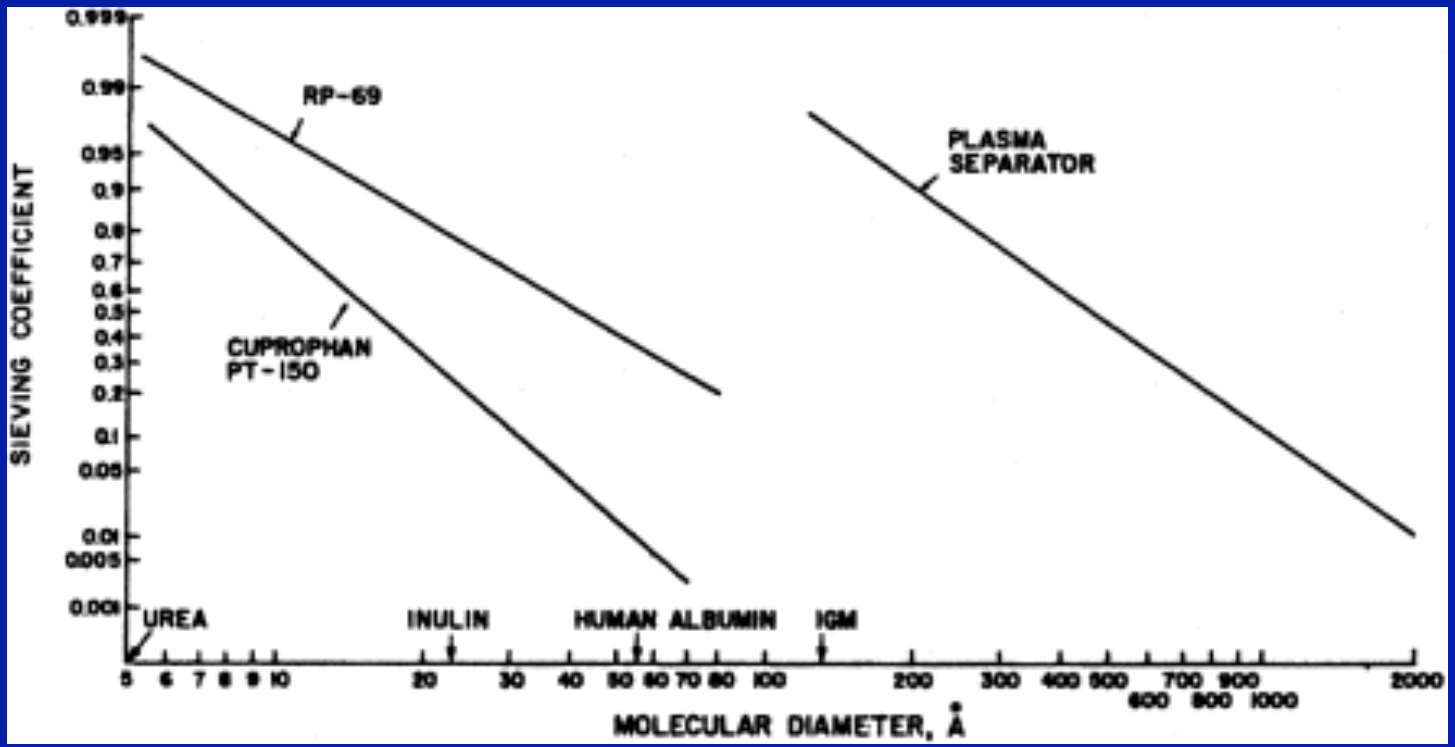
Sieving as a Function of Molecular Diameter

For membranes used in plasma separation, hemofiltration (RP-69) and dialysis (Cuprophan PT-150)



Malchesky, PS et al. *Ther Apher* 2000; 4:47-53.

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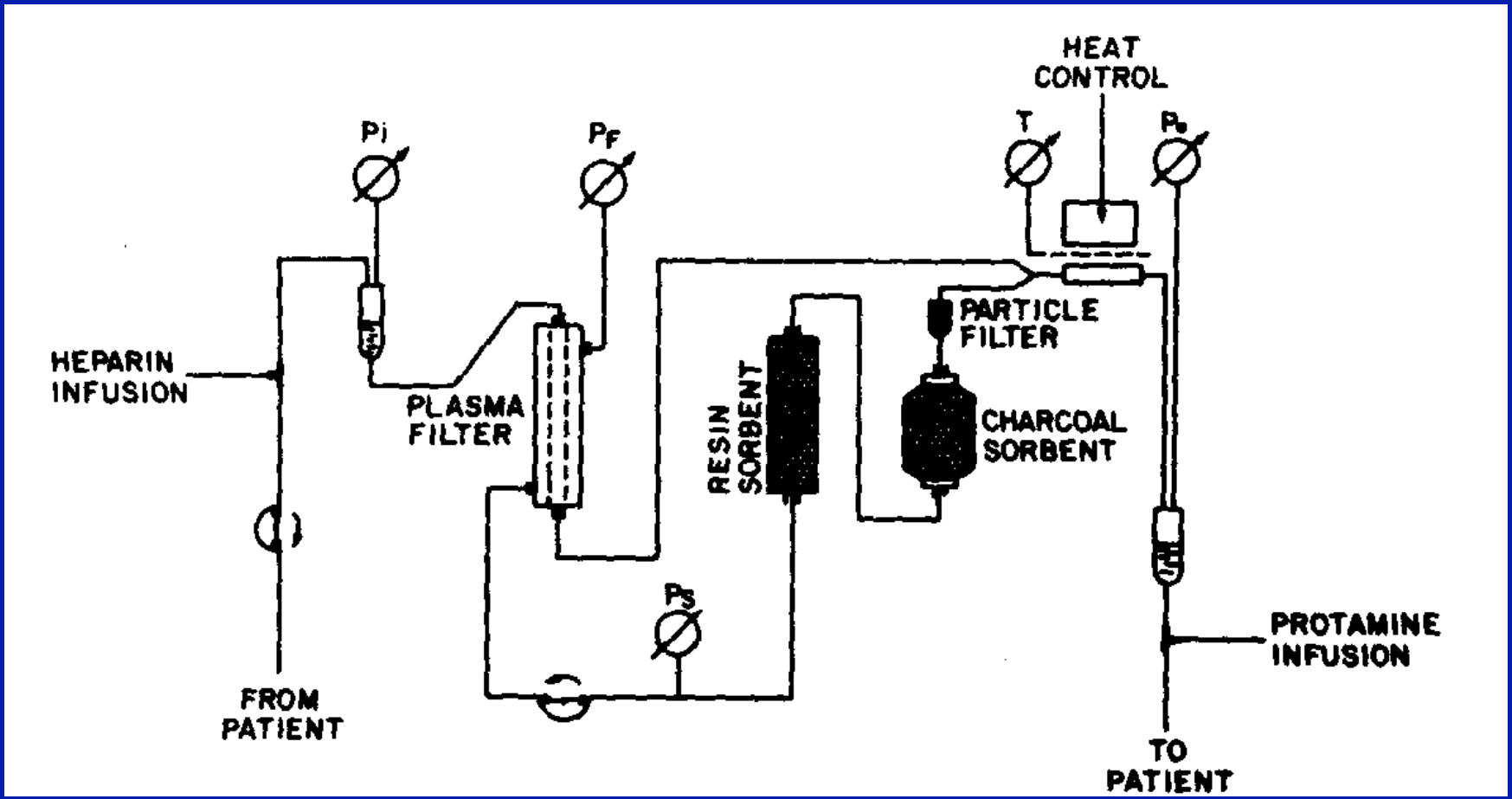
Schematic of Multiple Sorbent Plasma Perfusion



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Why Plasma Sorption?

- Specific solute(s) identified, not separable by membrane (i.e. IgG antibodies)
- Protein-bound solute, spare protein
- Possible direct removal from blood

Adsorbents

	Ligand	Adsorption material	Disease
Direct hemoperfusion	Polyacrylic acid	LDL, Lp(a)	Hyperlipidemia
	Hexadecyl or porous cellulosic beads	β_2-microglobulin	Amyloidosis
	Petroleum active charcoal	Drugs, bilirubin, bile acid, creatinine, amino acid	Toxicities, hepatic coma, acute renal failure
	Amberlite XAD-4 resin		Drug intoxication
	Polymyxin B	Endotoxin	Sepsis, endotoxinemia
Plasma perfusion	Blood type antigen fixed silica	Anti-A antibody, Anti-B antibody	ABO-incompatible transplantation
	Acetylcholine receptor peptide immobilized resin	αAChR ab	Myasthenia gravis
	Anti-LDL ab	LDL	Hyperlipidemia
	Anti-immunoglobulin ab	Immunoglobulin	Lack of coagulant factor
	Protein A	IgG	ITP, RA, Malignancy
	Dextran sulfate fixed cellulose fiber	LDL, anticardiolipin antibody immune complex, Anti-DNA antibody, antiphospholipid antibody syndrome	Hyperlipidemia, Arteriosclerosis obliterans, Nephrotic syndrome due to FGS, SLE, APS
	Styrene-divinylbenzene polymer	Bilirubin, bile acid	Fulminant hepatitis, Acute hepatic failure, Icterus
	Tryptophan fixed polyvinyl alcohol gel	αAChR ab immune complex	Myasthenia gravis, Guillain-Barré syndrome, MS, Malignant RA
	Phenylalanine fixed polyvinyl alcohol gel	Rheumatoid factor immune complex, Anti-DNA antibody	RA with vasculitis, SLE, Guillain-Barré syndrome, MS
Blood cell adsorption	Polystyrene unwoven fiber		IBD, RA, skin diseases
	Anti-cD4+ antibody immobilized fiber		Autoimmune diseases, MS

Akizawa T. *Ther Apher* 1999; 2:1-2 *and* Yang K-S et al. *Ther Apher* 2002; 6:184-8.

Why Not Sorption?

- Blood contact incompatibility
- Particle release
- Generally too disease-specific
- More costly

III. Summary of Results
2002 International Apheresis Registry

- Plasmapheresis accounted for 95.8% of all reported treatments on 93.8% of all patients treated
- Most total number of treatments was by plasma treatment only (51.9%) followed by plasma exchange only (41.6%)
- Average treatments per patient: 14.2
  - If diagnosis of hypercholesterolemia: 85.6/patient
  - If diagnosis of myasthenia gravis: 6.9/patient
- Treatments/patient varied by type
  - If plasma exchange, majority (55%) received 1-5 treatments
  - If plasma treatment, majority (40.8%) received >10 treatments

Malchesky PS et al. *Ther Apher Dial* 2003; 8:124-43.

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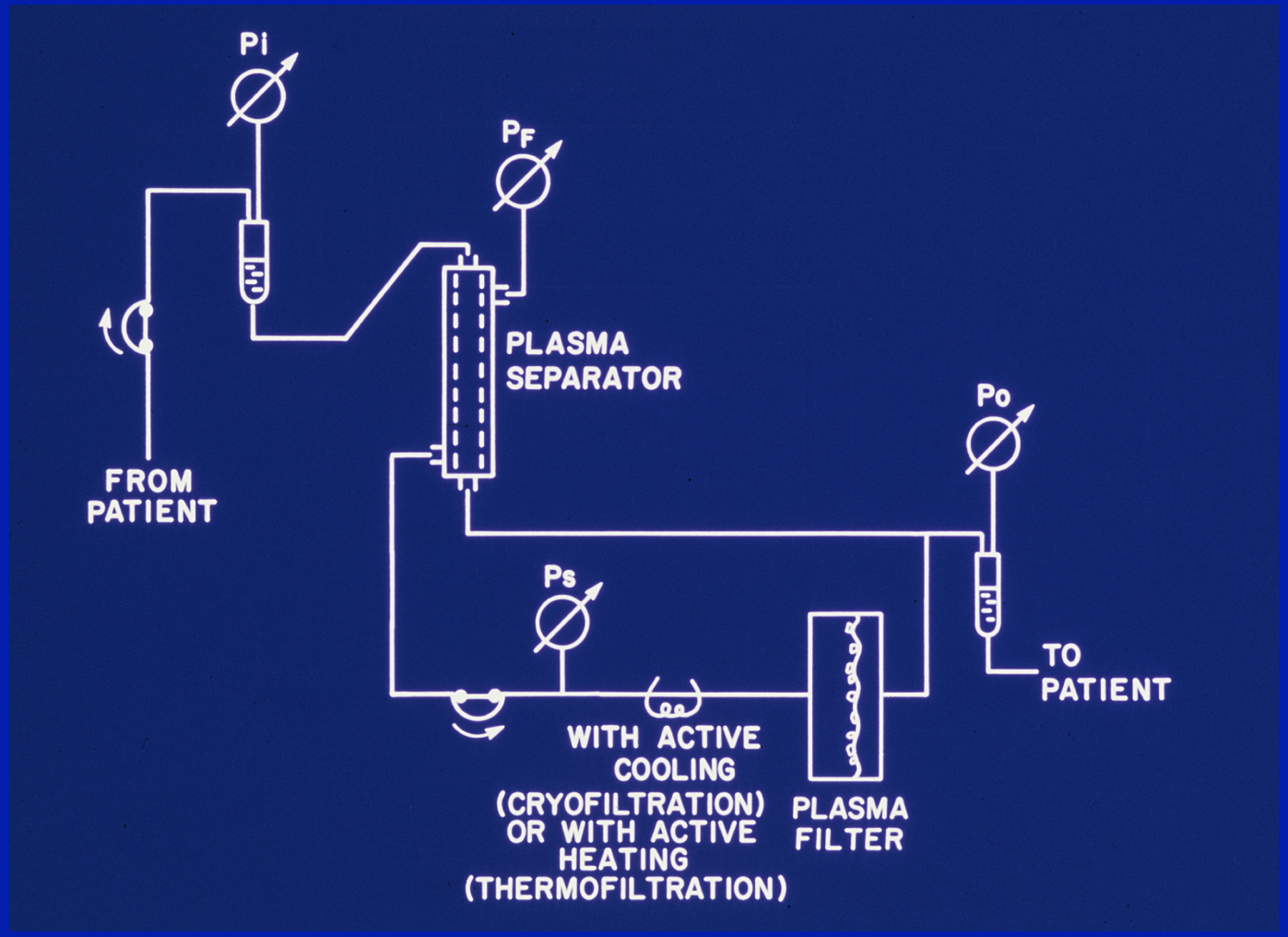
Schematic of Temperature Regulated Membrane Plasma Filtration



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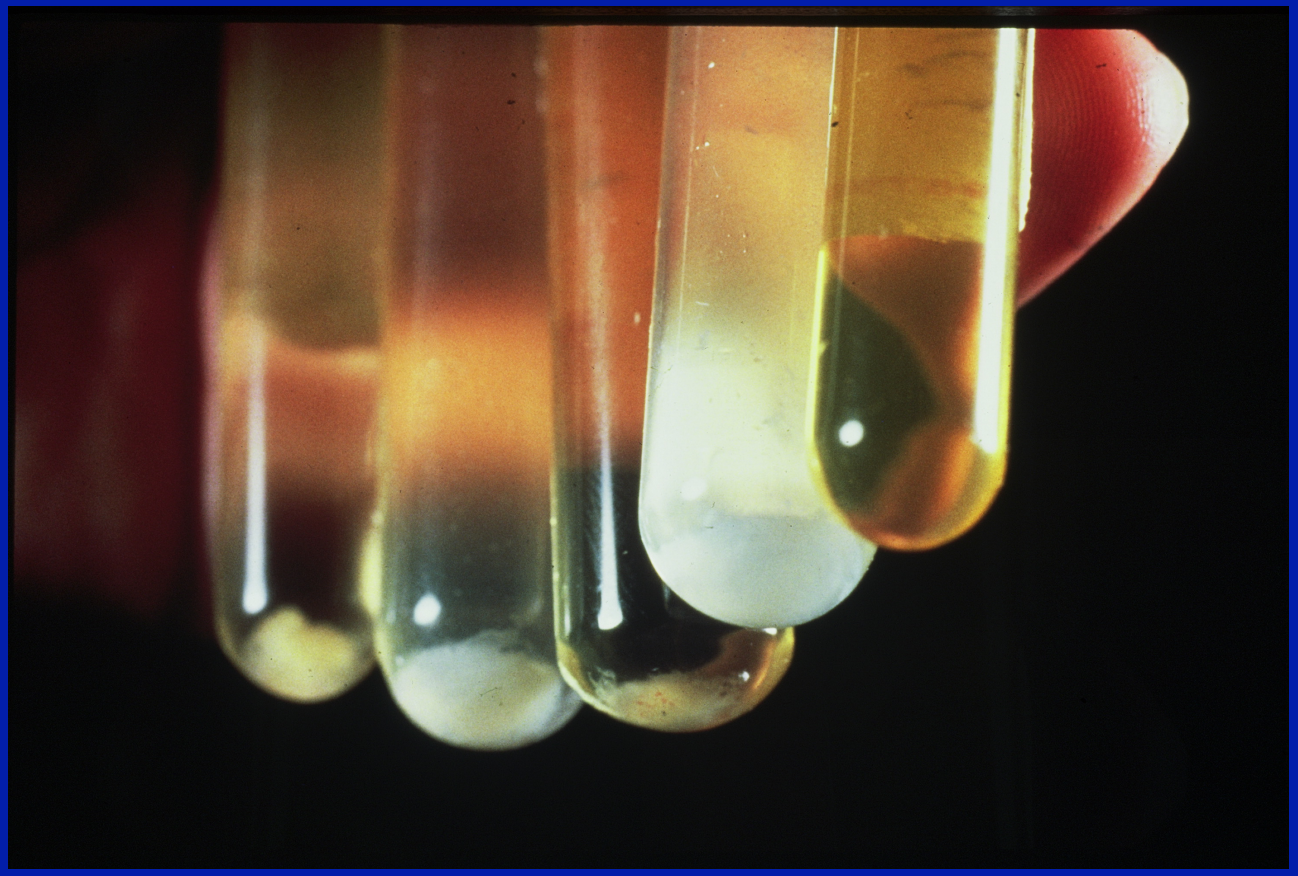
Cryoprecipitable Proteins in Patient Plasma with Various Autoimmune Diseases



From the right: normal control, rapidly progressing glomerulonephritis, rheumatoid arthritis, myasthenia gravis and Sezary syndrome

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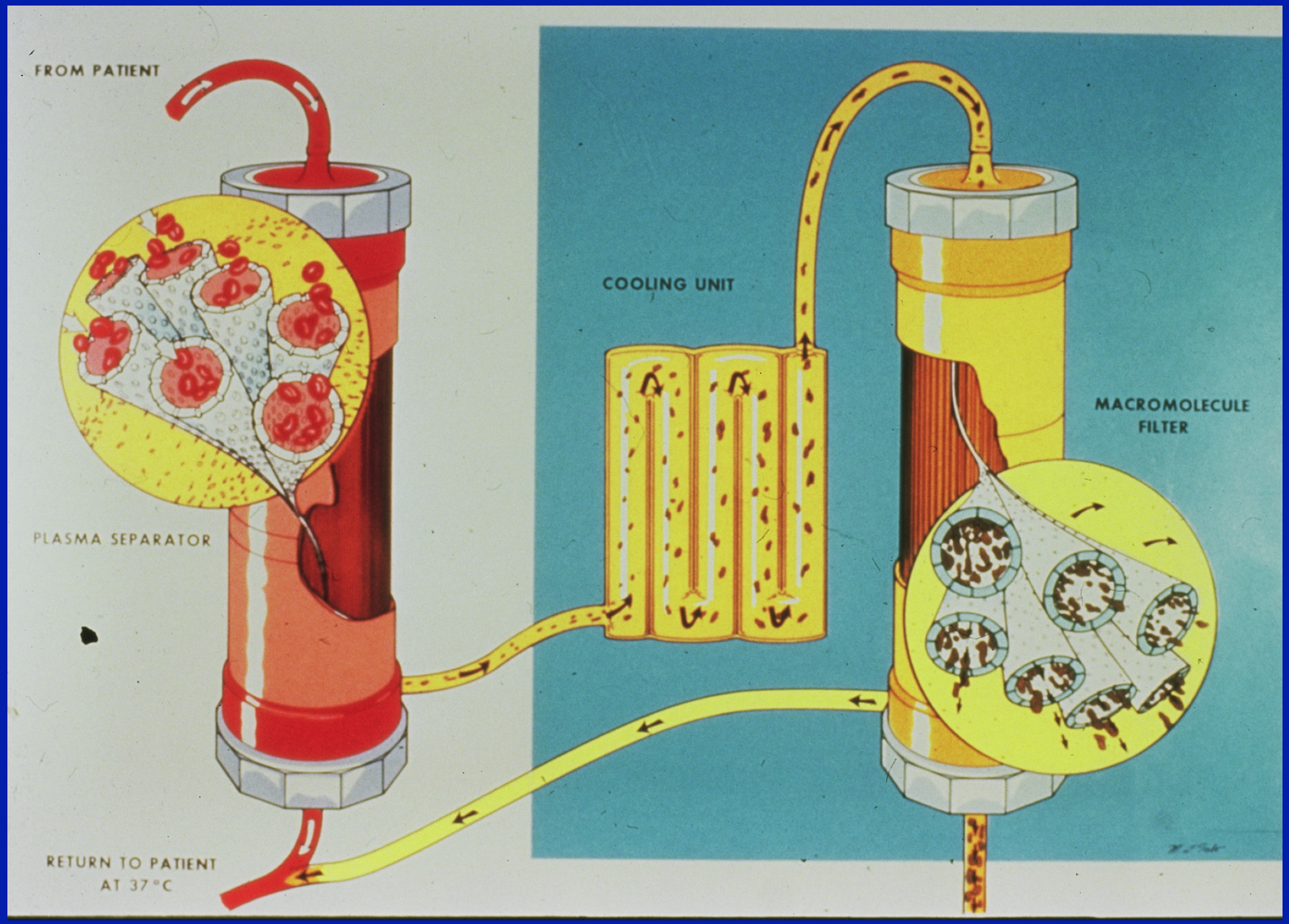
Scheme of Cryofiltration



Nosé Y et al. *Ther Apher* 2000; 4:38-43.

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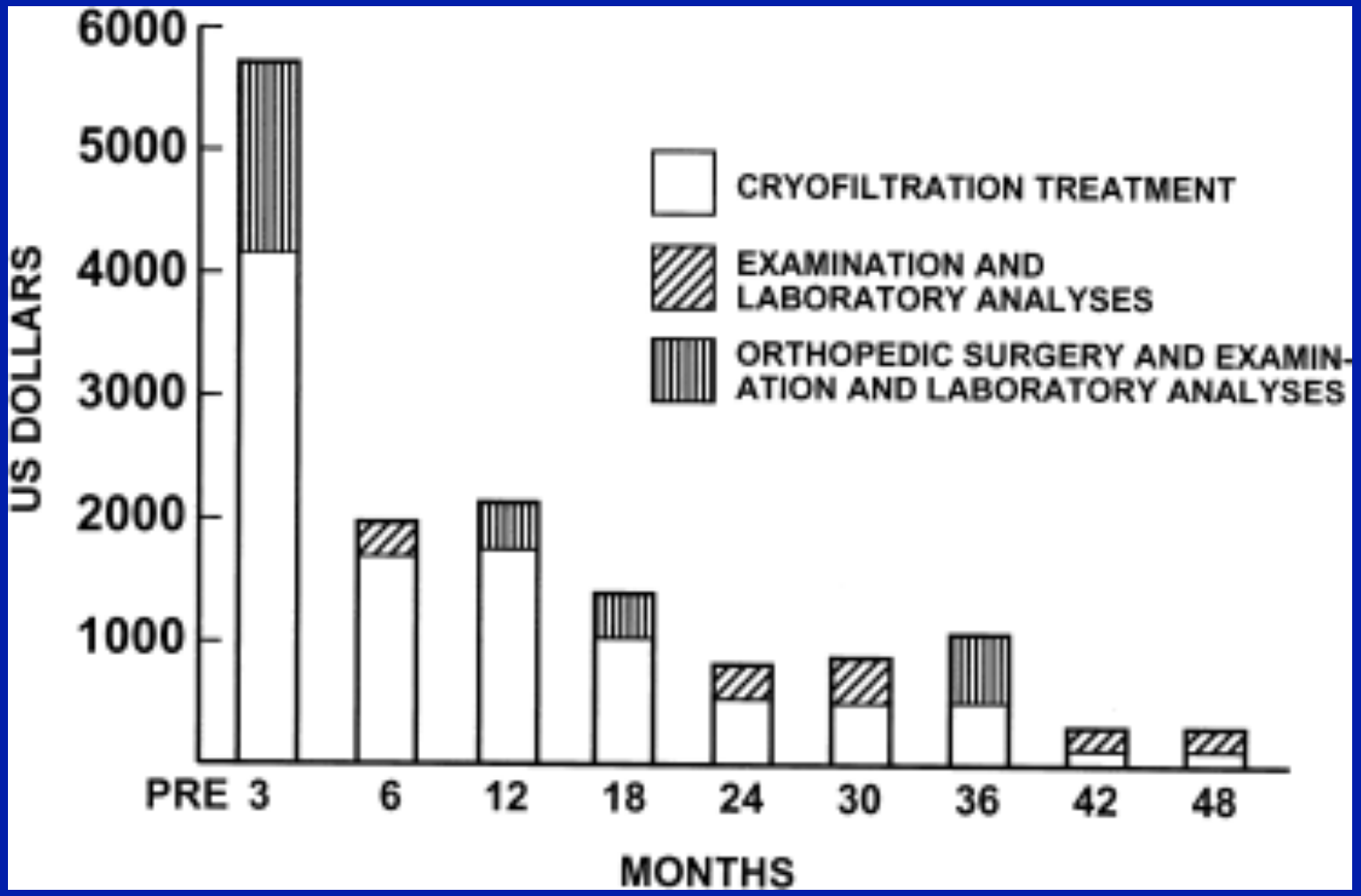
Treatment Costs for a Rheumatoid Arthritis Patient



(Excluding drugs, 62 year old female, functional class IV)

Malchesky PS. *Artif Organs* 2001; 25:75-88.

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Therapeutic Artificial Organs

- Early intensive therapy
- Less frequent maintenance treatments

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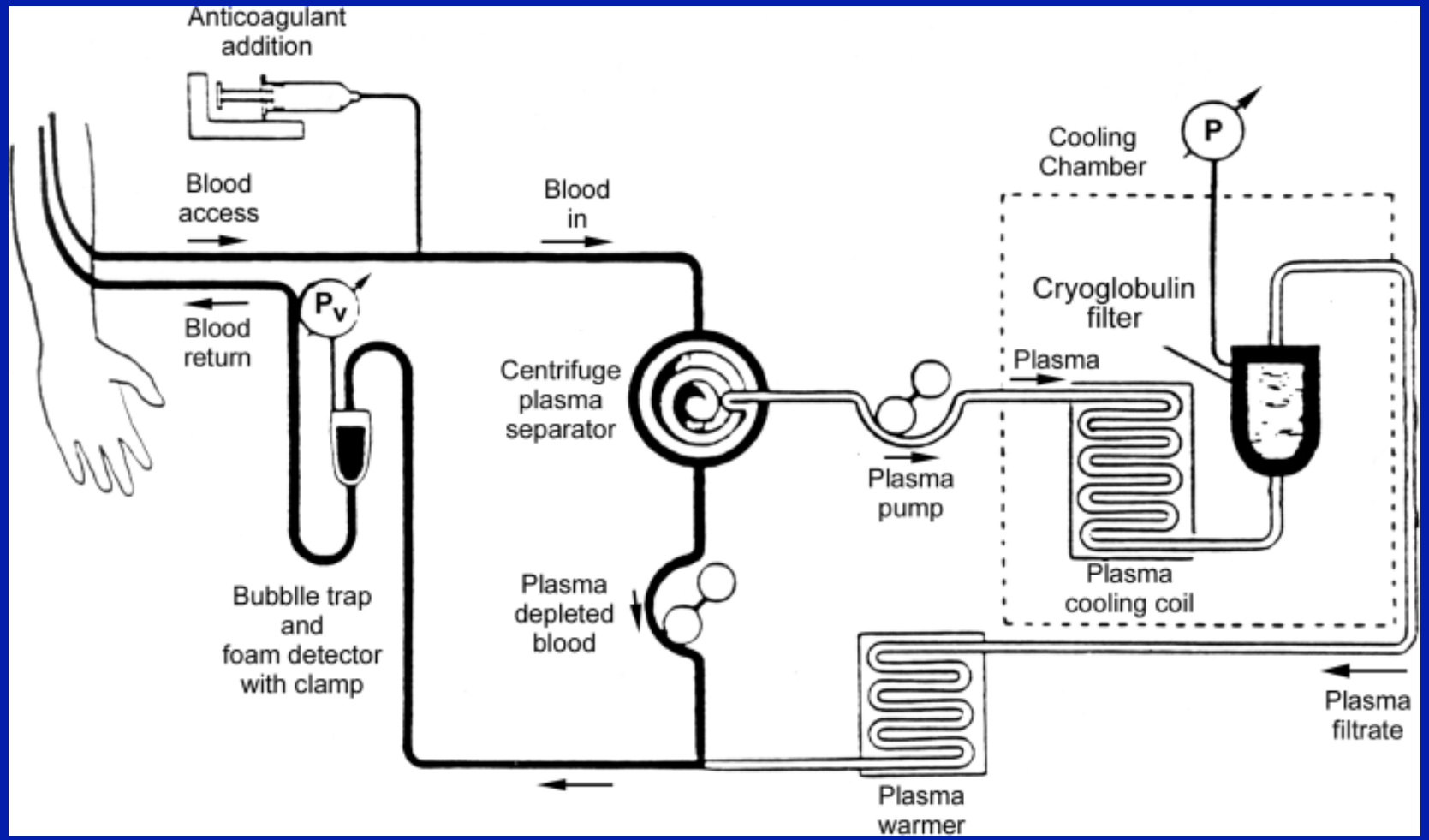
Diagram of Cryofiltration Apheresis System



Siami FS, Siami GA. *Ther Apher Dial* 2004; 8: 398-403.

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Diseases Successfully Treated by Cryofiltration

- Cryoglobulinemia
  - With renal impairment
  - Peripheral neuropathy
  - Vasculitis
- Cryofibrinogenemia
- Cold autoimmune hemolytic anemia
- Cold IgM with cryopositive agglutinin disease
- Hepatitis C virus infection
- B-cell lymphoma
- Chronic renal failure
  - Waldenström's macroglobulinemia
- Hypertension
- Ischemic heart disease
- B-cell lymphoma
- Rheumatoid arthritis
- Rheumatoid vasculitis
- Sjögren's syndrome
- Polyarteritis nodosa
- Polymyositis
- Myasthenia gravis
- Guillain-Barré
- Lupus nephritis
- TTP
- SLE with vasculitis
- Peripheral vascular disease
- Non-healing leg ulcers, gangrene
- Sepsis
- Monoclonal gammopathy
- ABO-incompatible transplants

Siami GA, Siami FS. *Ther Apher* 1998; 2:228-35 and various Cleveland Clinic Foundation and Japanese Investigators.

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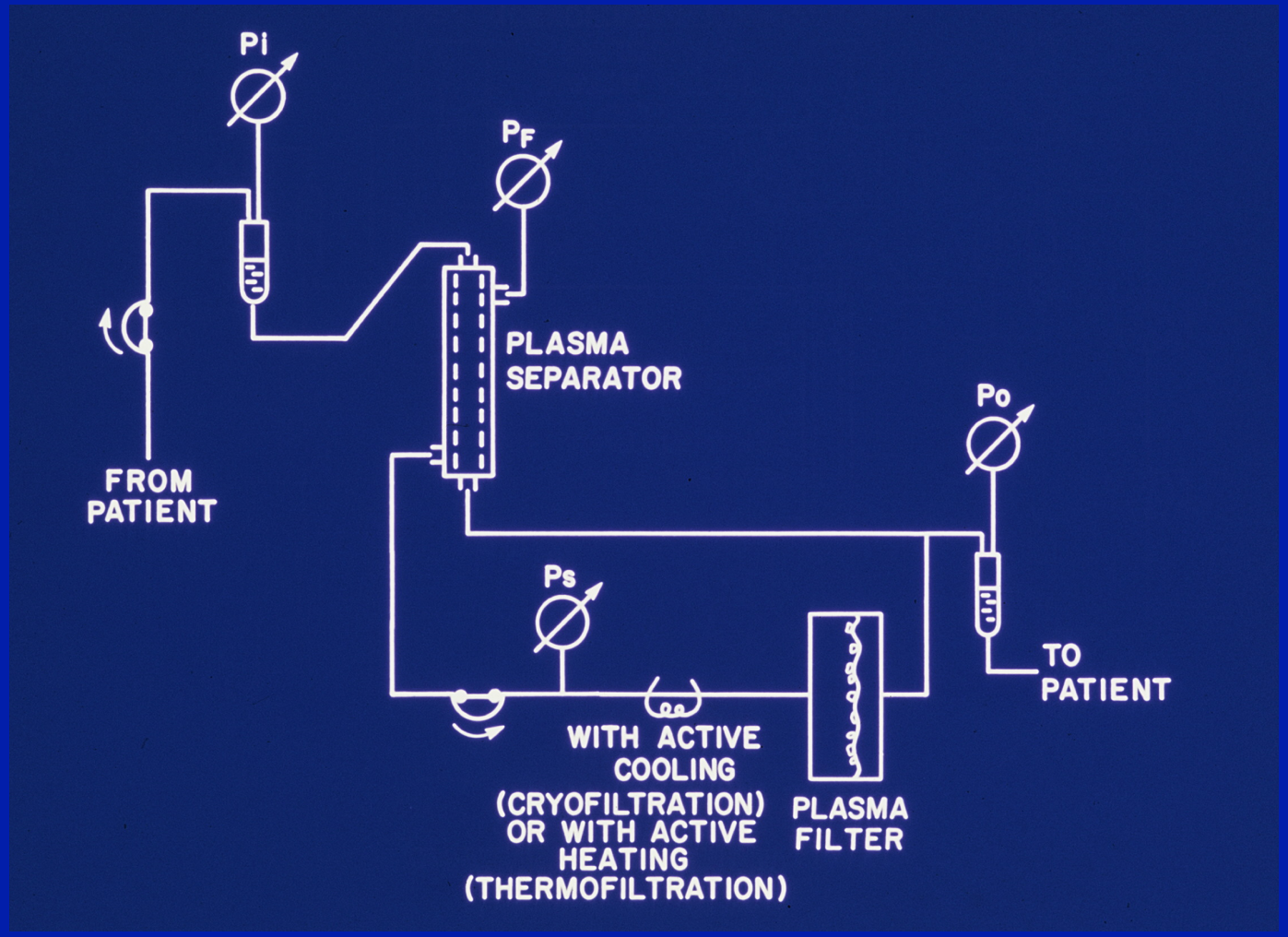
Schematic of Temperature Regulated Membrane Plasma Filtration



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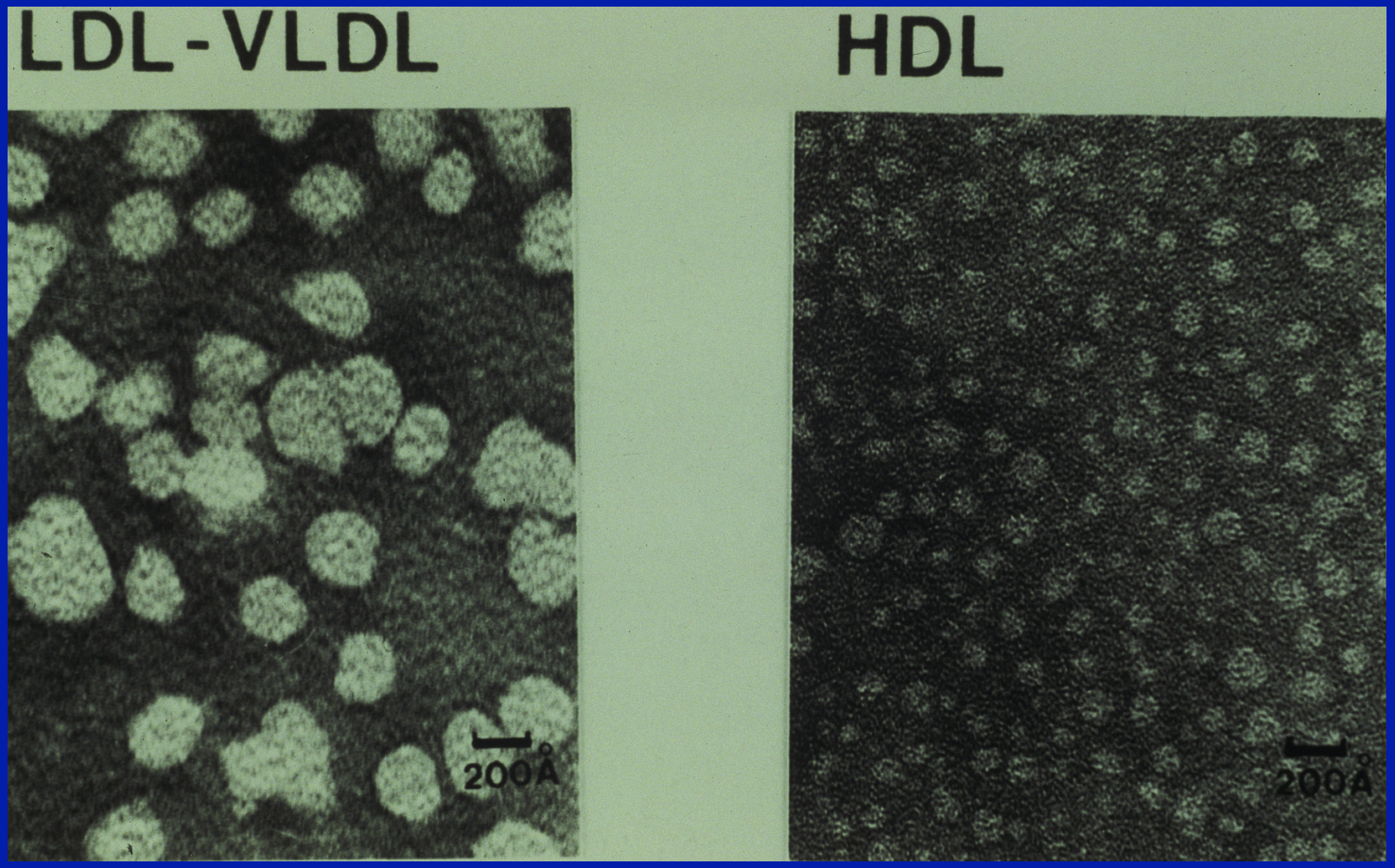
Size of Lipid Fractions



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German Guidelines for LDL Apheresis

- Homozygous FH or severe heterozygous FH with coronary artery disease
- LDL cholesterol below 2.6 mmol/L (100 mg %) to avoid progression of coronary artery disease
- 60% LDL cholesterol reduction per treatment

  – 1996 US FDA Approved LDL apheresis

Klingel R et al. *Ther Apher Dial 2003;* 7:350-8.

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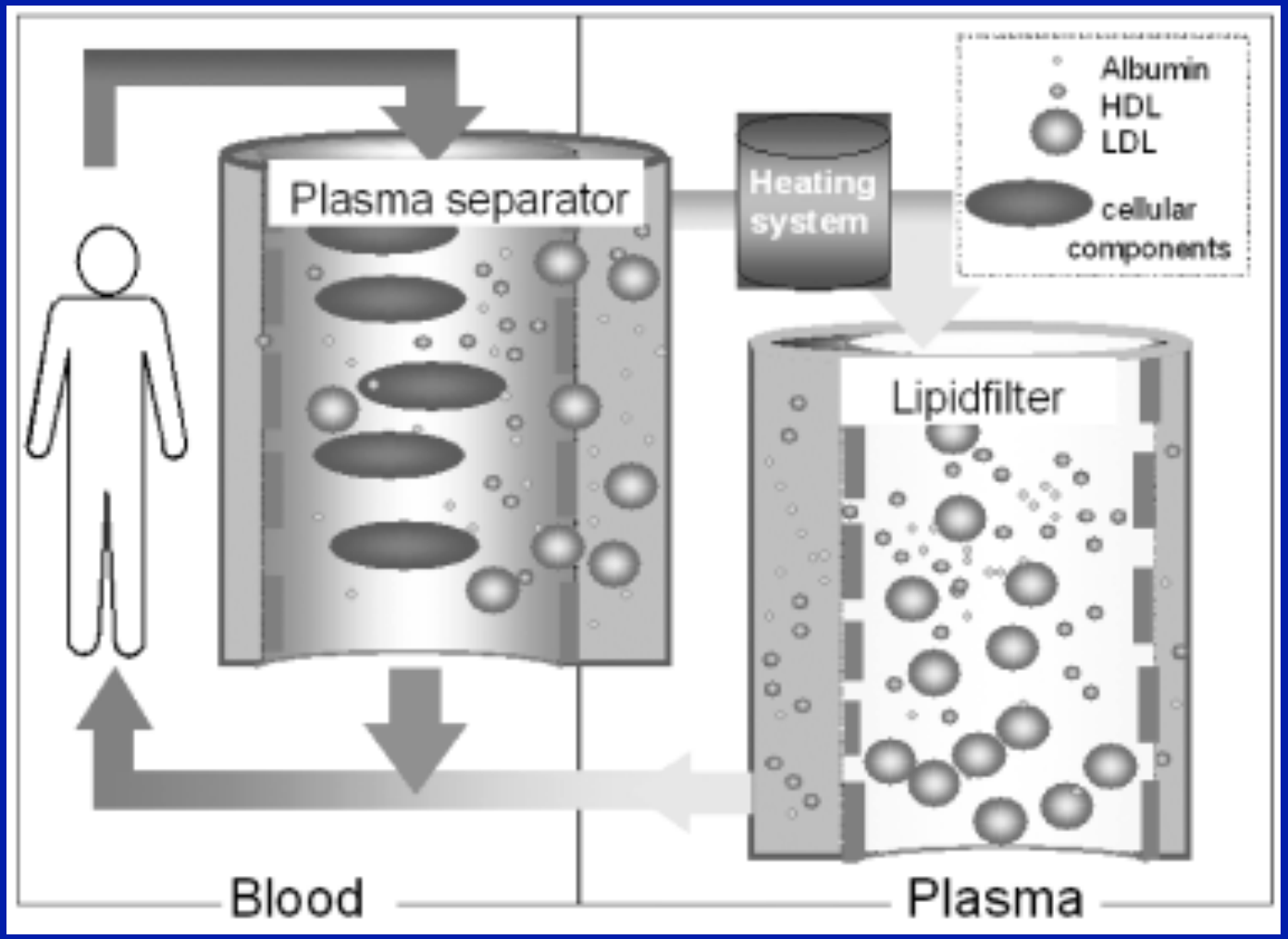
German Results with LDL Apheresis

- Immunoadsorption, HELP and dextran sulfate adsorption are comparable in halting the progression of coronary lesions in severe heterozygous FH
  - (Richter et al. *Ther Apher* 1999; 3:203-8)
- Dextran sulfate adsorption, immunoadsorption, LDL hemoperfusion, immunosorption with anti-Lp(a), showed no significant differences with respect to the clinical outcomes and cholesterol or triglyceride levels except Lp(a) column was most effective in removing Lp(a)
  - (Bambauer R et al. *Ther Apher* 2000; 4:213-7 and Bambauer R. *Ther Apher Dial* 2005; 9:142-7)
- Lipid apheresis is very expensive
  - (Schwandt P et al. *Ther Apher Dial* 2003; 5:283-4)
- HELP, specific immunoadsorption, dextran sulfate adsorption, direct hemoperfusion (DALI), and membrane (i.e. thermofiltration) are equivalent regarding safety and efficacy in reducing LDL cholesterol
  - (Klingel R et al. *Ther Apher Dial 2003;* 7:350-8)

Schematic of the Extracorporeal Circuit for Membrane Differential Filtration / Lipid Filtration



Klingel R et al. *Ther Apher Dial 2003;* 7:350-358.

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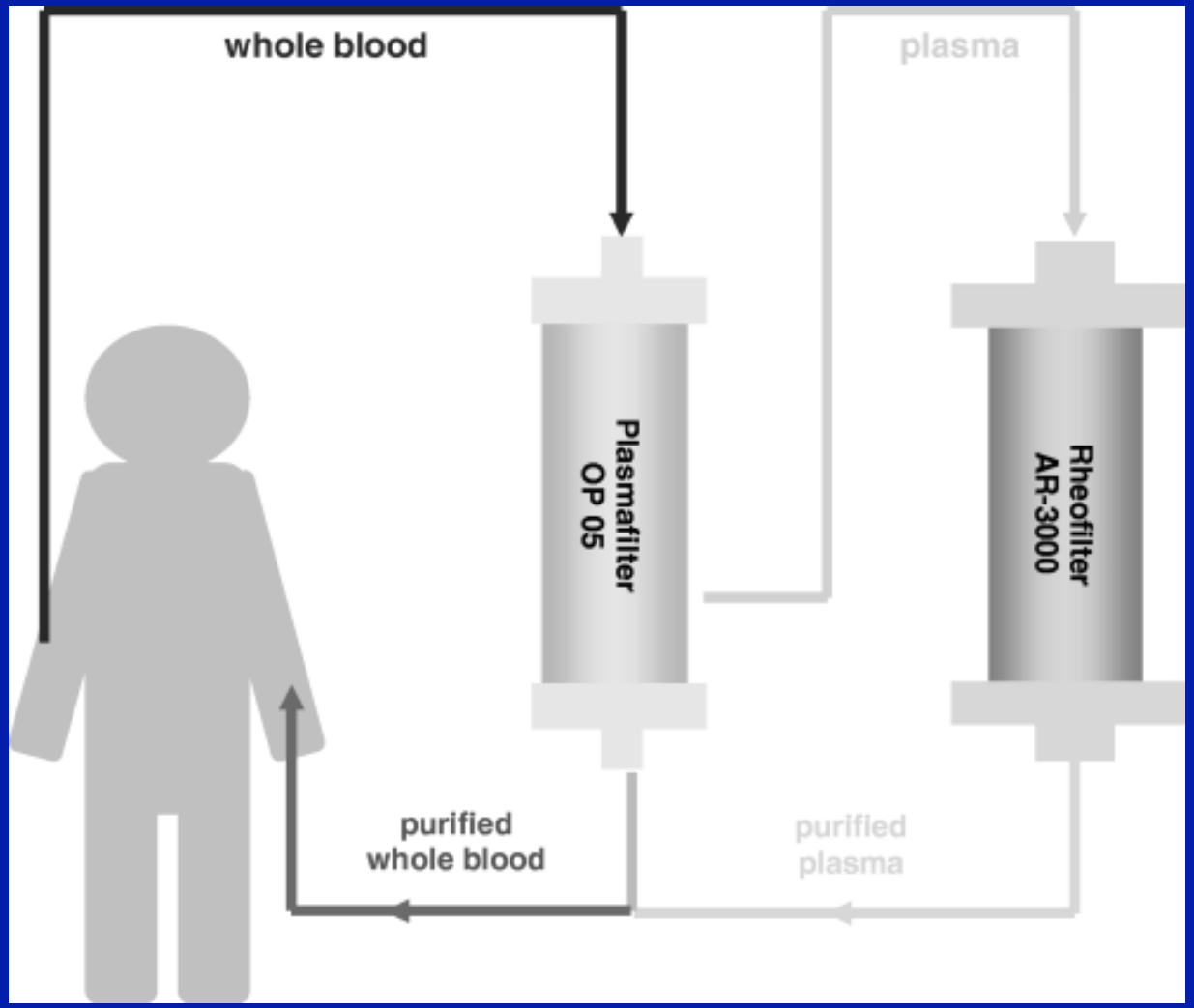
Extracorporeal Circuit Established for Rheopheresis



Klingel R et al. *Ther Apher Dial* 2003; 7:444-55.

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Membrane Technologies

- Major impact on artificial organ design and their clinical applications
- Provide means to develop therapies
- Can substitute for complicated, less physiologic and more costly technologies
- Provide unique opportunities in the development of new applications

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Development of a Medical Therapy

- Takes a long time
- Contributions of many from various disciplines
- Major breakthroughs/incremental improvements
- Requires continued research and development
- Limitations lead to new approaches

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Limitation to Achieving Potential

- Therapeutic efficacy not proven
  - Lack of clinical trials
- Cost of therapy
- Limited reimbursement
- Experience and education of clinicians
- Commercial push

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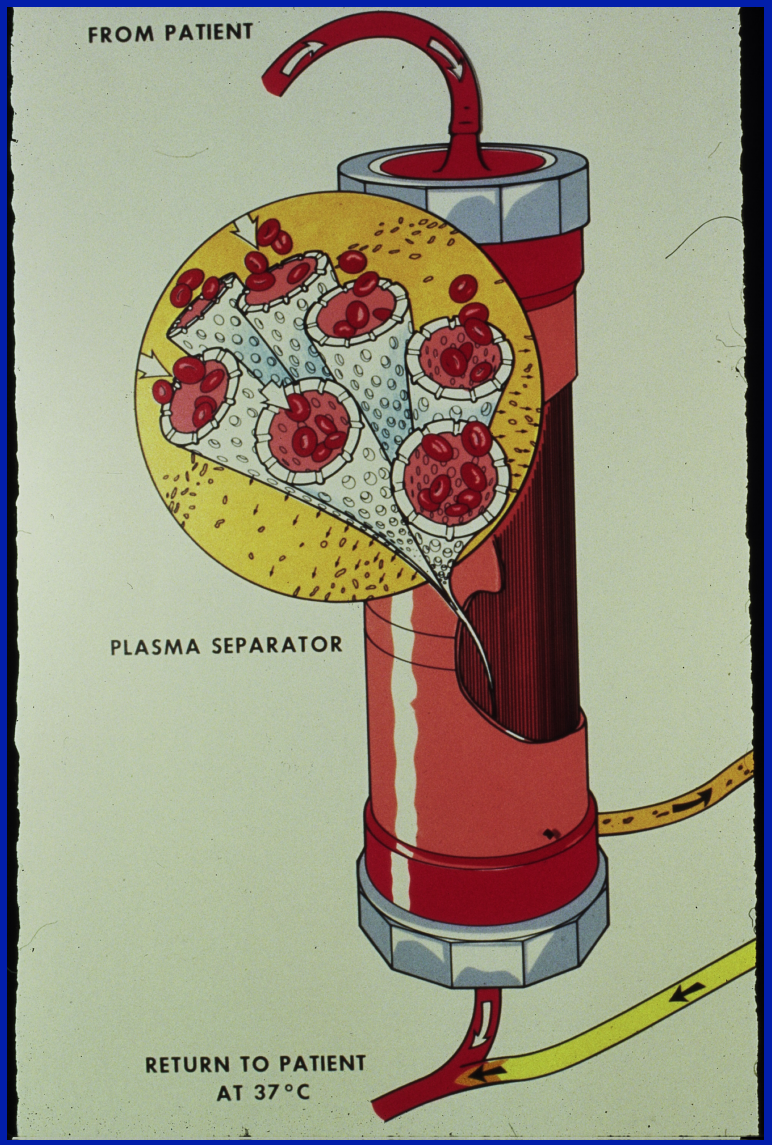
Additional Figures



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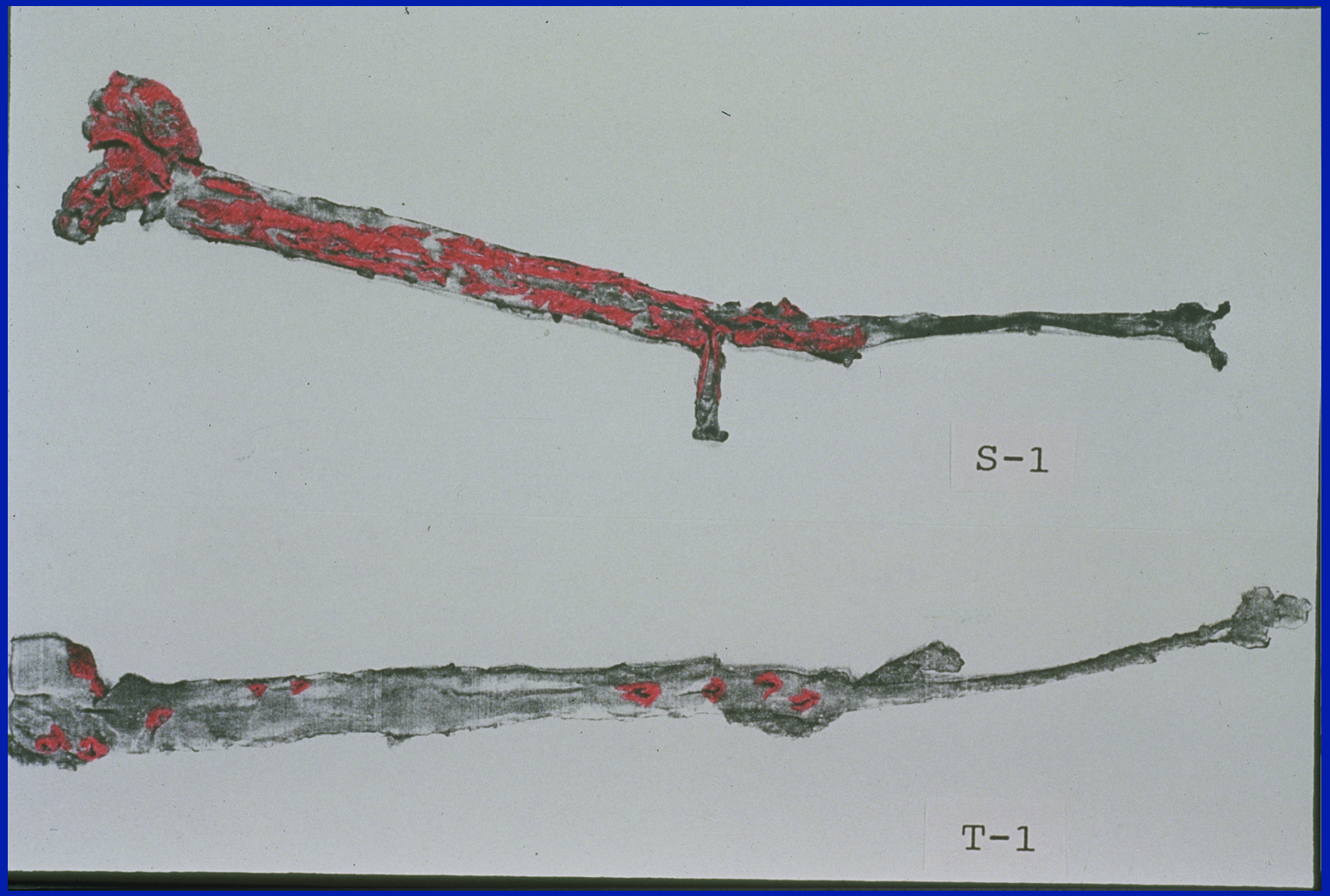

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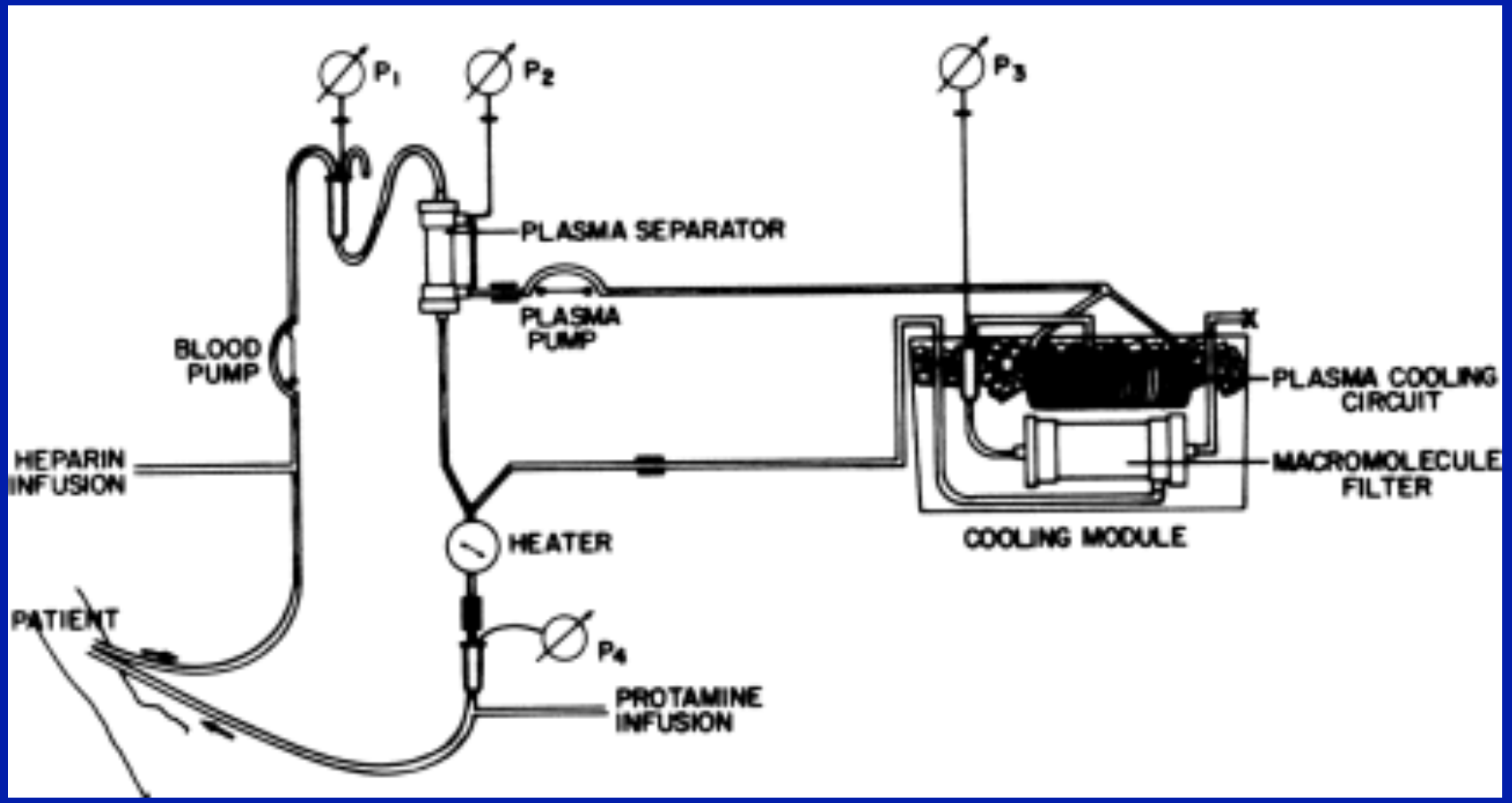
Plasma Separation with Filtration Scheme for the Removal of Cryoproteins



The cooling module is a water-ice bath. Regional heparinization is employed. Blood flow is 100 ml/min and plasma flow is approximately 20 ml/min.

Malchesky PS et al. *Ther Apher 2000;* 4:34-37.

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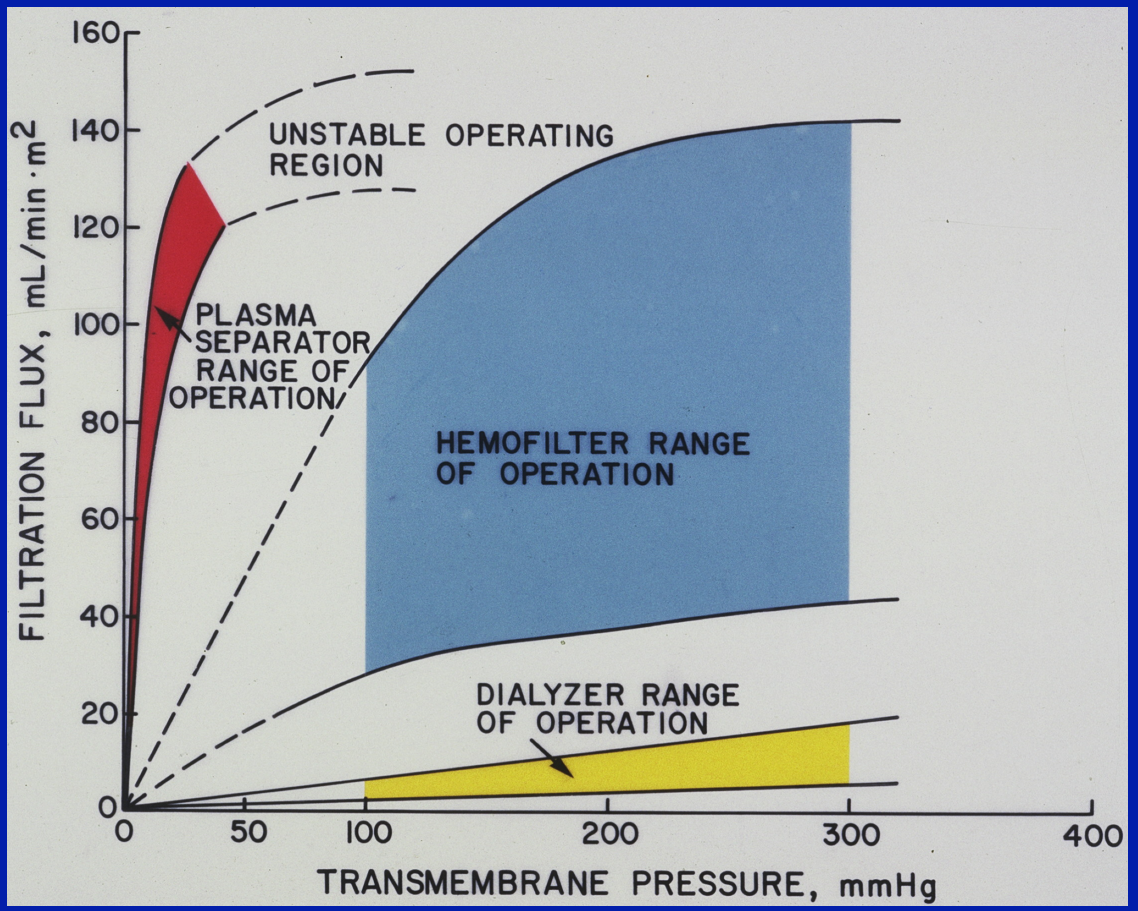
Filtration Flux as a Function of Transmembrane Pressure

For plasma separators, and ultrafiltration by hemofilters and dialyzers



Malchesky, PS et al. *Ther Apher* 2000; 4:47-53.

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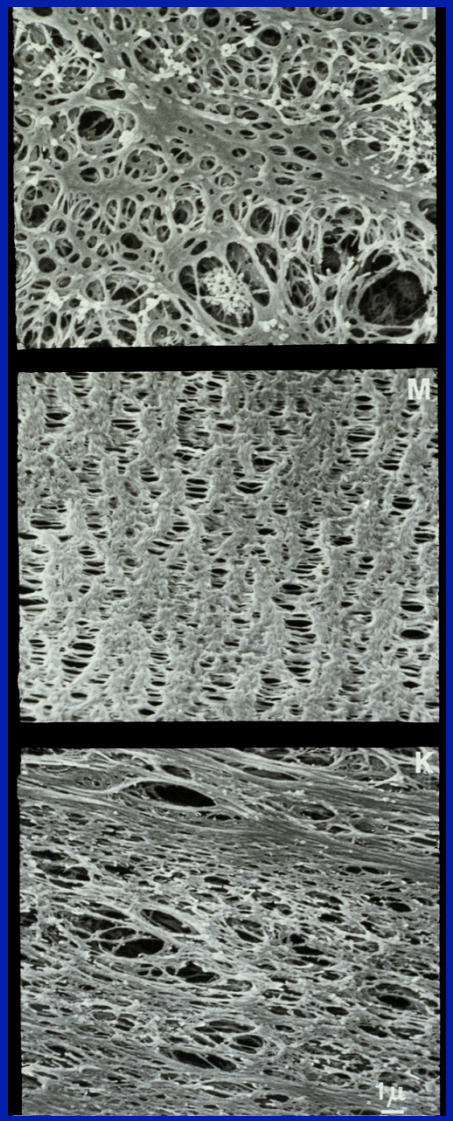
Membrane Materials



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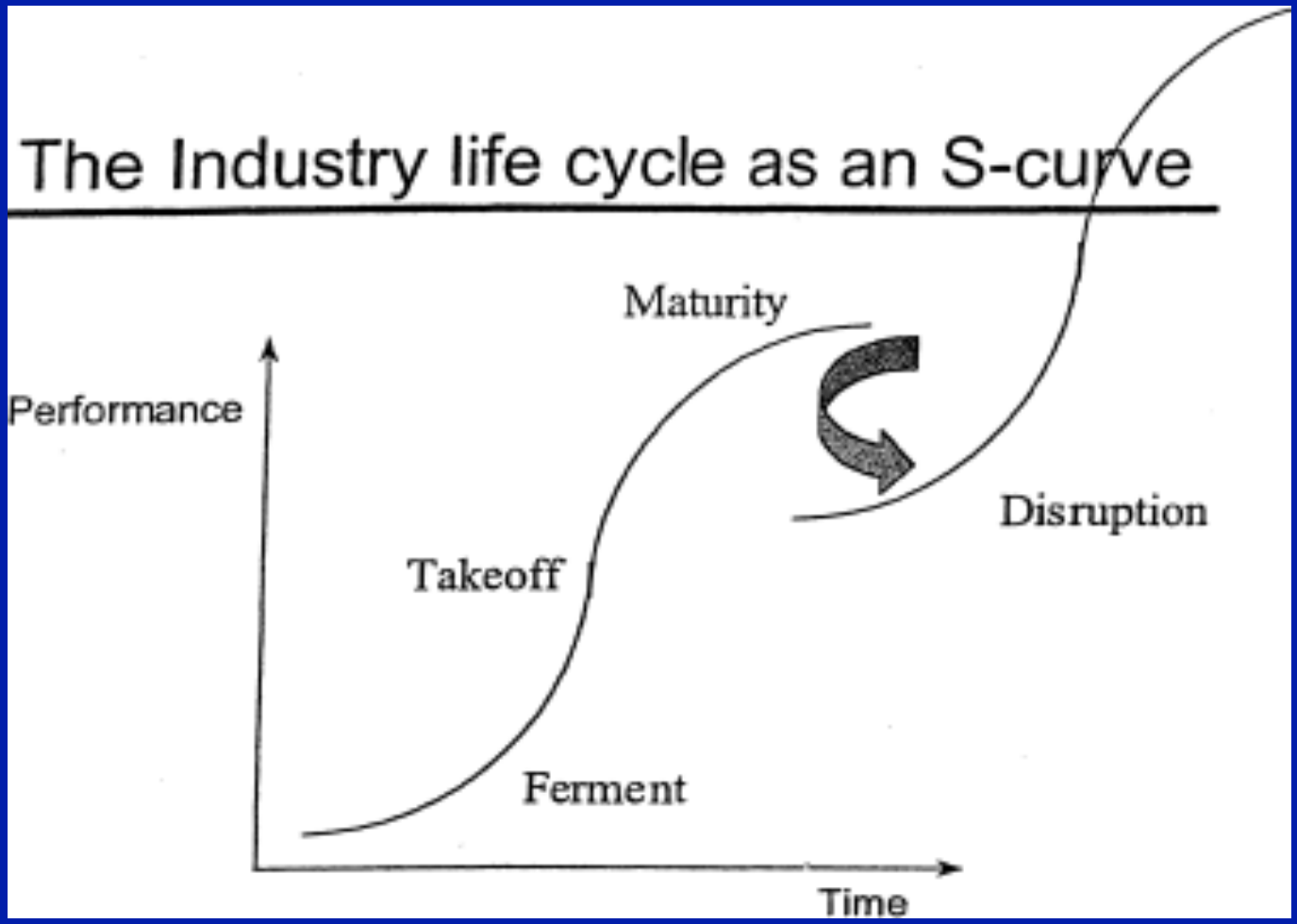
Industry Life Cycle



Malchesky PS. *Artif Organs* 2001; 25:75-88.

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