Membrane plasmapheresis and the developing technology of plasma therapy[1]

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Therapeutic plasmapheresis has been used increasingly in the treatment of a variety of diseases. Membrane plasma filters have been developed that produce a cell-free and particulate-free plasma ideally suited for on-line plasma treatment systems. Clinical experience with sorbent and filtration techniques for solute removal indicate promising directions for plasma therapy and its role in treating and understanding disease.

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Therapeutic apheresis procedures have increased dramatically during the past ten years. *Apheresis*, a term derived from Greek, means "to take from or to remove."[1] It includes techniques such as plasma exchange, leukocytapheresis, and thrombocytapheresis. Therapeutic plasma exchange, removal of plasma from the blood, and substitution of appropriate fluids for the plasma, have been the focus of this "new" technology, and have been used to treat numerous diseases, although often in an uncontrolled fashion without adequate rationale.

Centrifugal devices were initially used and continue to be used as the principal devices for plasma exchange. However, since 1978 hollow fiber membrane plasma separators have been available clinically, and have steadily increased in use.

New technologies for plasma separation have been under development for the on-line treatment of plasma for more

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specific removal of plasma solutes instead of complete discard and replacement as is performed in plasma exchange. Techniques for clinical use include sorbent materials and filtration systems. This is an overview of plasma separation and plasma treatment technology, especially as used at the Cleveland Clinic. Although not exhaustive in scope, devices in current clinical use are reviewed.

Plasma separation

The concept of removing "evil humours" dates from antiquity with blood letting and the application of leeches. Although these could be considered early forms of apheresis, the specific term *plasmapheresis* was first used by Abel et al[2] in 1914 to denote the separation of plasma from cellular elements of the blood with reinfusion of replacement fluids. In the 1960s centrifugal devices were developed and used clinically.[3] Many devices have since been developed for the centrifugal separation of various blood components, with many procedures providing source materials for harvest of albumin, Factor VIII, etc, or for therapeutic cytoreduction purposes. In the mid 1970s, the number of procedures and the number and variety of diseases treated by therapeutic plasma exchange greatly increased. *Table 1* lists some diseases treated by plasma exchange.[4] Most were performed by centrifugal devices, as they still are.

However, during this early period of increasing activity, other concepts were being developed, i.e., microporous membranes for plasma separation, and various on-line plasma treatment systems for removing specified "toxins" from the plasma with reinfusion of treated plasma. Membranes have been used for plasma separation since 1959, when Nosé et al[5] attempted to separate plasma from blood using a special form of Japanese filter paper with subsequent perfusion of the separated plasma over fresh frozen liver slices to provide metabolic support for hepatic coma patients. However, membrane technology was not well understood at that time and good plasma separation was not achieved. In the early 1970s, membrane technology using flat sheet membranes was under development.[6] Plate-type devices were constructed, which used sheet membrane, but these were plagued with difficulties in assembly and leakage problems, as well as operational restrictions that required blood recirculation or blood film thickness adjustor mehanisms to maintain high shear rates across the membrane. Therefore, we concentrated on hollow fiber membrane devices. Since 1974, we have

Table 1. Diseases treated by therapeutic plasmapheresis (plasma exchange)

Medical discipline	Circulating factors		
	Protein	Antibody	Immune complex
Hematology	Waldenstrom's macroglobulinemia	Idiopathic thrombocytopenic purpura Factor VIII autoantibody Rh disease Autoimmune hemolytic disease	Thrombotic thrombocytopenic purpura?
Rheumatology	Raynaud's disease?	Systemic lupus erythematosus	Rheumatoid arthritis Systemic lupus erythematosus Scleroderma? Other
Neurology		Myasthenia gravis Multiple sclerosis Polymyositis Polyneuropathy	Guillain-Barre syndrome?
Oncology	Multiple myeloma	Other cancers	
Nephrology		Progressive nephritis Glomerulonephritis Goodpasture's syndrome	Transplant rejection (?) Polyarteritis nodosa
Other	Toxins Poisons Hypercholesterolemia Thyrotoxicosis Primary biliary cirrhosis Hypertriglyceridemia Hepatic insufficiency	Chronic active hepatitis	

been developing membrane plasma separators for clinical use, primarily for on-line therapy systems.[7] Initial work had been aimed at metabolic support.

The first membrane plasma separators for clinical use were made from cellulose acetate, and were first used in 1977 in Japan[8] and in 1978 by our group in the United States.[9] The first hollow-fiber devices (manufactured by Asahi Medical Co, Tokyo, Japan) have been used extensively in Europe and Japan and more recently in the United States, after approval for clinical use by the Food and Drug Administration in early 1983. For the past 5 years, considerable attention has been focused on the development of membrane plasma separators; a variety of devices are now currently available for clinical use or are being clinically tested. Our experience with these devices is summarized in *Table 2.* A wide variety of polymeric materials is used in their construction.

Membrane plasma separators differ from hemodialysis and ultrafiltration devices in several important parameters, i.e. the pore size of dialyzers is in the range of angstroms and allows separation of solutes of approximately ≤5000 molecular weight versus membrane plasma separators, which have pore sizes in the range of 0.1–0.6 μm and allow the separation of solutes of several million molecular weight from the cellular elements. Hemodialysis typically operates at high transmembrane pressures (≥200 mm Hg) to ensure adequate ultrafiltration of water. In contrast, membrane plasma separators are operated at low hydraulic pressure, generally ≤50 mm Hg, which ensures separation of plasma at high rates and at high sieving coefficients.[10] The sieving coefficient is the ratio of solute concentration in the filtrate to solute concentration in the incoming blood. Increased transmembrane pressure can lead to deterioration of plasma flux, sieving, and, ultimately, to hemolysis.

Materials used in the construction of hollow fiber membrane separators differ in polymer type, hydrophobicity, and microstructure characteristics such as pore size and distribution. Use of a given membrane material in a plasma filtration device defines operating conditions for that device based upon the material and microstructure and the overall design of the device including such factors as the number of fibers, length of fibers, and internal diameter of the plasma capillaries. Thus, a given device must be operated according to specified conditions for that particular module, with consideration of the blood's cellular and macromolecular solute concentrations, which affect separator operation.[11]

Numerous studies have been reported on the safety, biocompatibility, and efficacy of membrane plasma separators for separating plasma from whole blood.[12] In both individual procedures and in chronic, repeated, long-term therapy, membrane plasma separators provide excellent blood cell compatibility, efficacious plasma removal from the blood, and the production of a cell-free, particulate-free plasma.[13] Procedures are performed without difficulty and without clinical sequelae, although certain changes occur during the extracorporeal procedures related to changes in formed blood elements[14] and activation of coagulation and complement systems in the blood.[15] Specifically, a phenomenon resembling hemodialysis leukopenia occurs with membrane separators.[16] Early reduction in leukocyte count is followed by reaccumulation of leukocytes with overshoot. This pattern appears to be material-dependent to some extent, with newer

Table 2. Membrane plasmapheresis filters used clinically at The Cleveland Clinic Foundation

Manufacturer filter name	Material	Inside diameter μm	Wall thickness μm	Effective length mm	Effective surface area m^2
Asahi* Hi-05	Cellulose diacetate	330	75	157	0.50
Kuraray† SA	Polyvinyl alcohol	330	125	290	0.60
Toray‡ PS-05	Polymethylmethacrylate	370	85	175	0.50
Mitsubishi§ MPS	Polyethylene	270	60	175	0.65
Cobe ‖ TPE	Modified polyvinylchloride	Variable thickness, 6 channels			0.13

* Asahi Medical Company, Tokyo, Japan.
† Kuraray Company, Osaka, Japan.
‡ Toray Industries, Inc, Tokyo, Japan.
§ Mitsubishi Rayon Co, Inc, Tokyo, Japan.
‖ Cobe Laboratories, Inc, Lakewood, Colorado.

membranes made of purer materials causing fewer white cell changes and slightly decreased effects on the complement system.[16]

On-line plasma treatment

Coupled with the development of various techniques for the separation of plasma from blood cells, on-line plasma treatment techniques have been under development for the removal of various specific plasma solutes *(Figure)*. These systems have evolved because of (1) increasing demand for plasma exchange for the treatment of various diseases; (2) high cost of replacement fluids, and (3) inadequacy of available supplies of protein replacement fluids should plasmapheresis be found effective in treating many diseases currently under investigation. Conceptually, these processes would also provide better understanding of disease pathophysiology.

Specific plasma solutes can be removed by physical, chemical, or immunologic methods. Hemoperfusion, the direct perfusion of blood over sorbent materials, has been used for acute conditions, such as various intoxications, especially poisoning. The primary difficulty with direct hemoperfusion is platelet loss because of adhesion to the sorbents. Membrane plasmapheresis with subsequent on-line treatment of the plasma by sorbent or other plasma treatment device prevents platelet loss while allowing repeated chronic treatment that is biocompatible and effective. Several on-line plasma treatment systems are described here with emphasis on sorbents and filtration systems used at the Cleveland Clinic. Other systems in clinical use are reviewed briefly.

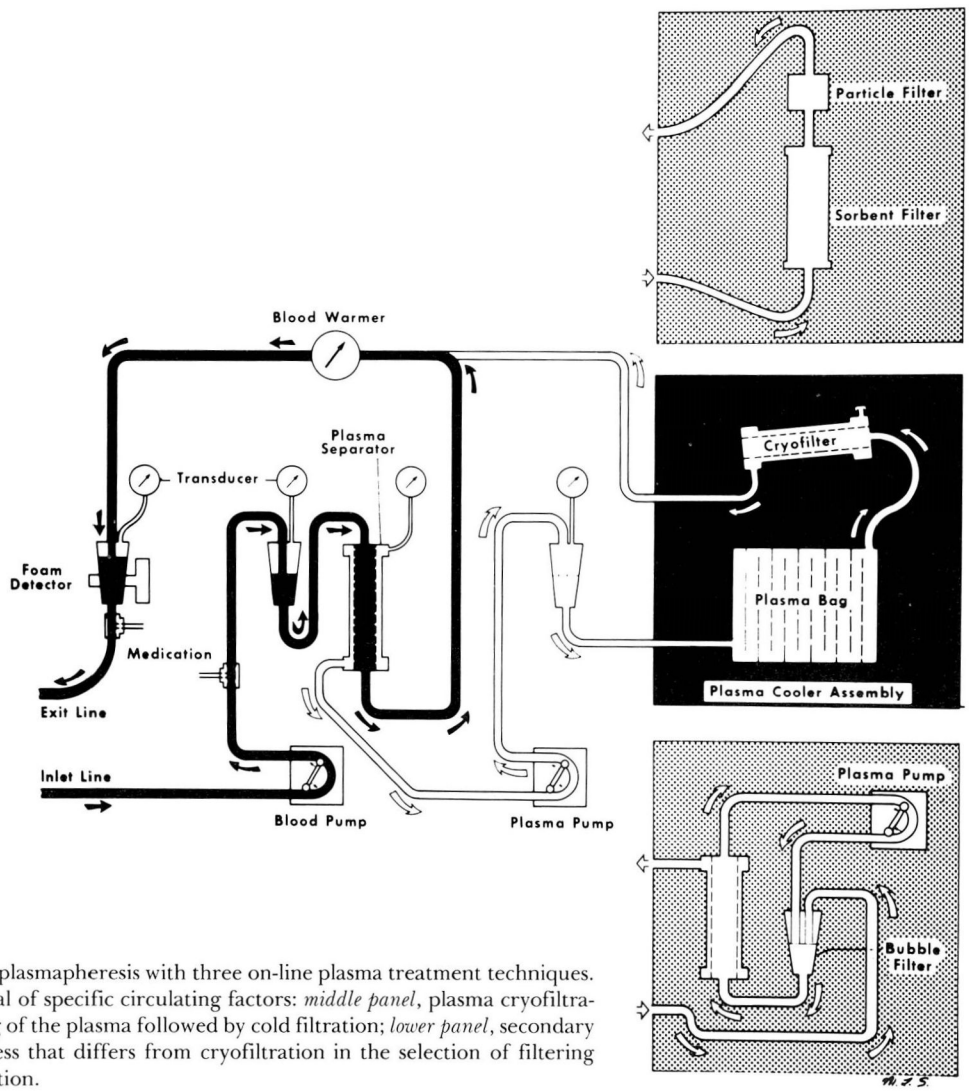

Figure. Schematic of membrane plasmapheresis with three on-line plasma treatment techniques. *Top panel*, sorbent column for removal of specific circulating factors: *middle panel*, plasma cryofiltration as performed with on-line cooling of the plasma followed by cold filtration; *lower panel*, secondary filter with recirculating flow, a process that differs from cryofiltration in the selection of filtering membrane and temperature of operation.

Sorbents for metabolic assist

During the past ten years, metabolic assist systems for the support of hepatic failure patients have been developed in conjunction with membrane plasma separation. Initially, it was thought that an artificial liver could be developed to substitute for all liver functions including biosynthesis, storage, detoxification, and biotransformation. However, clinical hepatic assist techniques cannot provide all these functions and are therefore usually directed toward detoxification. Numerous techniques have been used for solute removal for hepatic assist including dialysis,[17] hemofiltration,[18] hemoperfusion,[19] and plasmapheresis.[20] Because of the nature and size of metabolites occurring in hepatic failure, hemodialysis and hemofiltration (high permeability hemodialysis) have had limited application as hepatic assist procedures. Hemoperfusion of activated charcoal and other exchange resins has been used to remove toxic materials from patients with hepatic failure. Because of bioincompatibility, this method was rejected and plasma separation and sorbent perfusion elected.

Membrane plasmapheresis provides cell-free plasma for detoxification by sorbents. Problems of blood/sorbent incompatibility are thus eliminated and multiple biochemical abnormalities may be treated with the use of various sorbents.[21] With selective removal, most of the patient's plasma can be reinfused thus minimizing the need for substitution fluids such as albumin or fresh frozen plasma. Detoxification can then be performed often and chronically to provide hepatic assist. Combination of membrane plasma separation and sorbents was first used in acute hepatic failure in 6 patients with hepatic dysfunction.[22] Studies at other institutions also report the effectiveness of the system for the reversal of coma and for short-term survival; however, overall results are comparable to those obtained with conventional hepatic support, i.e., 20% to 30% survival.[23] Because of these limitations, this system has subsequently been used for patients with chronic cholestatic liver disease (*Table 3*).[17] It is directed toward the alleviation of major symptoms such as pruritis, neuropathy, xanthomatous skin lesions, and jaundice since these symptoms are due at least in part to elevated plasma levels of bile acids, cholesterol, and bilirubin.[24] The system can satisfactorily reduce pruritis and xanthomata and their corresponding biochemical parameters.[25] The system has also been shown to be hematologically and biochemically biocompatible.[26,27] Long-term efficacy and safety have been demonstrated in a patient with sclerosing cholangitis who has been on chronic out-patient plasmapheresis therapy for 2½ years (*Table 4*). In this patient, leukopenia, thrombocytopenia, and mild anemia have persisted, which is consistent with chronic liver disease. Coagulation and other biochemical values have remained normal. Those used to monitor the disease, bilirubin, serum glutamic oxaloacetic transaminase (SGOT), and alkaline phosphatase have remained elevated, although reduced from pretreatment

Table 3. Membrane plasmapheresis with plasma treatment for cholestatic liver disease

Patient age/sex	Diagnosis	Treatment method	Number of treatments	Treated plasma volume, L
52/F	PBC	Sorption	6	19.0
49/F	PBC	Sorption	6	23.3
57/F	PBC	Sorption	3	15.4
48/F	PBC	Sorption	3	16.0
20/M	CBD	Sorption	11	65.3
35/F	PBC	Sorption and filtration	4	6.2
36/F	PBC	Sorption and filtration	3	9.8
36/M	SC	Sorption, plasma exchange, sorption and filtration	100	321.3
58/F	PBC	Sorption, plasma exchange	2	5.2

PBC = primary biliary cirrhosis, CBD = congenital biliary disease, SC = sclerosing cholangitis.

Table 4. Hematologic and biochemical changes during 100 sessions of plasma treatment

Treatment number	1	20	40	60	80	100
WBC ($\times 10^9$/L)	8.0	7.8	13.5	5.1	6.9	5.7
RBC ($\times 10^{12}$/L)	3.22	3.45	3.00	3.05	2.94	2.98
HCT (%)	27.2	30.1	26.6	31.5	28.0	28.1
Fibrinogen (mg/dl)	400	430	...	...	327	...
PT (sec)	13	...	...	...	17	...
PTT (sec)	31	...	...	...	47	...
Total protein (g/dl)	7.2	8.0	7.1	7.4	7.3	7.2
Albumin (g/dl)	3.1	3.5	3.2	3.3	4.1	3.9
SGOT (U/L)	215	390	273	254	430	345
Alkaline phosphatase (U/L)	3740	3500	2580	2020	1730	2160
Bilirubin (mg/dl)	11.5	11.5	15.0	18.0	19.0	21.5
Cholesterol (mg/dl)	2195	875	496	309	388	445

WBC = white blood cell count, RBC = red blood cell count, HCT = hematocrit, PT = prothrombin time, PTT = partial thromboplastin time, SGOT = serum glutamic oxaloacetic transaminase.

levels. Total cholesterol has been substantially reduced and maintained. Lipoprotein composition has tended to normalize as seen by agarose electrophoresis, with decrease of beta lipoproteins and reappearance of pre-beta and alpha fractions in the plasma.

The resins used in these treatments consist of an activated charcoal and an anion exchange resin. Average reduction of bilirubin is approximately 31% per treatment; this is a function of initial concentration, length of perfusion, plasma filtration rate, and amount of sorbent materials used. Comparable reductions can be seen for other plasma solutes that have specificity for the resins. Although these reductions are adequate, the solute reduction capabilities of the system have been less than hoped for and additional modes of detoxification have been investigated.[27] A recirculating flow loop set up around the sorbent provides a higher fluid velocity, and a macromolecule filter with recirculating flow increases concentration of protein and any protein-bound substances. Both techniques result in higher sorption by the resin.

This experience indicates that membrane plasmapheresis with sorptive treatment may be used safely and effectively on a chronic basis for hepatic support. Improved methodologies for sorption and solute removal will help make this a more effective therapeutic method. Our experience at present indicates that large volume plasma exchange with appropriate substitution fluids appears to be as effective as any of the online treatment methods.

Cryofiltration

Interest has also developed in the removal of various macromolecular solutes from patients with immune-mediated diseases. Because of the complexity of many of the autoimmune diseases, the number of "pathologic" solutes that may be circulating in the blood, and the inability to remove many of these substances with specific sorbent materials, a filtration mechanism was envisioned that would remove macromolecules with molecular weights of greater than 100,000 daltons. Various membranes have been studied since 1975 in an attempt to find one with a macromolecular cutoff point that would allow albumin to return to the patient while trapping the larger molecular weight solutes. However, it is difficult to use a simple membrane filtration system effectively to separate macromolecules from albumin, because of the physiochemical properties of the macromolecules and the membrane properties.

Since cryoproteins occur in many patients with immune-mediated diseases, and various pathologic components such as immune complexes can be found in the cryoprotein, a process was devised by Malchesky and Nosé in 1980 called cryofiltration.[28] This process involves rapid cooling of the plasma in an on-line system to form cryogel, which is then filtered under cold conditions. The cryogel is retained on the filter and lower molecular weight materials are returned to the patient. This cryogel contains a number of substances including cryoproteins, if present in the patient's plasma. Cryoproteins or cryoglobulins are distinct from cryogel since they are separated from serum by refrigeration for two to five days in an off-line setting.

Use of the cryofiltration system produces a nonspecific reduction of macromolecular species including immune complexes, immunoglobulins, rheumatoid factor, fibrinogen, fibronectin, and other plasma solutes depending upon their presence and concentration in the patient's plasma.[29] This system has been used to treat several autoimmune-mediated diseases, primarily rheumatoid arthritis[30,31] (*Table 5*). The basic protocol for treating rheumatoid arthritis is 2 treatments per week for five weeks, with maintenance therapy dependent upon patient response. Other diseases such as vasculitides due to systemic lupus erythematosus or cryoglobulinemia have shown good response in both acute and chronic therapy. Hemolytic anemia, caused by cold-agglutinating antibodies or other metabolic abnormalities such as liver dysfunction, also show good removal with this system.

The total experience with cryofiltration has involved more than 60 rheumatoid arthritis patients at several centers throughout the world. In general, the response to therapy has been good, with good or excellent responses in clinical pa-

Table 5. Autoimmune diseases treated by cryofiltration at The Cleveland Clinic Foundation

	Number of patients	Total number of treatments
Rheumatoid arthritis	18	380
Systemic lupus erythematosus	3	9
Cryoglobulinemia	2	18
Cold-agglutinin hemolytic anemia	2	5

rameters noted in approximately 80% to 90% of severe active rheumatoid arthritis patients who have failed maximal trials of other anti-arthritic therapies. Reductions of immune complexes, rheumatoid factor, Westergren sedimentation rate, and other biochemical indicators of rheumatoid arthritis have accompanied clinical improvements in grip strength, walking time, articular index, and duration of morning stiffness. Overall results with cryofiltration indicate positive clinical responses in a variety of autoimmune-mediated diseases.[32]

Immunosorption

Plasma treatment by filtration is an initial step in the development of selective plasma treatment systems for immunologically mediated diseases. Sorption columns having immunologic specificity have been under development and used experimentally. Terman et al[33] developed a sorption column consisting of a DNA collodion charcoal sorbent used with plasma filtration. This system has been used in a patient with severe lupus glomerulonephritis, and produced reductions of DNA antibodies, immune complexes, and evidence of renal dysfunction.

Another sorptive system has been developed for use with bone marrow transplantation in which the donor and recipient are ABO-incompatible. Synthetic sugar chains analagous to A and B blood group trisaccharides are used to remove IgG or IgM isoagglutinins after membrane plasma separation. Significant reductions of antibody titer are obtained, preventing hemolysis when the allogeneic ABO-incompatible marrow is transfused.[34]

Preparations of the immunosorbent, protein A, derived from *Staphylococcus aureus*, have been used clinically, primarily in the treatment of cancer. These preparations make use of the affinity of protein A for the Fc portion of immunoglobulin G. Bansal et al[35] observed tumoricidal effect, using heat-killed formalin-stabilized *S. aureus* embedded in a filter. Others have used isolated protein A immobilized on collodion charcoal[36] or linked to crystalline silica.[37] Patients treated with this system have had dramatic reductions in tumor size. However, there are serious side effects apparently due to substances released from *S. aureus* columns. Further work is underway to determine mechanism of action (reduction of blocking activity, stimulation of the immune system) while reducing toxicity.

Summary

Membrane plasmapheresis is a relatively new form of apheresis therapy. The dramatic increase in plasmapheresis procedures is indicative of the growing interest in extracorporeal therapy. Membrane plasma filters will be useful in plasma exchange, and will also aid in the development of on-line plasma treatment systems because of the cell-free nature of the plasma generated by membrane separators. On-line plasma therapy, also a relatively new concept in extracorporeal therapy, promises to be a productive area for future research.

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