Cascade Filtration
ISBP 2015- September19th
St. Petersburg

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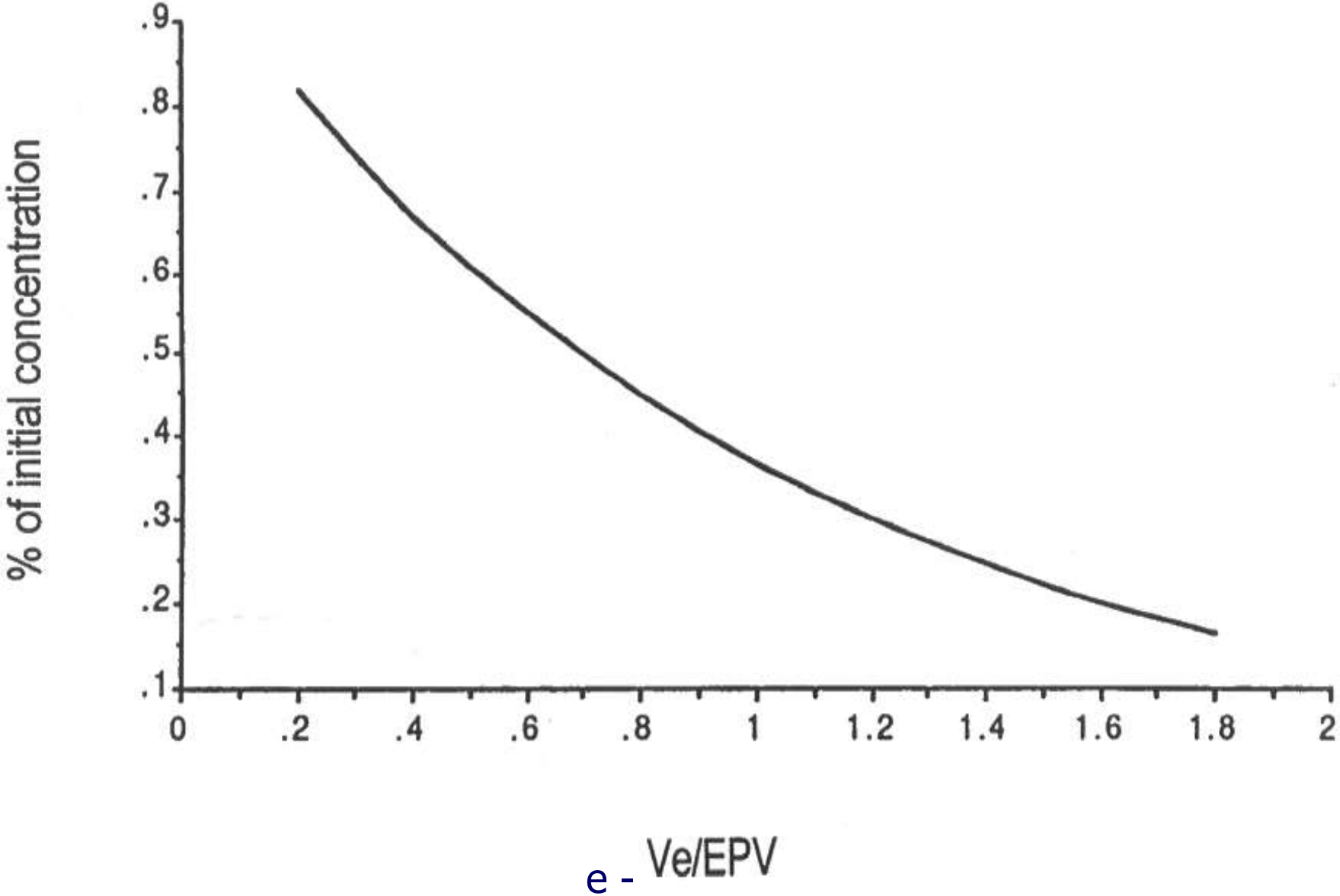
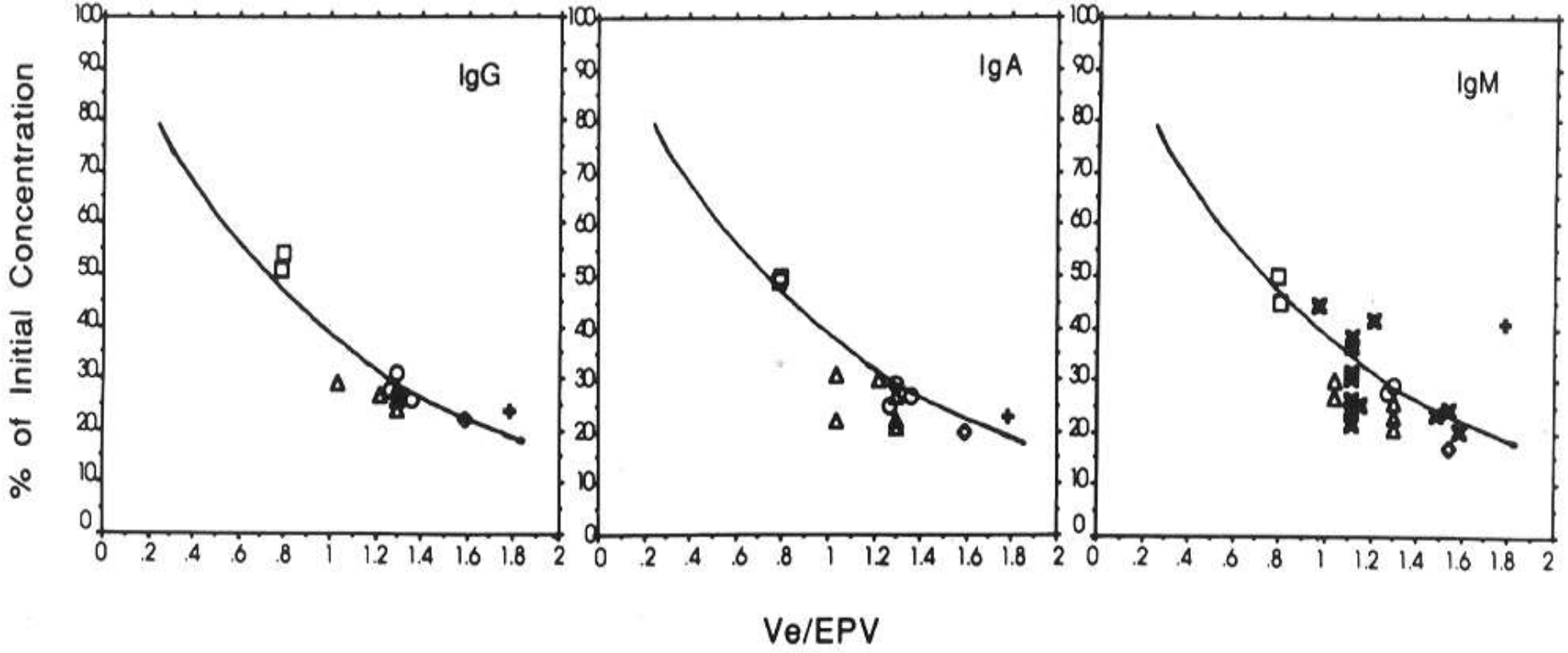
Therapeutic Plasma Exchange: Rationale as a Technique for Blood Purification

- Substance to be removed is sufficiently large (>15,000 daltons) so as to make other, less expensive techniques unacceptably inefficient (ie hemofiltration, high flux HD)
- Substance to be removed must have a comparatively long half life
- Substance to be removed is acutely toxic and/or resistant to conventional therapy

Immunoglobulin removal with standard plasma exchange


% of initial concentration
.9
.8
.7
.6
.5
.4
.3
.2
.1
0
.2
.4
.6
.8
1
1.2
1.4
1.6
1.8
2
e - Ve/EPV



Kaplan, Trans ASAIO 36, 1990

Table 1. Observed and predicted decline in anti-acetylcholine receptor (AChR) antibody during treatment for myasthenia gravis

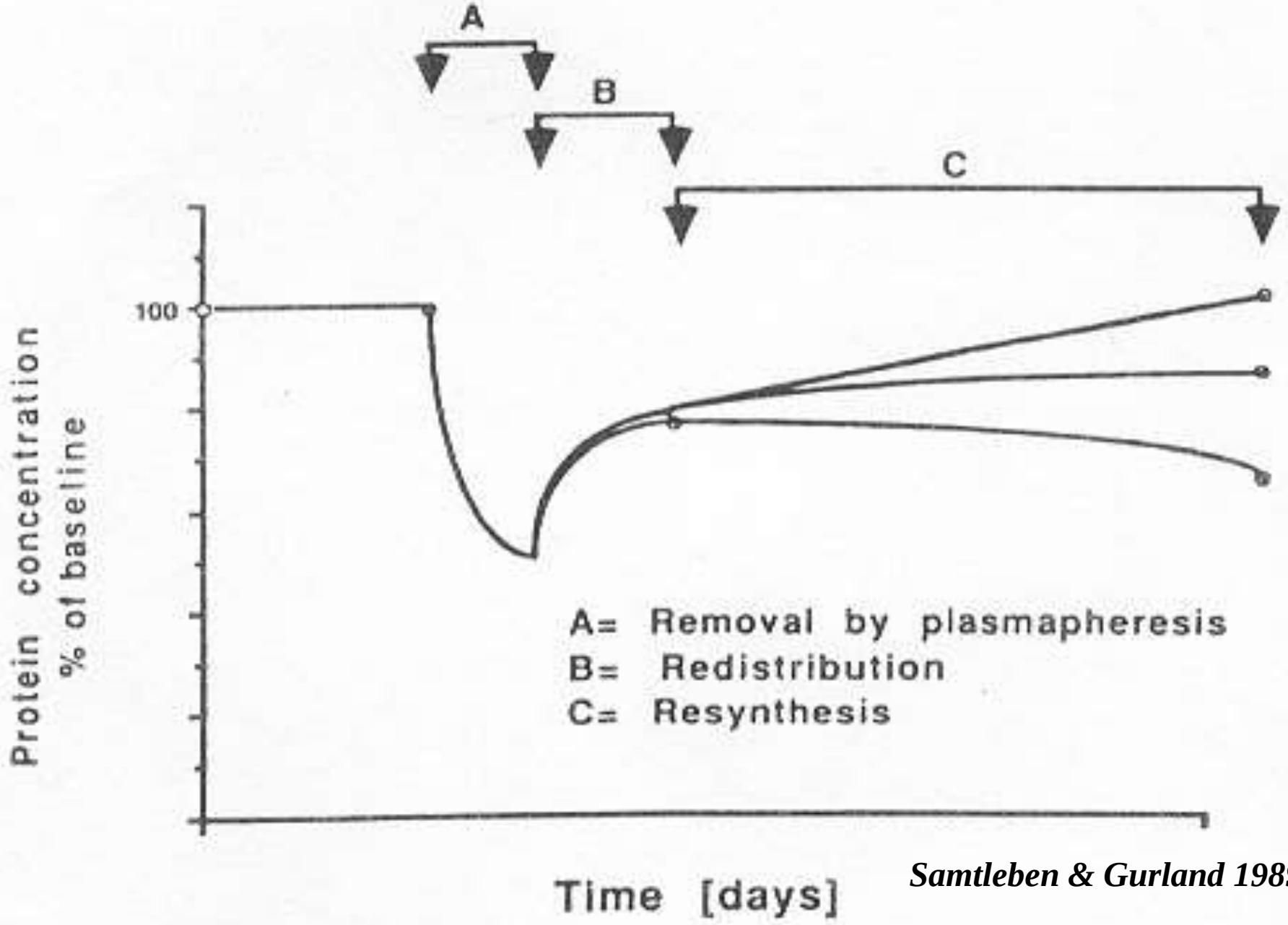
Date	Pre-RX	Post-RX	Ve	EPV	Ve/EPV	% Decline	
	nmols/liter		*liters*			Actual	Predicted
3/23	5.6	1.5	4	2.8	1.43	73	76
3/24	2.4	<0.5[a]	4	2.9	1.38	79	75
3/25	<0.5	<0.5	4	2.9	1.38	NA	75
4/12	6.9	3.7	1.2[b]	2.8	0.41	46[b]	35
4/13	5.9	1.0	5	2.8	1.79	83	83

Abbreviations are: Ve, volume exchanged; EPV, estimated plasma volume; NA, not applicable, due to the unmeasureable levels. Predicted values were obtained using first order kinetics and assuming the apparent volume of distribution of the antibody to be equal to the EPV (**Methods**).

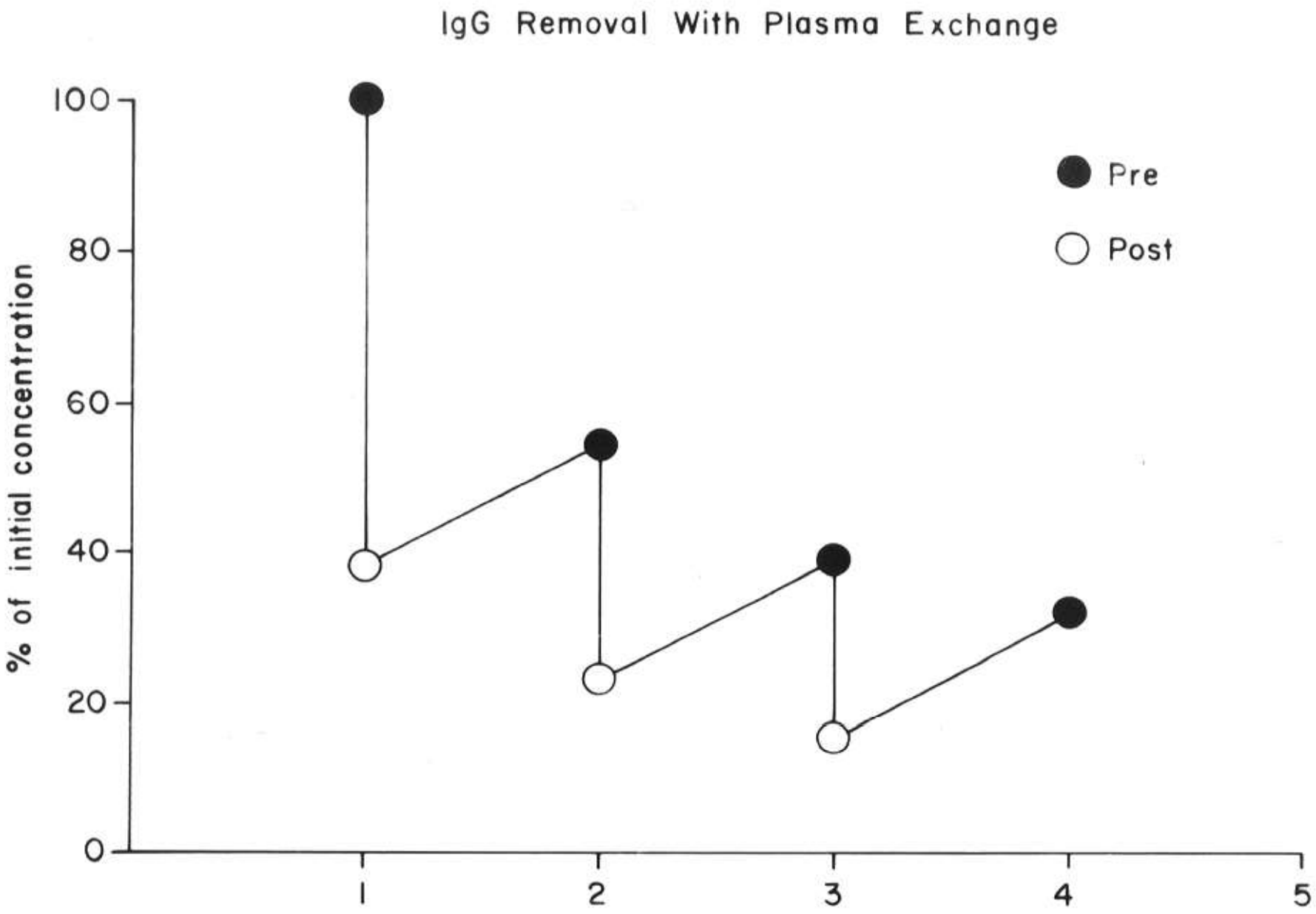
[a] This value was considered to be 0.5 for purpose of calculation

[b] This procedure was terminated prematurely due to access difficulties; large amounts of saline flushes may have contributed to the measured decline in post-treatment levels.

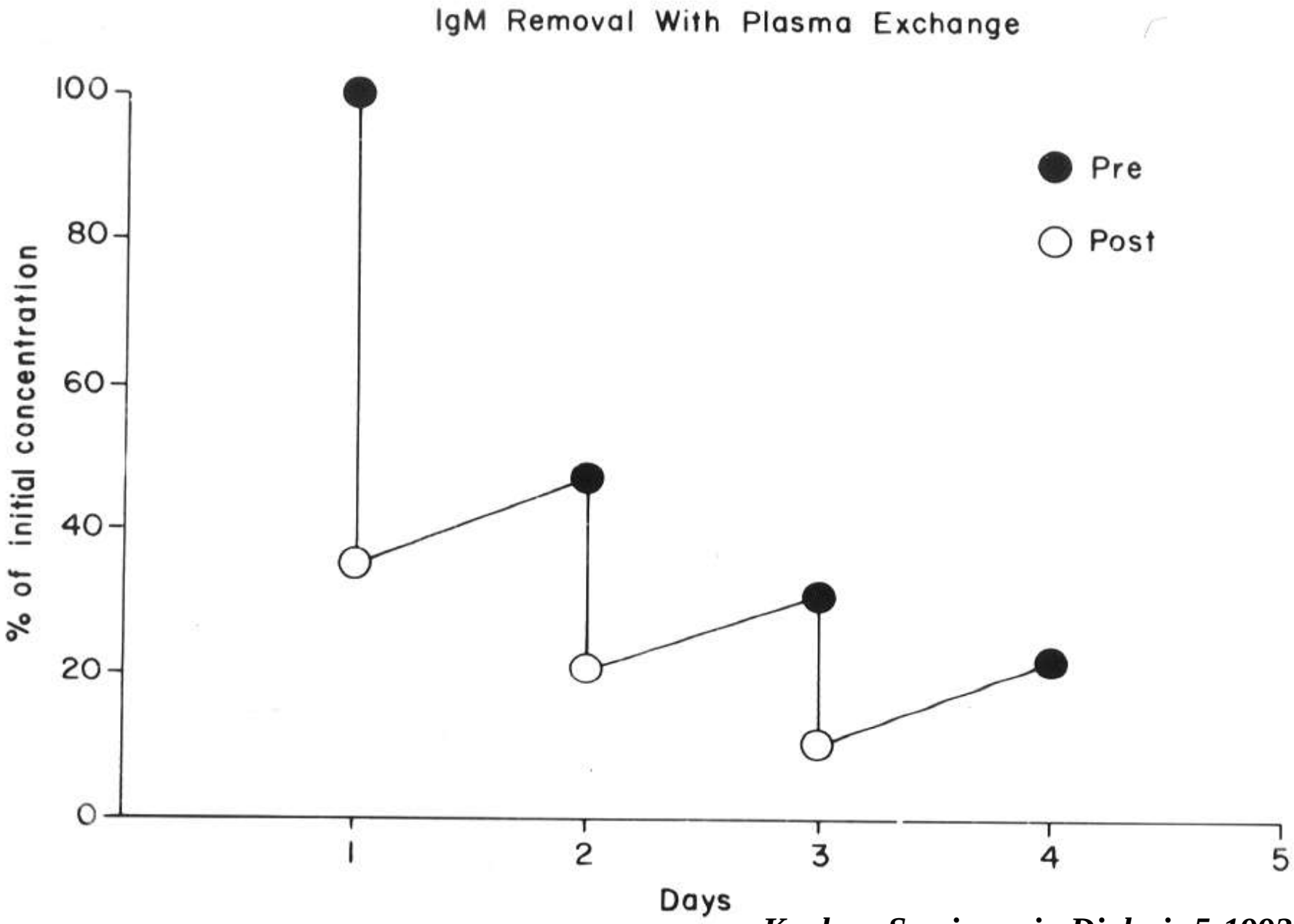
Kaplan & Halley, Kidney Int. 1990



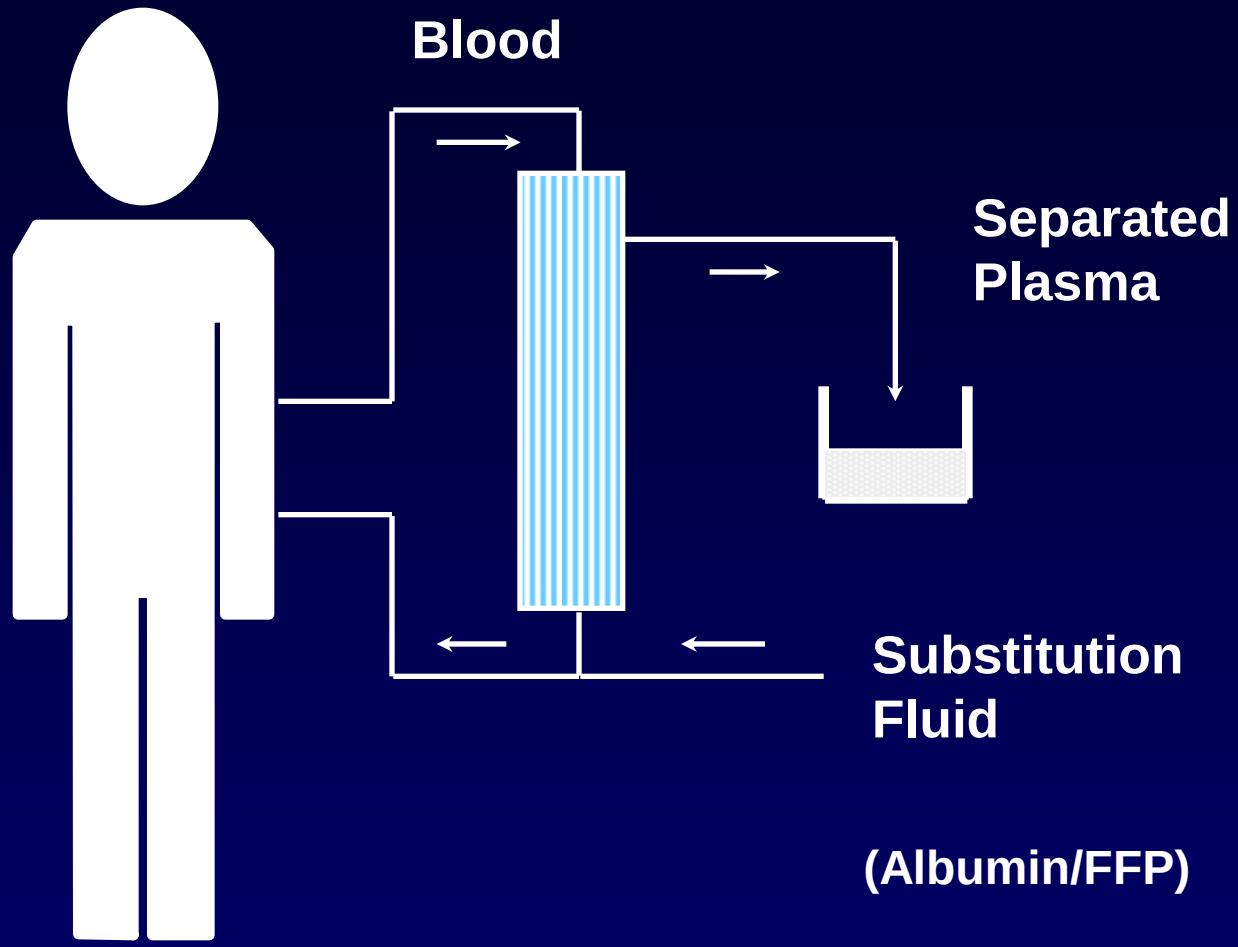
Samtleben & Gurland 1989

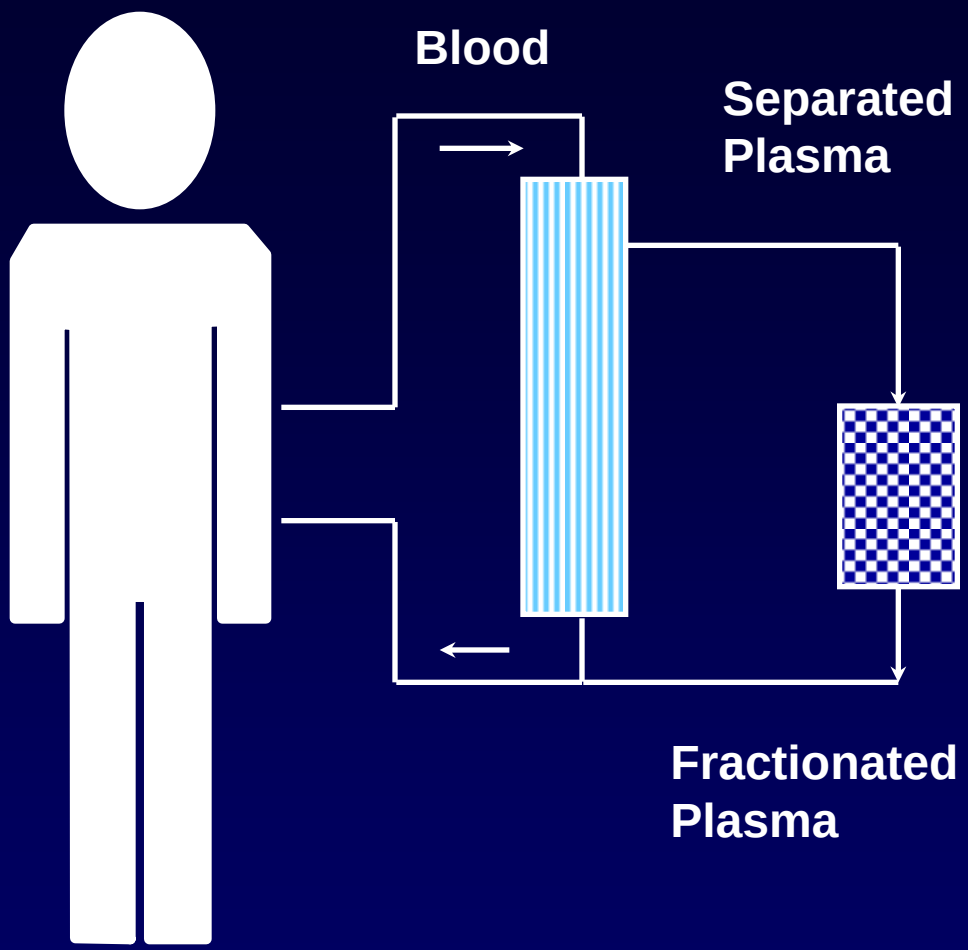


Kaplan: Seminars in Dialysis 5,1992



Kaplan: Seminars in Dialysis 5;1992


Blood
Separated
Plasma
Substitution
Fluid
(Albumin/FFP)



Selective

Adsorption/

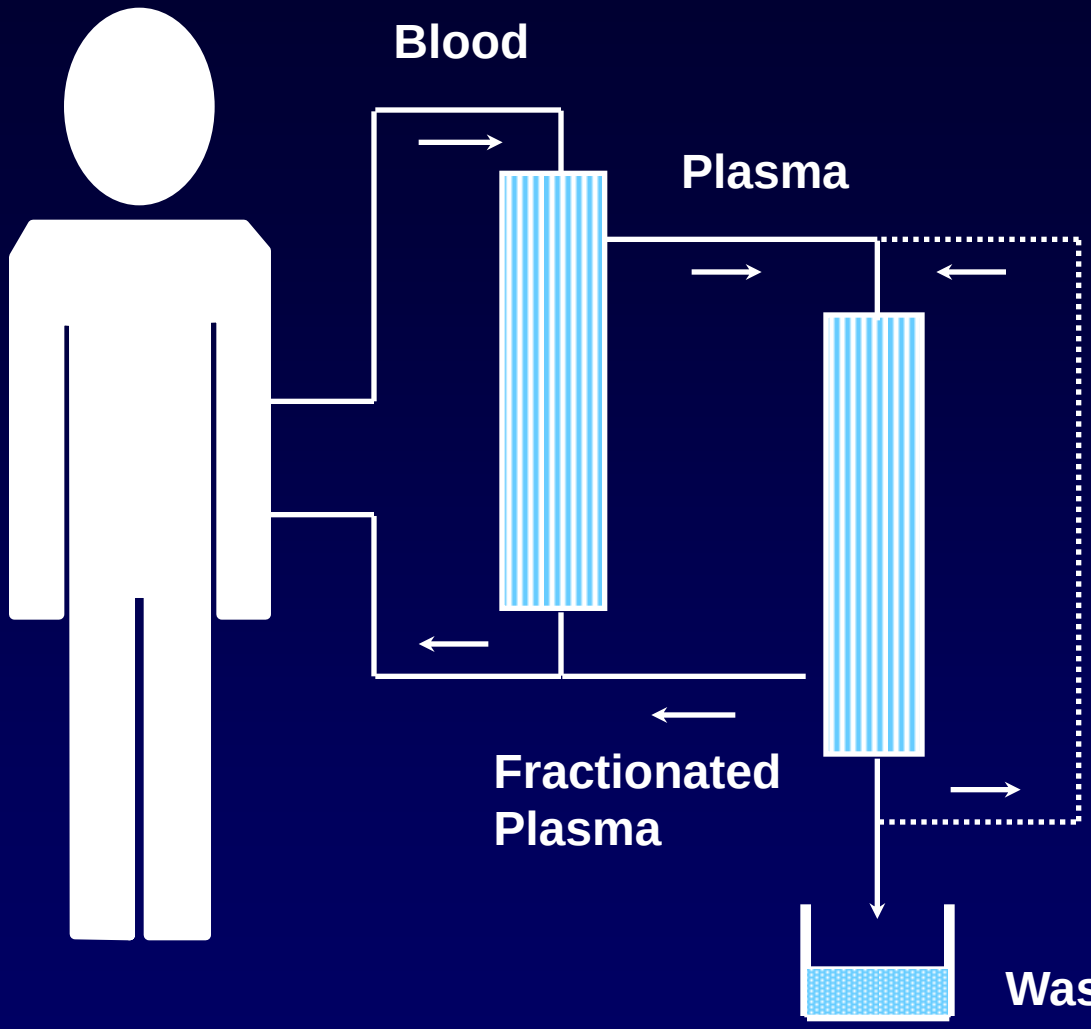
Precipitation

Absorptive columns

LDL removal

PMX: Endotoxin

Protein A: IgG



Recirculation Loop

<u>Large Molecular Targets</u>

Cryoglobulinemia

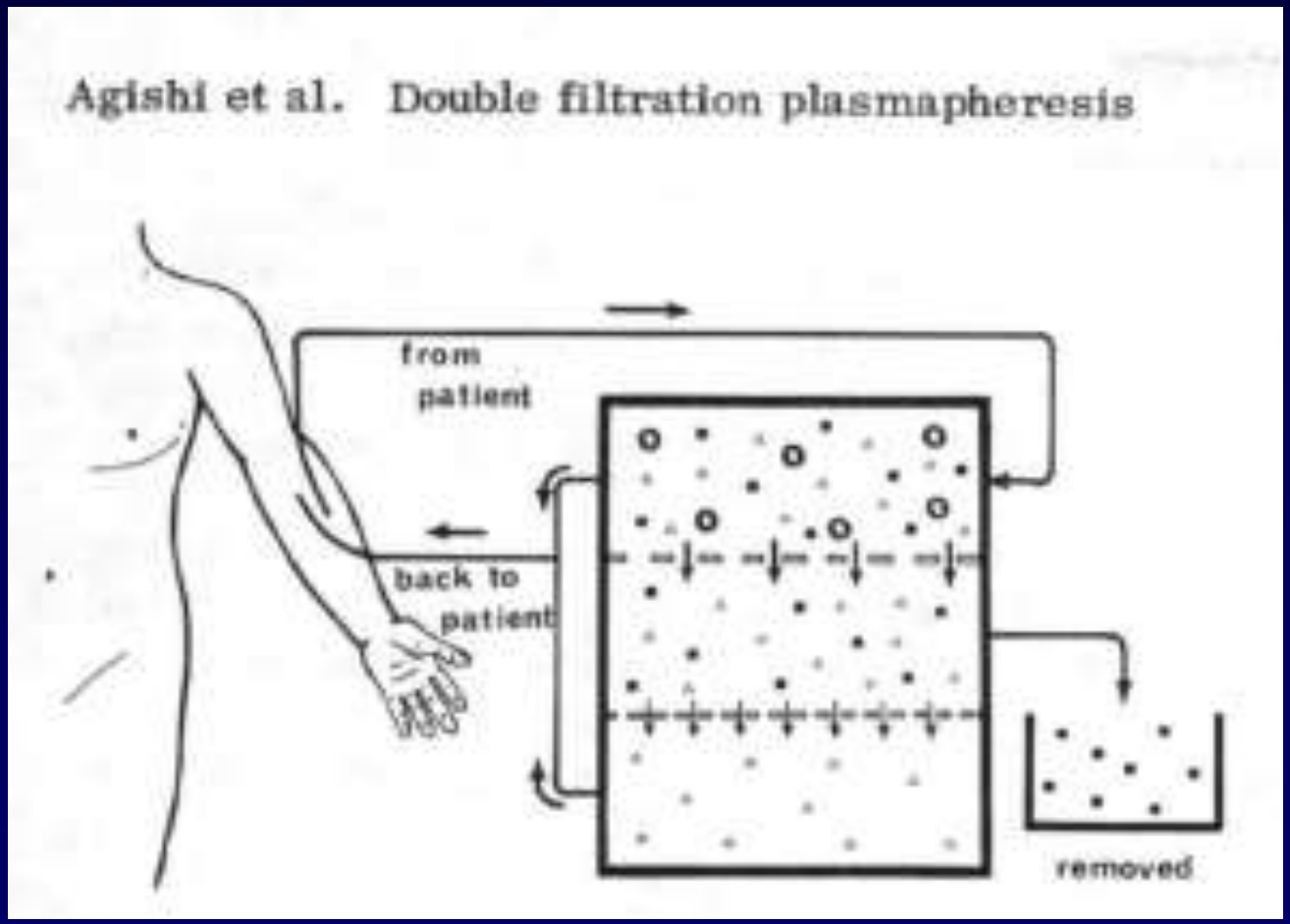
Waldentrom's Macroglobulinemia

CIDP (some)

DOUBLE FILTRATION PLASMAPHERESIS

T. Agishi, I. Kaneko, Y. Hasuo, Y. Hayasaka, T. Sanaka, K. Ota,
H. Amemiya, N. Sugino, M. Abe*, T. Ono*, S. Kawai+, and T. Yamane+

Vol.XXVI Trans Am Soc Artif Intern Organs 1980



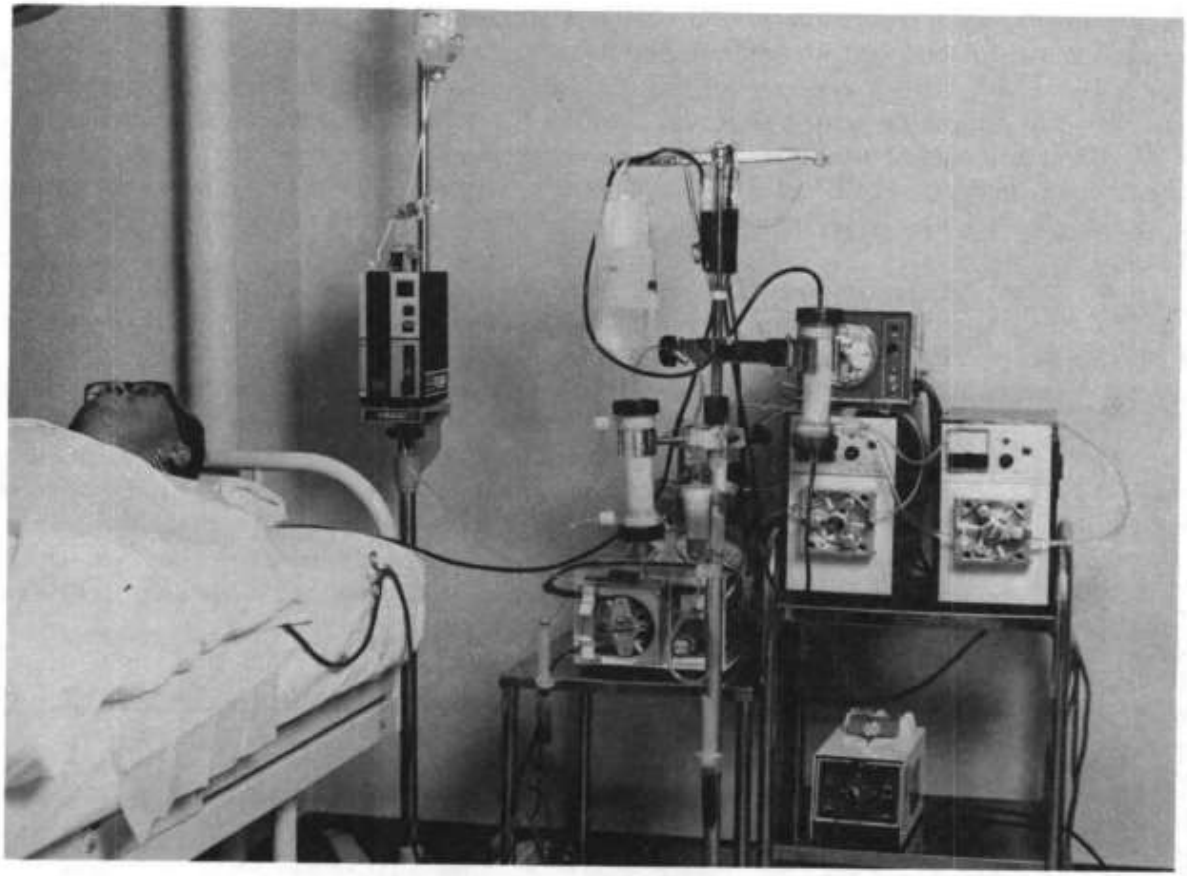
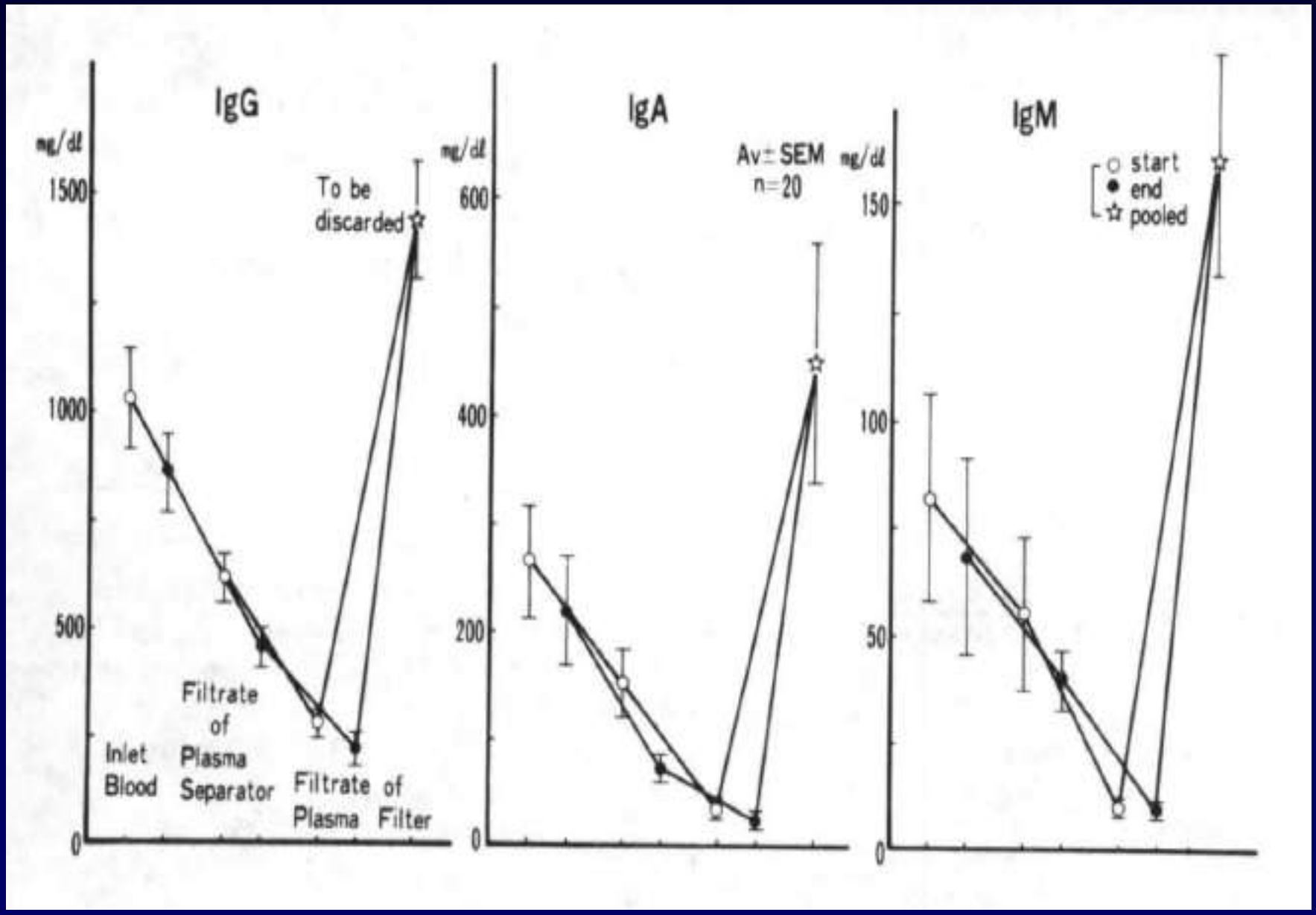
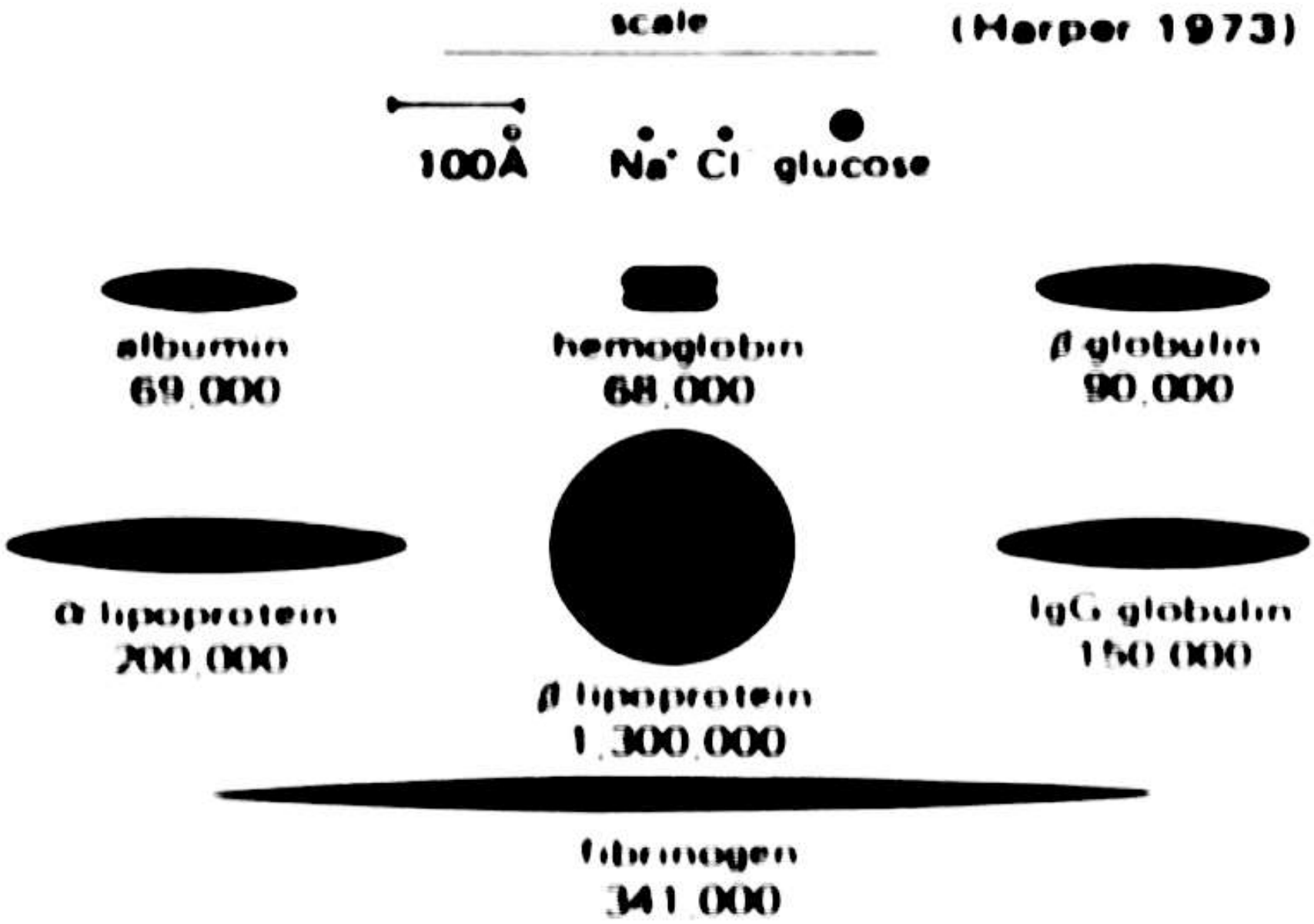


Figure 2. Clinical performance of double filtration plasmapheresis. A plasma separator is positioned on the right and a plasma filter is on the left.

Agishi et al. Trans ASAIO 1980


IgG
mg/dl
1500
1000
500
0
To be discarded
Filtrate of Plasma Separator
Inlet Blood
Filtrate of Plasma Filter
IgA
mg/dl
600
400
200
0
Av± SEM
n=20
IgM
mg/dl
150
100
50
0
start
end
pooled

Relative dimensions of plasma components



Cascade Filtration: Issues for Discussion

What are the advantages/disadvantages of CF? Consider safety of plasma supply, etc

Is there a cost advantage for CF?

What disease states are candidates for cascade filtration (CF)?

Cascade Filtration: Issues for Discussion

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Replacement fluids: Albumin and FFP

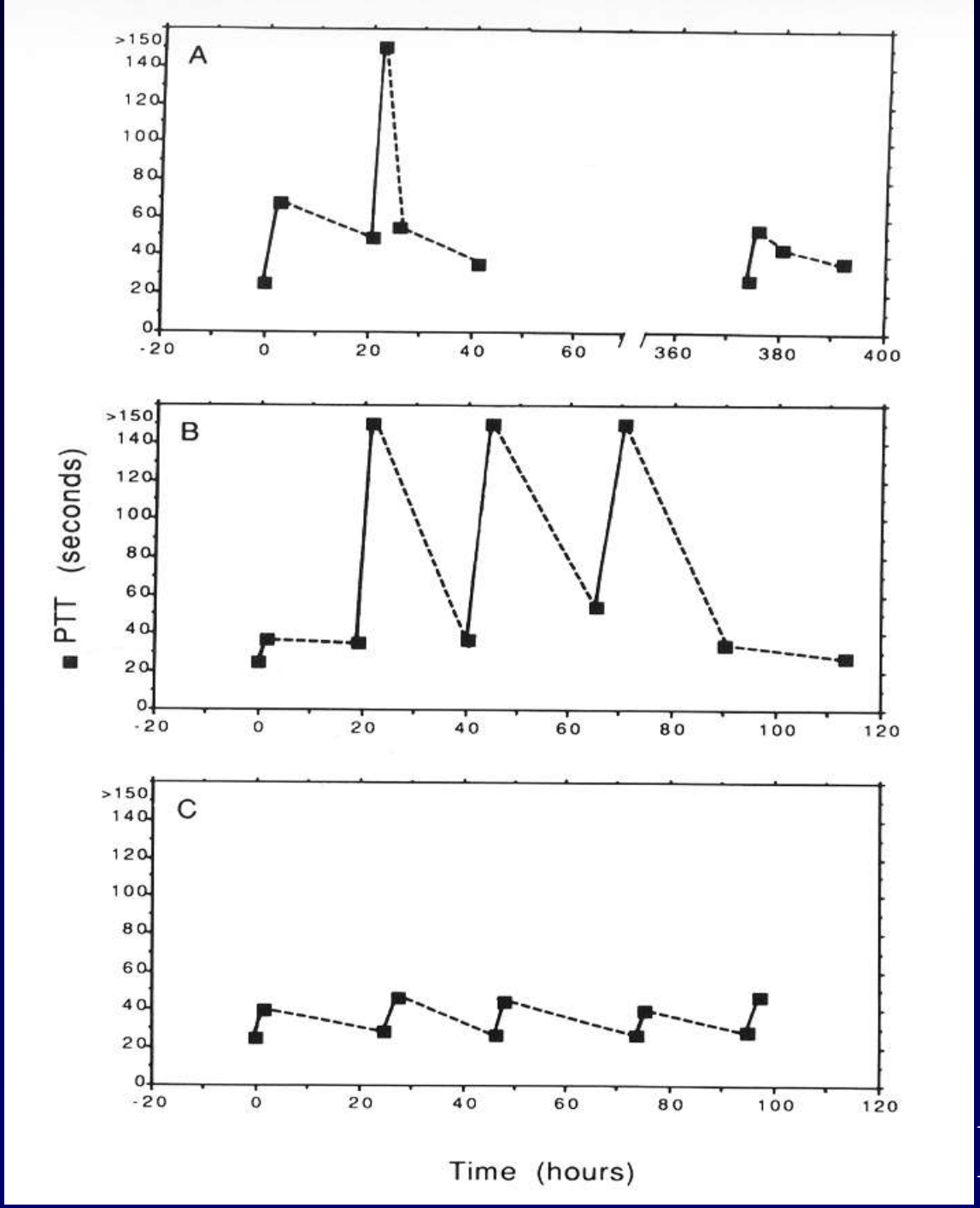
- Allergic Reactions
- Infections
- Cost

Albumin as replacement fluid in TPE

- No risk of viral transmission
- Very low risk of anaphylactoid reactions: 7/60,000units (*Ring and Messner; Lancet 466,1977*)
- Contaminants such as aluminum may accumulate with high volume exchanges in pts with renal failure

Plasma factor depletion with albumin replacement

- Depletion coagulopathy
- Immunoglobulin depletion
- Other factors?



Kaplan & Halley, Kidney Int. 1990

Risk of transfusion-transmitted viral infections per unit transfused

HIV:	1–2/1,000,000
Hepatitis C virus:	1–2/1,000,000
Hepatitis B virus:	1/200,000 – 1/500,000

Estimates are for the United States and assume the use of modern screening tests.

Stramer et al. N Engl J Med 351:760–768, 2004

Stramer et al. SLArch Pathol Lab Med 31:702–707, 2007

Dwyre et al. Vox Sang 100:92–98, 2011

Complications of Plasmapheresis (9 studies, >15,000 treatments)

Mokrycki & Kaplan, Am J Kidney Dis 23:817, 1994

- Urticaria 0.7-12 %
- Paresthesias 1.5-9
- Muscle Cramps 0.4-2.5
- Dizziness <2.5
- Headaches 0.3-5
- Nausea 0.1-1
- Hypotension 0.4-4.2
- Chest pain 0.3-1.3
- Dysrhythmia 0.1-0.7
- Anaphylactic 00.3-0.7

- Rigors 1.1-8.8
- Hyperthermia 0.7-1.0
- Bronchospasm 0.1-0.4
- Seizure 0.03-0.4
- Pulmonary edema 0.2-0.3
- Myocardial ischemia 0.1
- Shock/MI 0.1-1.5
- Hypoxemia / PE 0.2
- CNS ischemia 0.03-0.1
- Hemorrhage 0.7

Cascade Filtration: Issues for Discussion

What are the advantages/disadvantages of CF? Consider safety of plasma supply, etc

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What disease states are candidates for cascade filtration (CF)?

Cost of Albumin in U.S.

5% (250 mL): $60.00

Solution (Albumin Human Intravenous)
5% (250 mL): $75.00
25% (50 mL): $64.50
Solution (Albuminar-25 Intravenous)
25% (50 mL): $112.50
Solution (Albuminar-5 Intravenous)

=$720 for 3 Liters

5% (250 mL): $112.50

Solution (Albutein Intravenous)
5% (250 mL): $113.94
25% (50 mL): $108.00
Solution (Buminate Intravenous)
5% (250 mL): $111.10
25% (20 mL): $44.44

= $1344 for 3 Liters

Does your secondary plasma filter cost more or less than albumin?
If procedure is prolonged, how much more will you pay the apheresis nurse?

Cascade Filtration: Issues for Discussion

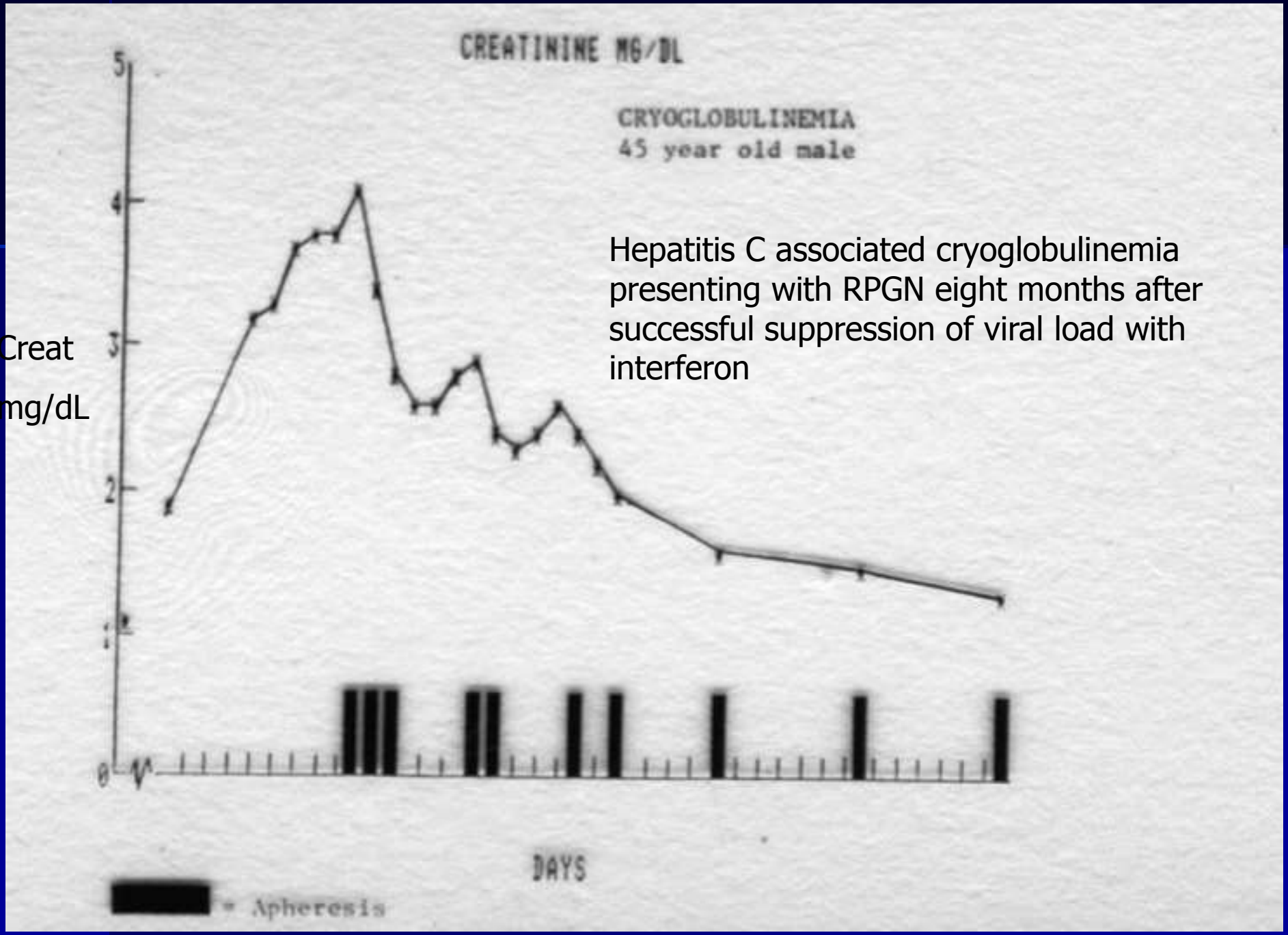
What are the advantages/disadvantages of CF? Consider safety of plasma supply, etc

Is there a cost advantage for CF?

What disease states are candidates for cascade filtration (CF)?

Cryoglobulinemia

- Despite lack of randomized, controlled trials, there is a general consensus that plasmapheresis is useful for rapid removal of cryoglobulins.
- Concomittant hepatitis C infection may render chemotherapy problematic.
- Some patients may respond to plasmapheresis alone. *Ferri et al. Nephron 43, 246, 1986*



Creat mg/dL

Hepatitis C associated cryoglobulinemia presenting with RPGN eight months after successful suppression of viral load with interferon

Cryoglobulin Removal with Therapeutic Plasma Exchange (TPE)

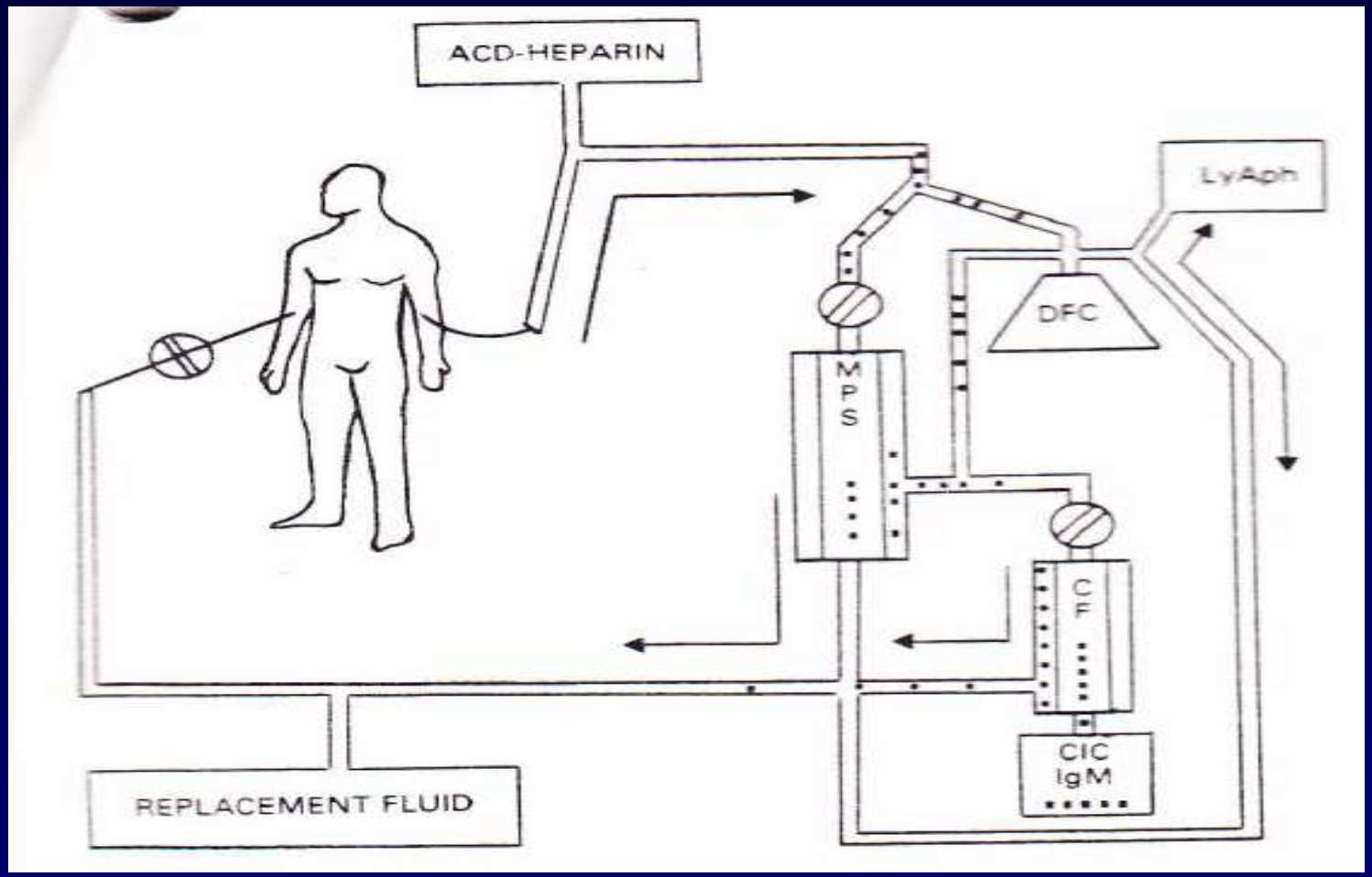
DATE	IgM mg/dL	Crycrit %
Day 1 pre TPE post TPE	294 97	8%
Day 2 pre TPE post TPE	119 61	 trace

The International Journal Of Artificial Organs / Vol. 6 no. 6, 1983 / p.p. 303-307

Cascade filtration: clinical application in 26 patients with immune complex and IgM mediated diseases

M. Valbonesi, L. Mosconi, F. Montani, G. Florio, U. Rossi

Immunohematology Service,
Saronno Hospital,
Saronno, Italy



Plasma component	Plasma composition		
	in the patients following treatment (%)	in the CF returnline (%)	in the CF waste material (%)
Lysozyme	98±1.31	98±2.70	NT
Antithrombin III	93±1.71	87±1.35	NT
Albumin	81±2.74	85±1.43	97±4.32
IgG	77±1.59	71±3.71	98±5.63
IgA	72±3.21	67±3.66	121±7.25
IgM	53±5.72	27±1.34	194±11.32
CIC	36±4.11	22±1.06	209±14.95
Cryoglobulins	23±1.20	0	241±17.36
Lipoproteins	56±0.58	21±1.63	198±11.43
Fibrinogen	55±3.21	23±0.76	181±7.22
C3 conversion	< 5	< 5	NT

Valbonesi et al Int J Artif Organs, 1983

Waldenstrom's Macroglobulinemia

- Funduscopic abnormalities in hyperviscosity syndrome include dilated and tortuous retinal veins, giving a "sausage link" appearance(8)
- Other retinal lesions include hemorrhages, exudates and papilledema

Clinical Manifestations of Waldenstrom's Macroglobulinemia

Garcia-Sanz R et al. Br J Haematol 2001 Dec;115(3):575-82

Anemia/fatigue 80%

Bleeding 23%

Fevers, Night sweats, Weight loss: 23%

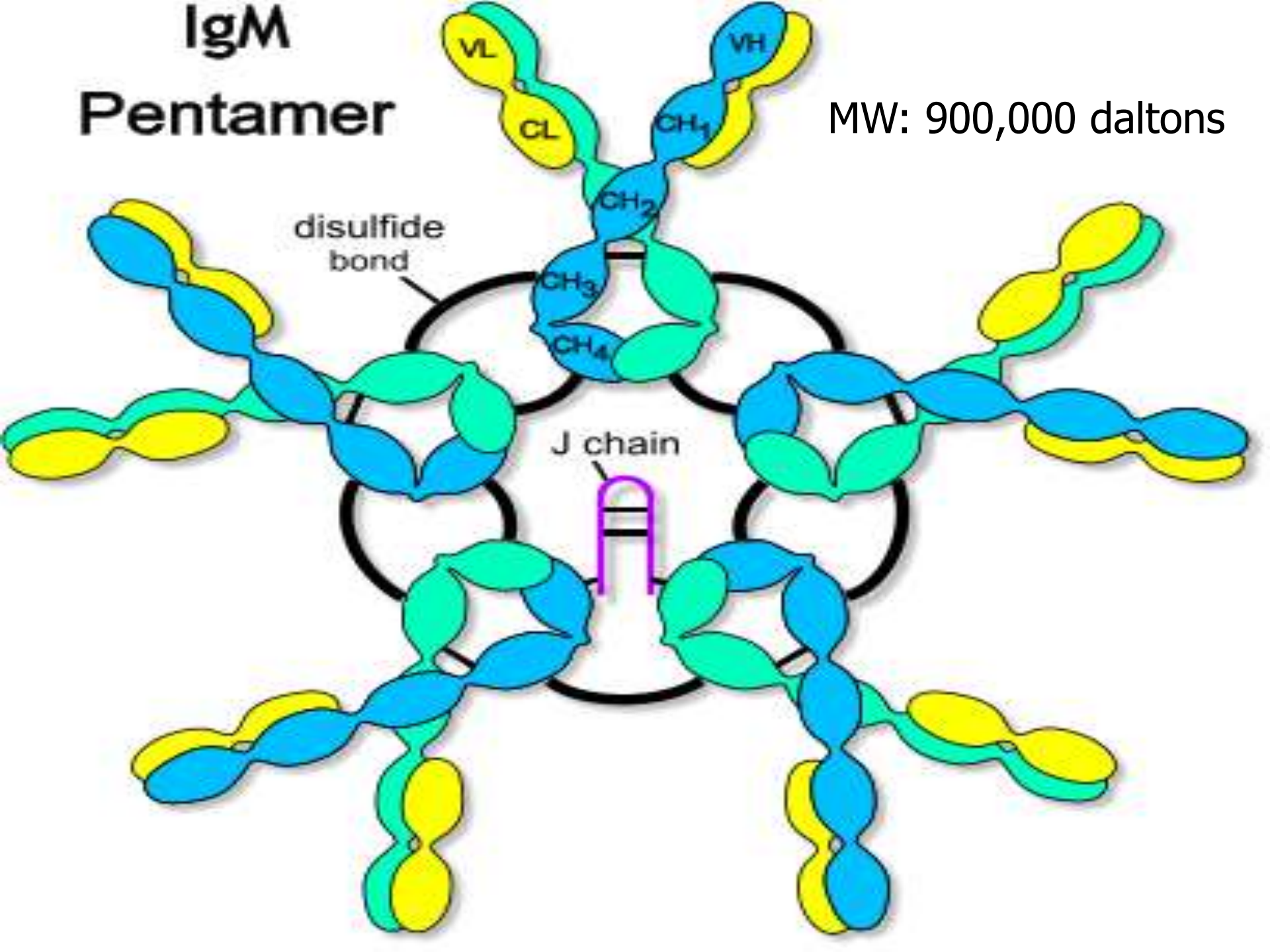
Neurologic symptoms 27%

- **Distal, symmetric, and slowly progressive sensorimotor peripheral neuropathy causing paresthesias and weakness**

Lymphadenopathy 40%, hepatomegaly or splenomegaly30%, and hepatosplenomegaly(25%)

Hyperviscosity related symptoms due to increased levels of IgM (31%)

Loss or blurring of vision, nystagmus, ataxia, tinnitus, sudden deafness, diplopia, vertigo, headache, dizziness


IgM
Pentamer
MW: 900,000 daltons
VL
VH
CL
CH1
CH2
disulfide
bond
CH3
CH4
J chain

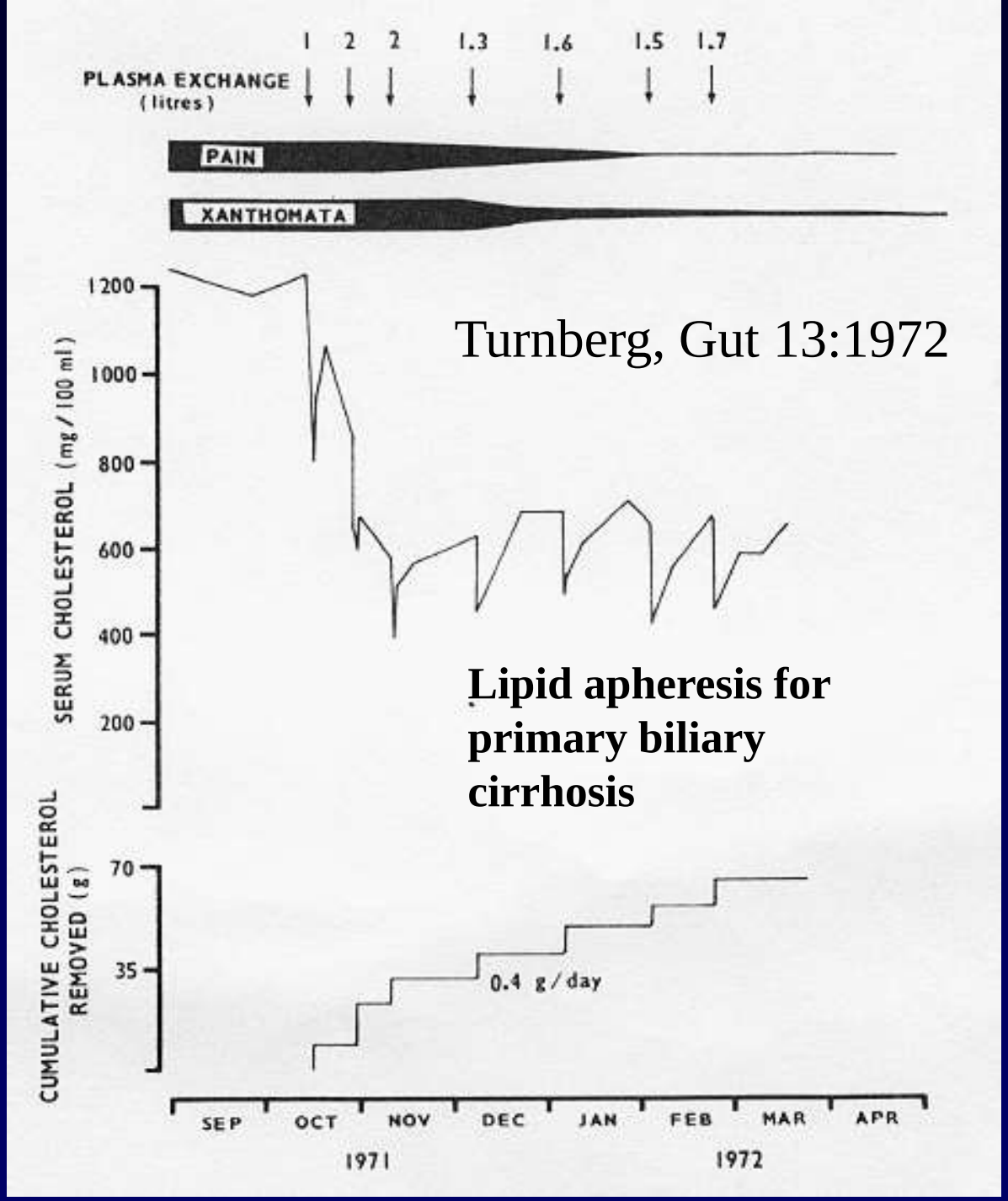
Date	IgM Mg/dl	Viscosity (1.1-1.8 centipoise)
Day 1 Tpe 1	5887 3141	4.22 2.2
Day 2 Tpe 2/Rituxmab	3893 1644	2.17 1.52
Day 3	2690	1.6
Day 5 Tpe 3	4074 1748	2.71 1.41
Day 6 Tpe 4	2378 1204	1.65 1.13
Day 7	1994	1.36

Hyperviscosity syndrome: efficacy and comparison of plasma exchange by plasma separation and cascade filtration in patients with immunocytoma of Waldenstrom's type:
Hoffkes, HG et al. Clin Nephrol, 1995, May 43(5):335-8.

Conventional plasma exchange and cascade filtration was compared at random in cases of hyperviscosity syndrome due to immunocytoma of Waldenström's type (n = 11/group).

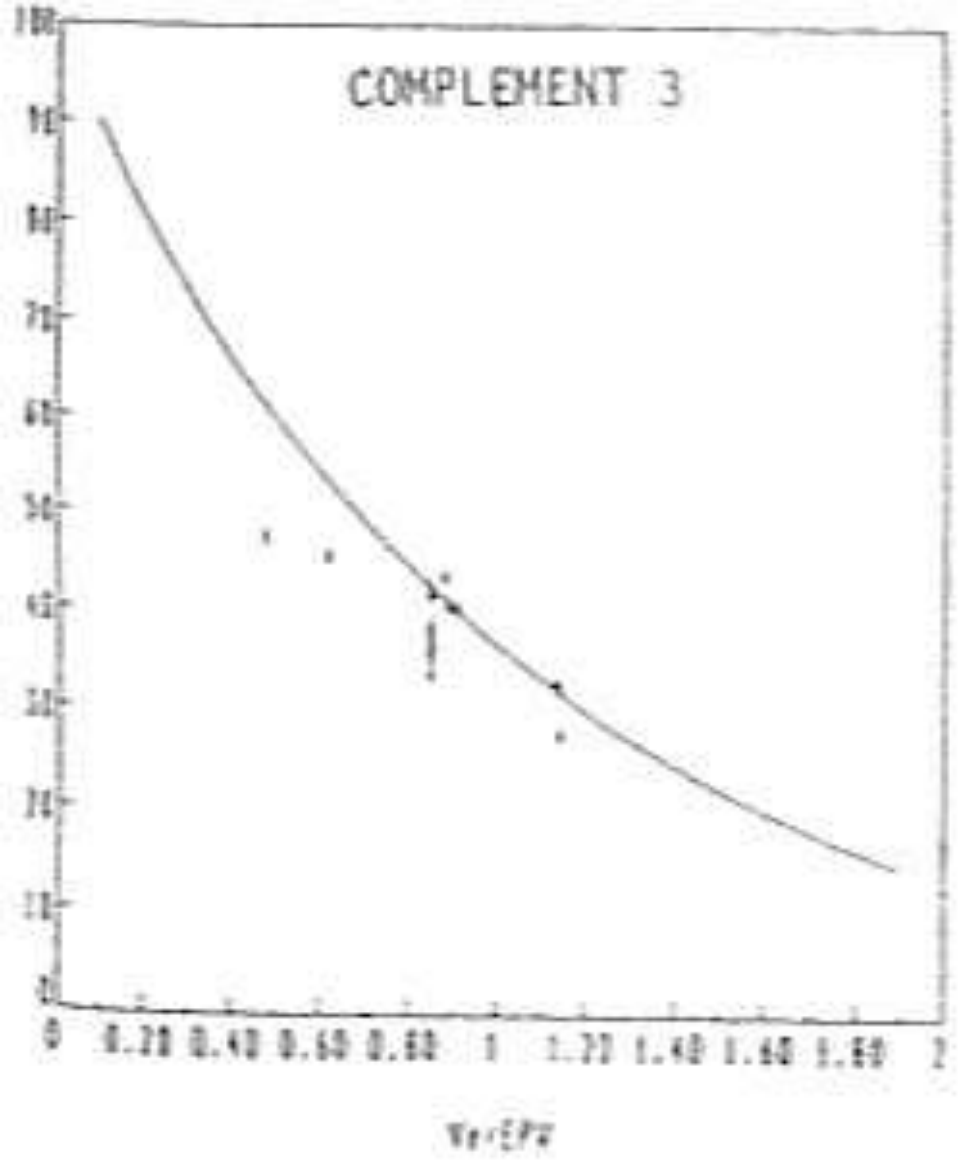
Conventional plasma exchange decreased plasma viscosity by 48%; cascade filtration was less effective (26%), correlating with a smaller decrease of IgM (conventional plasma exchange 42% vs cascade filtration 27%). The profile of other plasma proteins studied did not change significantly with either treatment. In conclusion, we could not demonstrate a superior effect of cascade filtration as compared to conventional plasma exchange in the treatment of hyperviscosity.

TPE for Hyperlipidemia



Turnberg, Gut 13:1972

Lipid apheresis for primary biliary cirrhosis



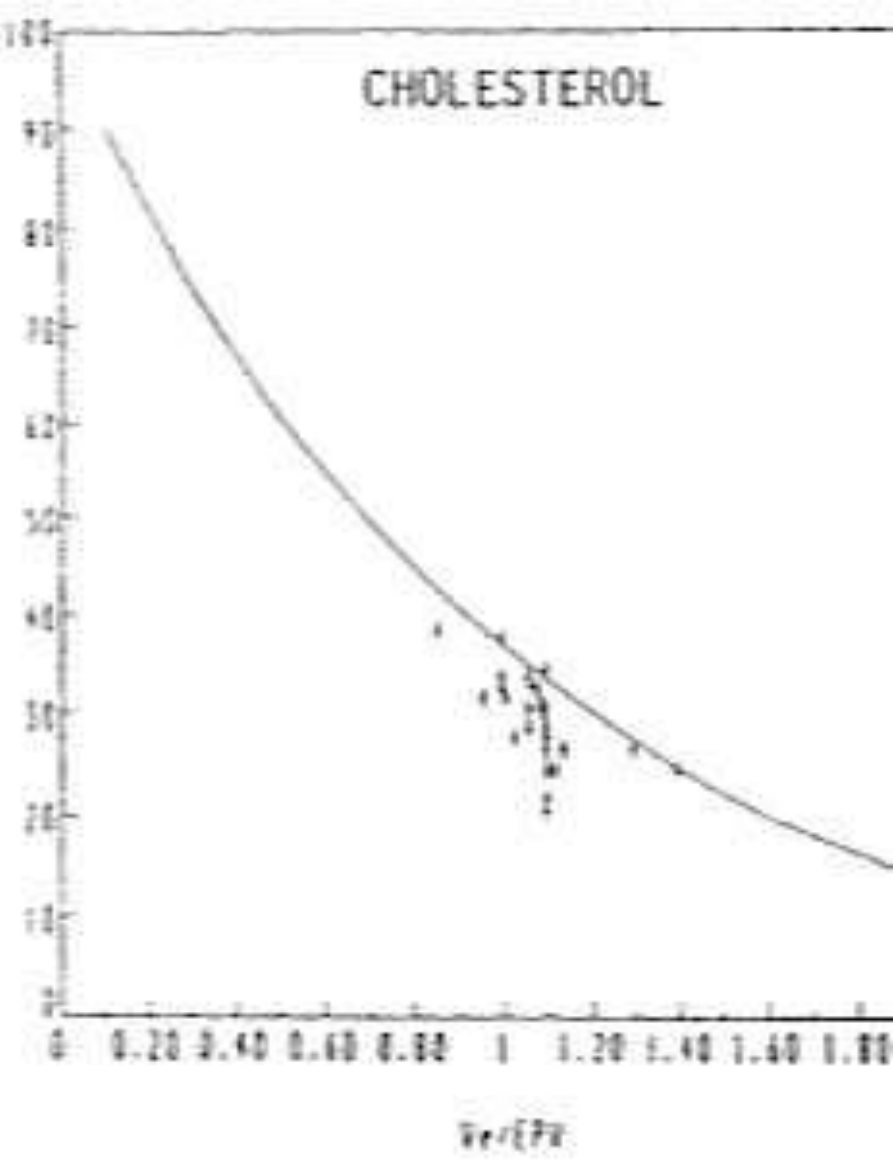


Figure 2. Correlation between predicted and actual decline i
serum levels for the third component of complement and total cho
lesterol (see **Figure 1** and **Table 1**).

Kaplan: Trans ASAIO 36, 1990

Single plasma volume exchange in Primary Biliary Cirrhosis

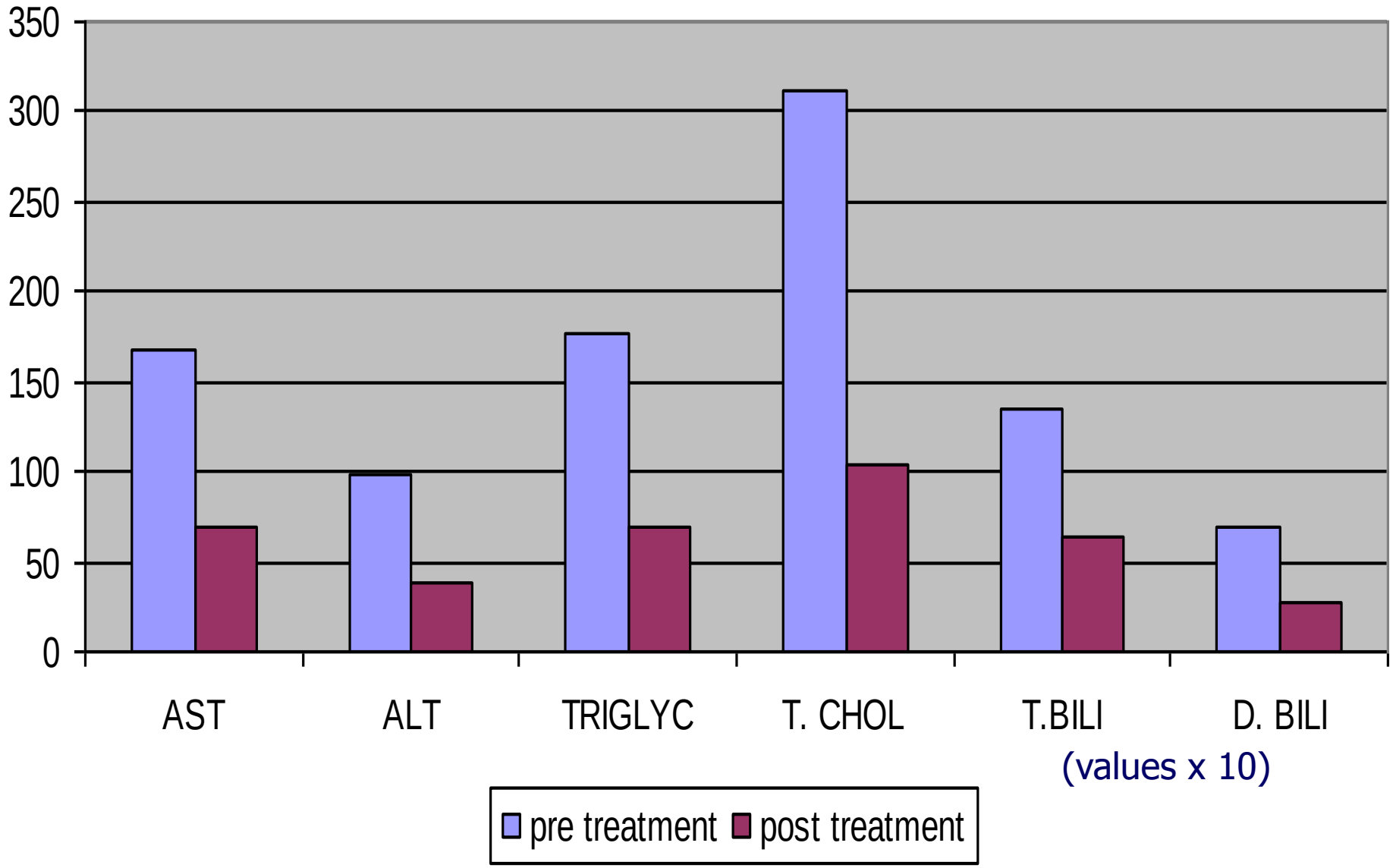


Table 1. Double Filtration: Chemical Evaluation

Substance	Serum Pre (mg/dl)	Serum Post (mg/dl)	Discarded Plasma* (mg/dl)	Net Amount Removed (mg)
Total Bilirubin	14.3	12.4	11.1	134
Direct Bilirubin	7.4	5.7	5.6	68
Total Cholesterol	415	189	404	4868
HDL Cholesterol	19	16	16	193
Triglycerides	153	96	375	4519
VLDL Cholesterol†	31	19	75	904
LDL Cholesterol†	365	154	313	3772

* Total volume of discarded plasma was 1205 ml, including 340 ml of saline flush and 865 ml of concentrated plasma.

† VLDL and LDL cholesterol fractions were calculated using the formulas: LDL cholesterol = Total cholesterol − (HDL cholesterol + VLDL cholesterol); and VLDL cholesterol = (Triglycerides [mg]/5).

HDL, high density lipoprotein; VLDL, very low density lipoprotein; LDL, low density lipoprotein.

Kaplan et al. TransASAIO 1989

Our trial with double filtration revealed a net removal of 4.9 g of cholesterol and a return of 80% of the plasma processed, thus allowing for a reduced requirement for albumin replacement. Unfortunately, the procedure required use of an expensive secondary filter, lasted for substantially more time (82 min versus 60 min), and removed significantly less cholesterol (4.9 g versus 6.7 g) than the single filtration treatments performed on this patient.

Acta Neurol Scand 2001: 104: 78–82
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ACTA NEUROLOGICA
SCANDINAVICA
ISSN 0001-6314

Double filtration plasmapheresis in the treatment of myasthenic crisis – analysis of prognostic factors and efficacy

Yeh J-H, Chen W-H, Chiu H-C. Double filtration plasmapheresis in the treatment of myasthenic crisis – analysis of prognostic factors and efficacy.
Acta Neurol Scand 2001: 104: 78–82. © Munksgaard 2001.

J.-H. Yeh, W.-H. Chen, H.-C. Chiu
Department of Neurology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan

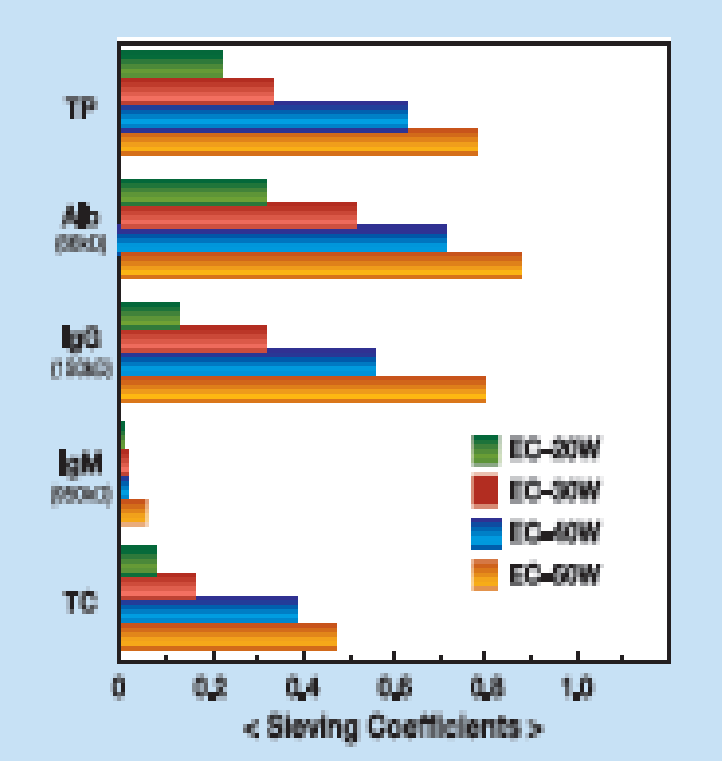
Yeh J-H, Chen W-H, Chiu H-C. Double filtration plasmapheresis in the treatment of myasthenic crisis – analysis of prognostic factors and efficacy.
Acta Neurol Scand 2001: 104: 78–82. © Munksgaard 2001.

Objectives – To examine the prognostic factors and outcome of myasthenia gravis (MG) patients in crisis with double filtration plasmapheresis (DFP) treatment. *Material and methods* – A total of 15 patients experienced 20 episodes of crisis during the study period. Plasmapheresis was carried out using a double filtration method. Demographic information, clinical features of crisis, and associated complications were analyzed. *Results* – The median duration of crisis was 9 days. Chest infection was the most common precipitant of crisis. Twelve out of the 20 episodes (60%) responded well to DFP and mechanical ventilation was discontinued after the third session of DFP in 8 of them. Three significant predictors for prolonged crisis were shorter intervals between the onset of MG and the first crisis ($P = 0.04$), higher serum bicarbonate levels at baseline ($P = 0.03$) and the thymic pathology of thymoma ($P = 0.03$). *Conclusion* – DFP can ameliorate the profound weakness in crisis and seems to be a rational therapy for patients with myasthenic crisis.

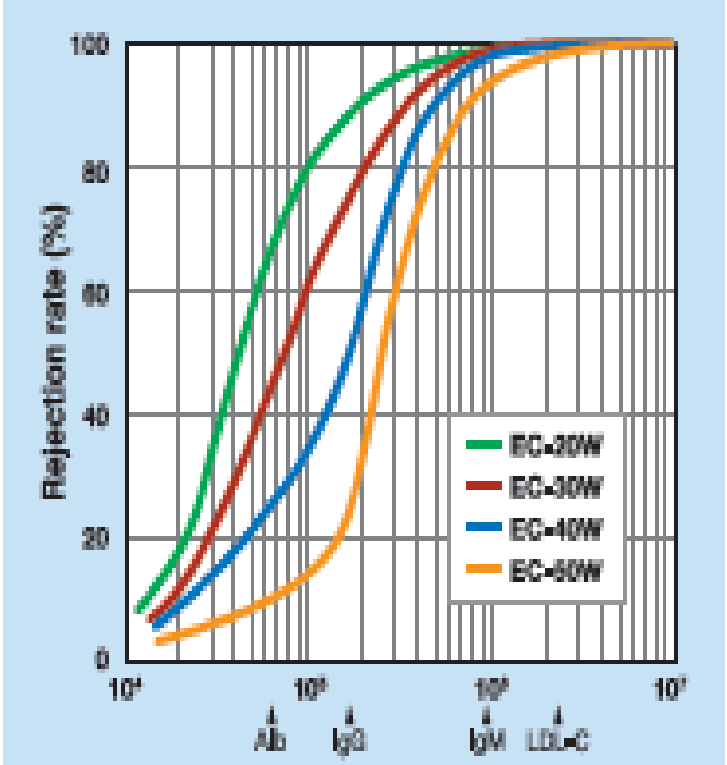
Cascadeflo™ EC

Asahi Plasma Component Separator
for Double Filtration Plasmapheresis (DFPP)

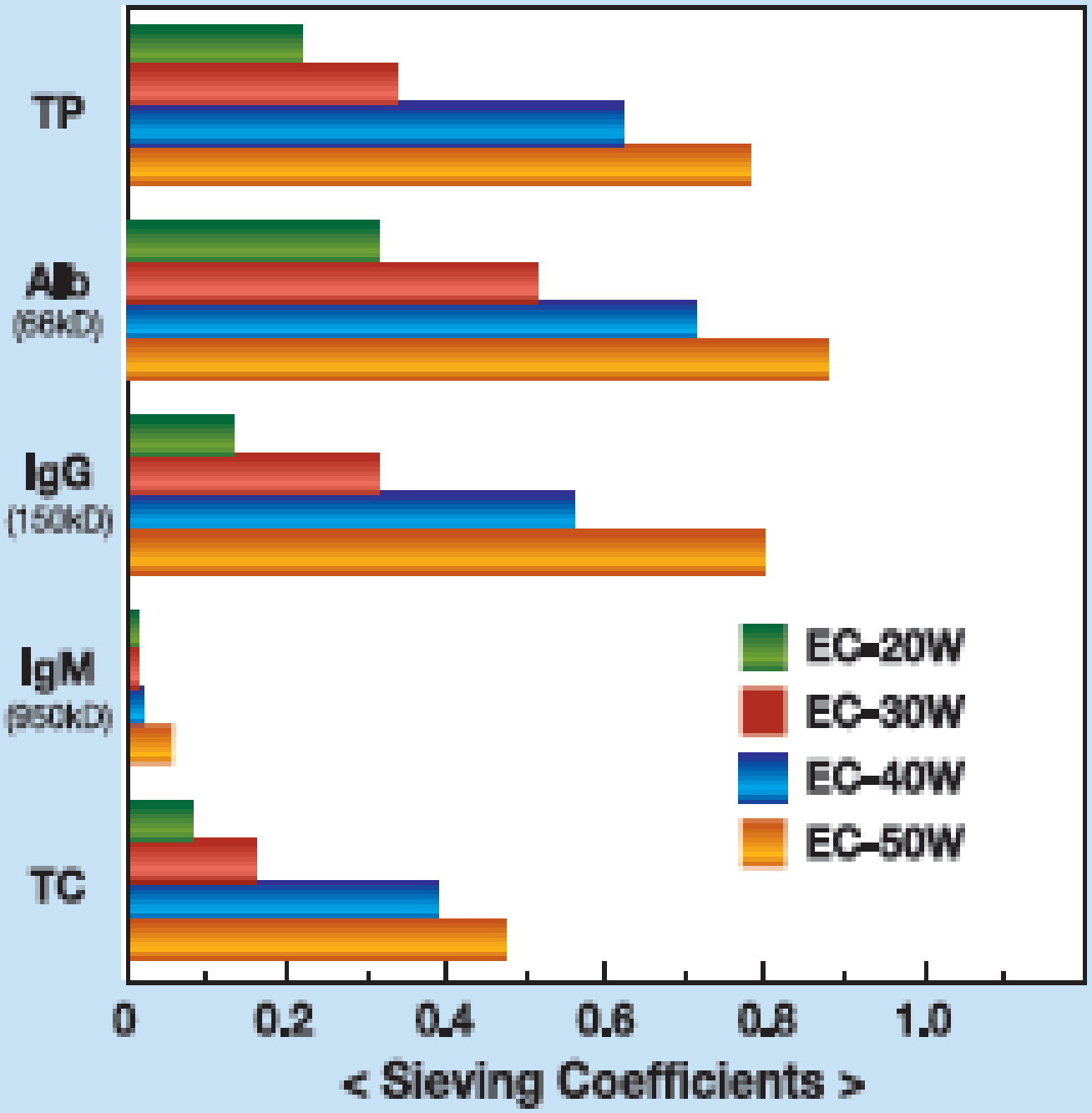
a) Permeability

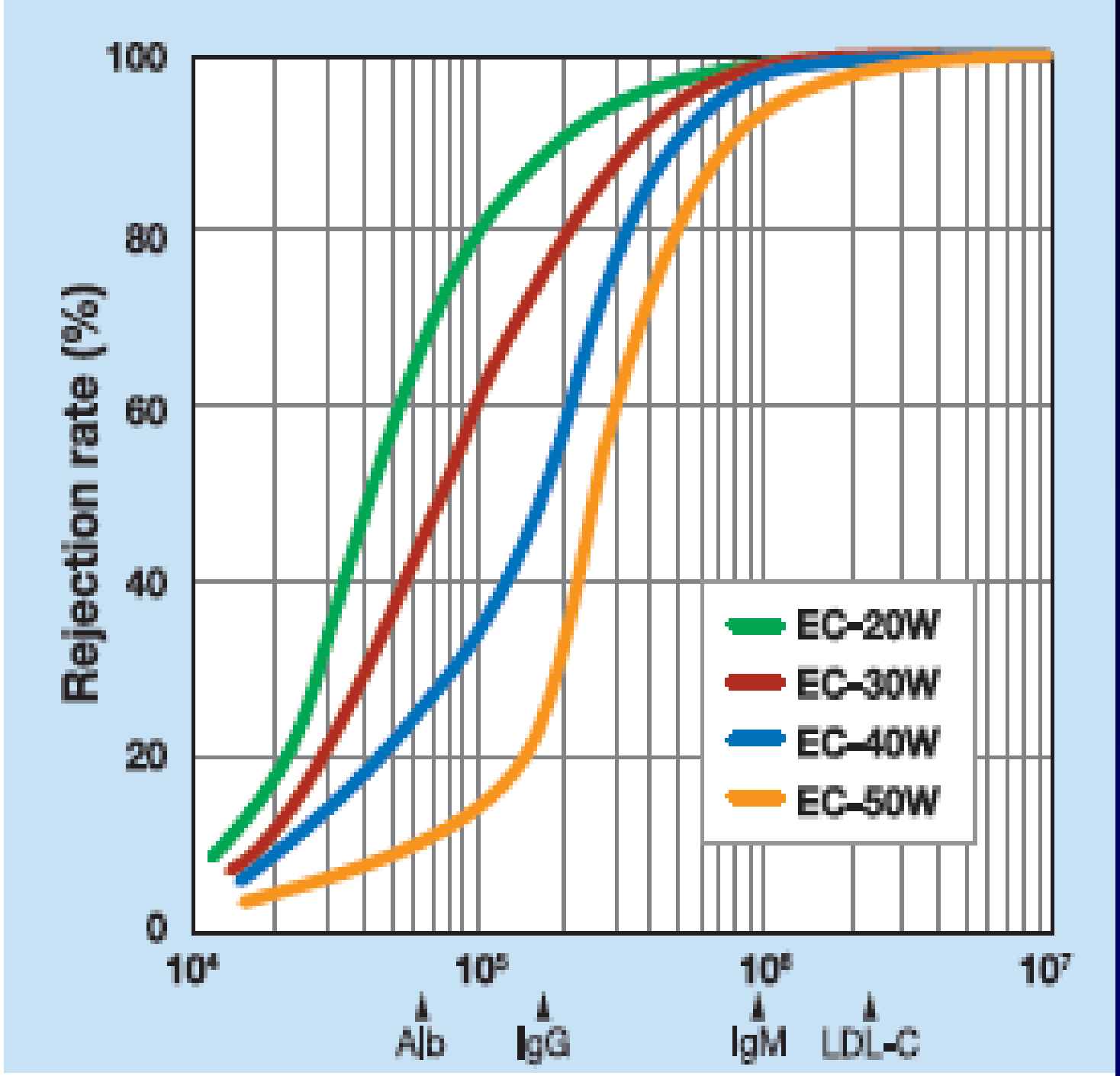


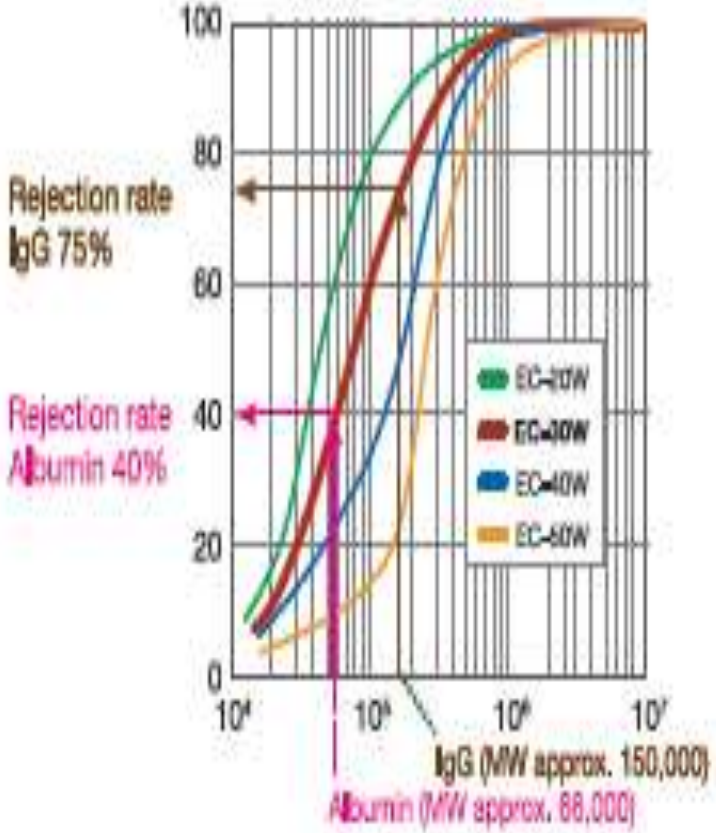
b) Cut-off Curve



In vitro data
Plasma flow rate : 30mL/min
Dicard flow rate : 6mL/min


TP
Alb
(66kD)
IgG
(150kD)
IgM
(950kD)
TC
EC-20W
EC-30W
EC-40W
EC-50W
0
0.2
0.4
0.6
0.8
1.0
< Sieving Coefficients >


Rejection rate (%)
100
80
60
40
20
0
10⁴
10⁵
10⁶
10⁷
Alb
IgG
IgM
LDL-C
EC-20W
EC-30W
EC-40W
EC-50W



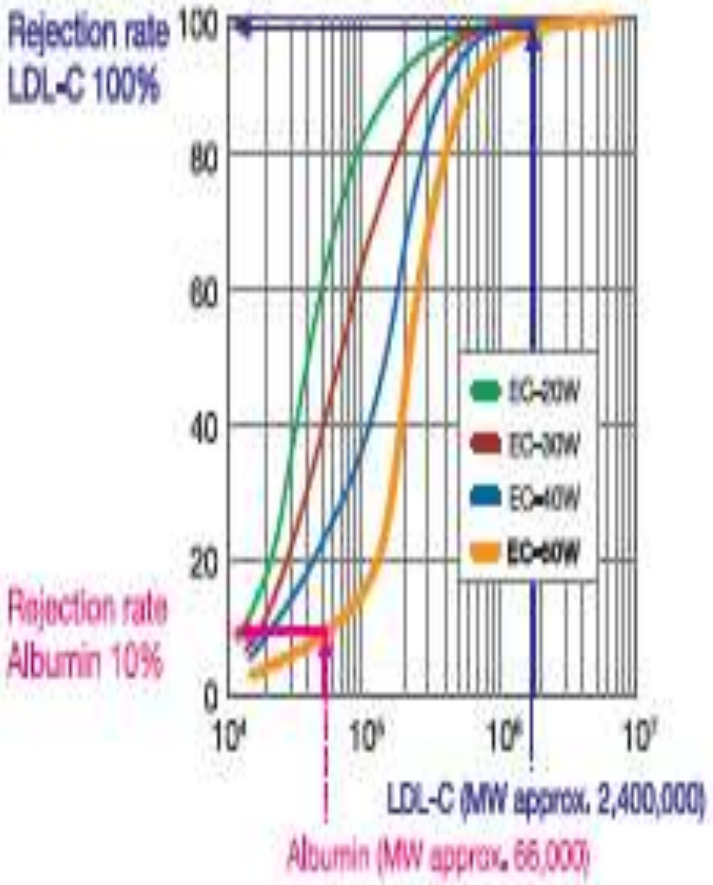
Use of EC-30W

EC-30W is used mainly for IgG removal. 75% of IgG can be removed using EC-30W based on the rejection rate of IgG (molecular weight (MW) approx. 150,000).

Since 40% of albumin (MW approx. 66,000) is removed, replacement fluid such as albumin solution is necessary to compensate for the removed albumin.

Note: EC-20W has a higher removal performance than EC-30W, and a higher possibility of filter clogging. Albumin removal is higher, and a larger amount of replacement fluid is necessary.

In vitro data
Plasma flow rate: 30mL/min
Discard flow rate: 6mL/min



Use of EC-50W

EC-50W is mainly used for LDL-C removal.

Approx. 100% of LDL-C can be removed using EC-50W based on the rejection rate of LDL-C (MW approx. 2,400,000). Albumin removal is only 10%, and albumin replacement is NOT necessary.

In vitro data
Plasma flow rate: 30mL/min
Discard flow rate: 6mL/min

Cascade Filtration: Conclusions

CF is an elegant method of removing large molecules while minimizes the amount of replacement fluid required.

Advantages: less risk of allergic reactions and "depletion" syndromes. Possibly lower cost.

Disadvantages: Possibly more expensive and longer procedures.