

Plasmapheresis therapy of immunologic disease

Report of nine cases and review of the literature

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The term plasmapheresis (removal of plasma with or without replacement with physiologic solutions) was first used in 1914 by Abel et al¹ in their paper "Plasma removal with return of corpuscles," which was an account of their attempt to develop an artificial kidney. Modern experience with plasmapheresis began in the early 1950s when the technique was used to remove abnormal plasma protein in a patient with multiple myeloma.² In the early 1960s, the procedure was successfully employed to treat the clinical manifestations of hyperviscosity in a patient with Waldenstrom's macroglobulinemia.³

In the past decade, great advances have been made in the technique of plasma exchange, and the scope of diseases treated with this method has broadened greatly. In theory, any disease in which a humoral phase is important in pathogenesis may be at least partially mitigated by removal of patients' plasma and subsequent replacement with another physiologic solution. This therapy might benefit patients with either of two types of immunologic disease: that mediated by antibody (either blocking or cytotoxic) or that mediated by circulating immune complexes (CIC) or both. We report our experience in treating nine patients with a number of different disease states, all of whom had

elevated CIC levels. Included are dynamic data concerning the effects of plasma exchange on levels of CIC.

Methods

Assays

1. CICs were determined by Clq binding as described by Zubler et al.⁴ Results are expressed in units (1 unit = amount of Clq bound by 0.1 μ g aggregated IgG). The upper limit of normal for the assay is 120 units/ml. This value is the mean Clq binding plus two standard deviations of sera from 20 normal volunteers.

2. Rheumatoid factor (RF) was determined by nephelometric assay (LAS-R, Hyland) (normal, < 10 units/ml).

3. Plasma volume was calculated by using established normal values for total blood volume (expressed in ml/kg) minus the patient's red cell volume determined by hematocrit immediately before plasmapheresis. Example:

Normal (male) total blood volume (TBV) — 66 to 100 ml/kg

Normal (female) TBV — 63 to 85 ml/kg.

For a 70-kg male with hematocrit, 40%, estimated plasma volume:

TBV (range) $\times$ weight — TBV (range) $\times$ hematocrit

(66 to 100) ml/kg $\times$ 70 kg — (66 to 100) ml/kg $\times$ 40%

(4620 to 7000) ml — (2640 to 4000) ml = 2000 to 3000 ml.

4. Clearance of CIC (actual). The clearance of CIC following the first plasmapheresis was calculated by the formula:

estimated plasma volume (ml) $\times$ (CIC concentration [preexchange] units/ml — CIC concentration [postexchange] units/ml)

5. Clearance of CIC (theoretical).

The clearance of a given substance (e.g., CIC) via plasmapheresis, when considered as a function of volume alone, would logically depend on the fraction of plasma volume removed per exchange. The fractional rate of exchange can be calculated using the following equation:

$$r = \frac{\text{volume exchange/hour}}{\text{plasma volume}} \quad \cdot (\text{equation 1})$$

If the plasma volume is considered a closed system from which a known volume of fluid is removed simultaneous with replacement by the same volume of fluid lacking immune complexes, the concentration of CIC remaining (x) after a given volume of exchange is given by the equation:

$$x = x_0 e^{-rt} \quad (\text{equation 2})$$

where x_0 is the original concentration of CIC, r is the fractional rate of exchange and t is the duration of the exchange in hours. From this expression, a family of curves can be generated predicting the effect of a given volume of plasma exchanged on the CIC level of a patient with any given plasma volume.

Procedure

All patients studied had significantly elevated CIC levels. Each plasma exchange consisted of removal of 2 L of the patient's plasma and simultaneous replacement with an equal volume of solution consisting of 50% purified protein fraction and 50% normal saline with acid citrate dextrose solution. Seven of the nine patients received three daily plasma exchanges, one received two daily exchanges, and one received one exchange (Table 1). Wherever possible, blood was obtained immediately before and after each plasma exchange

for determination of CIC and RF. Concomitant therapy and postplasmapheresis therapy are outlined in *Table 2*.

Results

1. Effect of plasmapheresis on CIC.
In the eight patients treated with two or more plasma exchanges, CIC levels fell from a mean of 970 ± 178 units/ml (SEM) to a mean level of 190 ± 44 units/ml (*Fig. 1*). Follow-up data were available for seven of these eight patients. At 16 weeks, postexchange data were available on five patients (1, 2, 5, 6, 9) (*Table 1*). Only patient 9, who was treated with cyclophosphamide, demonstrated sustained suppression of CIC. In patient 1, treated with low-dose methotrexate weekly, CIC rose from the normal range to 50% of the pretreatment CIC level at 16 weeks. At 12 weeks,

patient 3, treated with postexchange intravenous methylprednisolone (IVMP) and then low-dose prednisone had relapsed to pretreatment CIC levels. At 2 weeks postexchange, patient 4, the only patient undergoing one plasmapheresis, and patient 7, treated with only conventional high-dose prednisone and plasmapheresis, had experienced a prompt rebound of CIC levels.

2. Clearance rates of CIC. To compare the theoretical rate of clearance of CIC based solely upon the fraction of plasma removed versus the actual amount of CIC cleared, it was necessary to generate a family of curves representing percent CIC remaining for a given volume of plasma exchange utilizing equation 2 in the methods section. Since the volume of plasma exchange was constant in each patient, and since individual plasma volume could be estimated

Table 1. Effects of plasmapheresis on CIC levels

Patient	Age, sex	Diagnosis	Ex-change	Dynamics of CIC and RF with plasmapheresis, units/ml						Postplasmapheresis CIC and RF, units/ml		
				I		II		III		2 wk	4 wk	16 wk
				Pre	Post	Pre	Post	Pre	Post			
1	64, F	RA	CIC	801	452	288	110	164	111	110	111	400
			RF	153	126	128	111	111	98	...	...	...
2	62, F	RA	CIC	218	166	168	108	105	104	...	...	165
			RF	107	61	67	27	67	24	...	104	...
3	60, F	RV	CIC	844	206	527	110	179	105	155	155	...
			RF	317	291	259	138	216	135	...	...	...
4	62, F	RV	CIC	7922	2023	...	...	...	...	5812	...	...
			RF	...	...	...	...	...	...	...	...	...
5	33, F	RV	CIC	1090	308	423	122	...	...	...	...	1082
			RF	...	...	...	...	...	...	...	...	...
6	54, M	RA with Felty's syndrome	CIC	1228	651	656	384	...	459	...	...	1042
			RF	196	...	...	144	...	129	...	...	...
7	61, M	Necrotizing vasculitis	CIC	1007	672	...	581	...	250	700	...	...
			RF	...	...	...	...	...	...	...	...	...
8	71, F	Necrotizing vasculitis	CIC	1989	1261	1236	756	1071	278	...	...	...
			RF	194	172	198	139	154	92	...	...	...
9	29, F	SLE	CIC	739	120	...	105	...	99	105	104	...
			RF	...	...	...	...	...	...	...	...	...

RA = rheumatoid arthritis, RV = rheumatoid vasculitis, SLE = systemic lupus erythematosus.

Table 2. Clinical results

Patient	Concomitant therapy	Methylprednisolone, 1 g	Postexchange therapy	Clinical outcome
1	Prednisone, 7.5 mg/day Hydroxychloroquine	x1	Prednisone, 7.5 mg/day Methotrexate, 7.5 mg/wk	Sustained remission from RA despite partial serologic relapse
2	Prednisone, 15 mg/day Aspirin	x3	D-penicillamine	Temporary improvement following treatment, but clinical and serologic relapse by 3 weeks and no response to penicillamine by 8 weeks
3	Prednisone, 80 mg/day	x1	Prednisone, 40 mg/day	Immediate improvement in central nervous system (CNS) symptomatology, improvement in peripheral vasculitis and secondary ischemia and sustained remission in RA at 12 weeks
4	Prednisone, 20 mg/day	...	Prednisone, 20 mg/day	Transient increase in white blood cell count (WBC), which subsequently fell with rebound of CIC levels. Progressive healing of leg ulcers
5	Prednisone, 15 mg/day Hydroxychloroquine	...	Prednisone, 15 mg/day	Slow healing of ulcers despite prompt serologic relapse
6	Prednisone, 15 mg/day Aspirin	...	Prednisone, 15 mg/day	No consistent effect on WBC count, RA in remission before therapy
7	Prednisone, 80 mg/day	...	Prednisone, 80 mg/day	Patient was already on hemodialysis and mechanical ventilator when plasmapheresis was instituted and despite prompt serologic improvement, no change was noted; patient died 10 days later
8	...	...	Prednisone, 20 mg/day	No immediate improvement in long-standing neurologic symptoms; patient lost to follow-up
9	Prednisone, 80 mg/day Cytosan, 150 mg/day	...	Prednisone, 60 mg/day Cytosan, 150 mg/day	Dramatic and sustained improvement in lupus CNS symptomatology and sustained remission of all serologic abnormalities (CIC levels, complement levels, anti-DNA antibody levels)

based upon known weight, hematocrit, and established normograms for blood volume (see methods, 3), one can construct a graph representing percent CIC remaining for a 2-L plasma exchange versus any given plasma volume (*Fig. 2*). The calculated (actual) clearances based upon the mean of the upper and lower limit of estimated plasma volume are the points represented on the graph.

Clinical findings

Diagnoses of the nine patients treated are given in *Table 1*. Of these nine, six experienced some degree of clinical improvement following plasma exchange. A summary of the clinical outcome is given in *Table 2*. Since all patients received corticosteroids in at least small doses and several patients received cy-

toxic drugs, it is difficult to separate the beneficial effects of plasmapheresis and other treatments in this small and nonrandomized study.

Case reports

Case 1. A 36-year-old white woman with a 5-year history of active (anatomic Stage III, functional Class III) seropositive rheumatoid arthritis (RA) had failed to respond to several treatment programs, including gold and penicillamine. Four months prior to admission she had responded dramatically to a 1-g bolus of IVMP; however, the effect was temporary, lasting only 3 weeks after treatment. The duration of her morning stiffness was then more than 2 hours, and

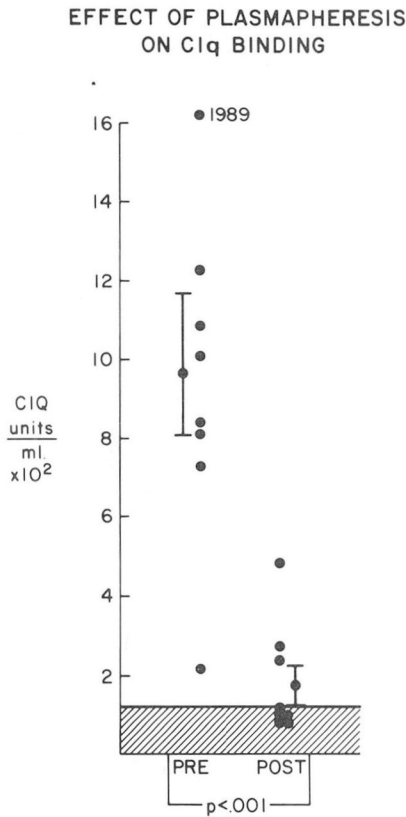


Fig. 1. CIC levels immediately before and after two or more plasma exchanges.

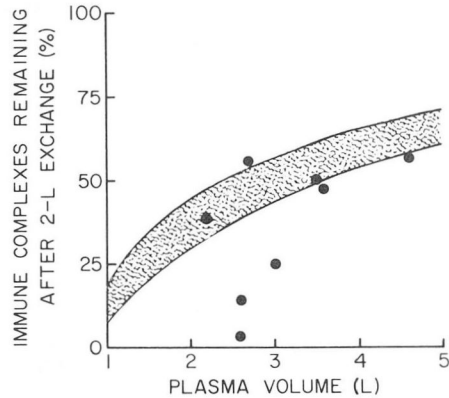


Fig. 2. Shaded area represents the predicted clearance of CIC after a 2-L exchange for a patient with known plasma volume. Black dots represent actual clearances for eight patients after the first plasma exchange.

on physical examination she had acute synovitis of several joints. Treatment began with three 2-L plasma exchanges followed by 1 g of IVMP. The day after receiving a steroid bolus she noticed a virtual absence of morning stiffness and her joints were much less painful. Methotrexate, 7.5 mg weekly, was started and she was discharged. Four weeks later she was still in both serologic and clinical remission, but after 8 weeks, her CIC level began to rise. The arthritis is still in remission at 16 weeks.

Comment. This patient's RA responded dramatically to therapy. The combination of IVMP and a low dose of methotrexate has seemingly helped to maintain the clinical remission and to delay the rapid rebound of CIC to pretreatment levels.

Case 2. A 62-year-old white woman had a 2-year history of progressive seropositive RA (anatomic Stage III, functional Class III). At the time of examination she had synovitis of most peripheral joints and 4 to 5 hours of morning stiffness. The only medications were small doses of aspirin and frequent injections of corticosteroid, which no longer provided relief. Because of her disability and the acute nature of the disease, she was hospitalized for plasmapheresis and IVMP. Following therapy, prompt serologic and clinical improvement occurred. Treat-

ment was begun with D-penicillamine. The symptoms recurred one week following therapy and by 6 weeks she had a total relapse.

Comment. This patient with severe RA had the lowest levels of CIC in the pretreatment period. After a brief period of improvement, the disease was essentially unchanged from the pretreatment period.

Case 3. A 60-year-old white woman was transferred to the Cleveland Clinic because of gangrenous changes of the right foot. She had a 20-year history of seropositive deforming RA (anatomic Stage III, functional Class II) for which she was taking only aspirin. For several weeks before admission she had noted discoloration of the toes and pain in the right foot. On physical examination she had the stigmata of chronic destructive RA. Her right foot was cool with blistering and darkish discoloration of the skin from the midfoot distally (*Fig. 3*). Pulses were absent in the right foot but Doppler pressures were normal to the ankle.

Laboratory data included an extraordinarily high RF of 837 units/ml (normal, < 10 units/ml), elevated CIC (*Table 1*), positive antinuclear factor (ANF) (1:320), erythrocyte sedimentation rate (Westergren) 110 mm/hr, normal serum viscosity, strongly positive cryoglobulins, and normal serum complement (total hemolytic complement).

During the first 48 hours, this patient became acutely psychotic. There were no focal neurologic symptoms. In light of the strongly positive laboratory profile, and the clinical signs and symptoms, the diagnosis of RA was made. A regimen of prednisone, 80 mg per day, was begun, and a series of three plasmaphereses were performed. After the first plasma exchange, there was dramatic improvement in her mental status. Unfortunately, irreversible tissue necrosis of the forefoot was present before plasmapheresis; however, no progression of the necrotic process occurred. After a stabilization period, a transmetatarsal amputation was successful. During the following 3 weeks, the arthritis was clinically inactive and rehabilitation was successful.

Comment. This patient had large vessel vasculitis of the lower extremity and a psychosis



Fig. 3. Foot immediately before plasmapheresis (patient 3).

that was possibly secondary to the arteritis. The central nervous system symptoms, which were new, promptly regressed with therapy. Unfortunately, irreversible necrosis was present and a transmetatarsal amputation was performed. The rapid clearing of CIC is shown in *Figure 4*.

Case 4. A 54-year-old white woman had a long history of seropositive RA. During the 6-month period before admission, progressive vasculitic ulcerations of the lower extremities had developed. She was treated with aggressive topical therapy followed by high-dose prednisone therapy (60 mg/day) without success. The physical examination showed multiple long-standing joint deformities and, in addition, there were four ulcerated lesions on the legs that were necrotic with purulent drainage. Laboratory evaluation revealed a white blood cell count (WBC) of 2400/mm³ and markedly elevated RF and CIC (*Table 1*). Splenomegaly was evident on liver-spleen scan. Because of failure to respond to conventional therapy and in light of the markedly elevated CIC, plasmapher-

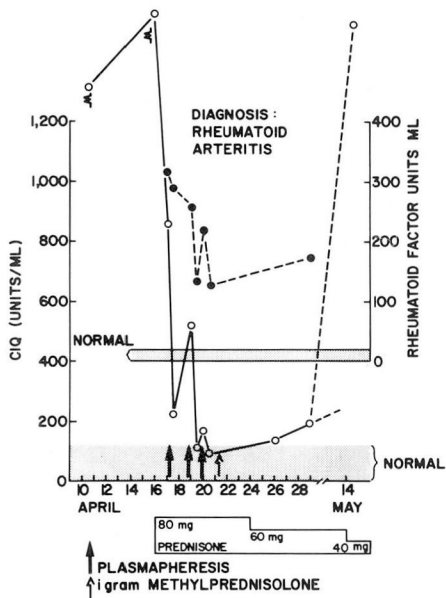


Fig. 4. Effect of therapy on CIC and RF (patient 3).

esis was initiated. A transient rise in the WBC was noted while CIC levels were falling, and a subsequent fall in the WBC count was noted with rebound of CIC to pretreatment levels (Fig. 5). The ulcerated lesions healed over the next several months.

Comment. This patient's peripheral ulcers showed progressive healing following plasma exchange; exacerbations of these lesions required two more exchanges, after which improvement was noted and healing was complete.

Case 5. A 33-year-old white woman with seropositive RA and features of progressive systemic sclerosis had a history of recurrent painful vasculitic ulcers of the anterior aspects of the lower legs. These ulcers failed to heal despite aggressive local therapy. In March 1978, she was admitted for more intensive topical ulcer therapy. After one month of bed rest and topical therapy the lesions were unchanged and increasingly higher doses of narcotics were required for relief of pain. Because of high CIC levels, low complement levels, and failure to respond to conventional therapy, two 2-L plasma exchanges were done. Within 10 days

of plasmapheresis treatment, granulation tissue began to appear in the ulcer sites and slow, progressive healing was observed during the next several months despite prompt serologic relapse (Table 1).

Comment. It is difficult to assess the efficacy of plasmapheresis in this patient since the clinical course extended over many months. Chronologically, the period of plasmapheresis appeared to be a turning point in her condition. The brief period of serologic improvement may have reflected a suppression of the immune response, allowing the conventional local therapies, which had failed to work in the past.

Case 6. A 54-year-old white man had a 7-year history of seropositive RA. The arthritis was in remission. He had no morning stiffness or painful joints. In March 1977, Felty's syndrome was diagnosed. The WBC count was $2500/\text{mm}^3$; however, there was no sign of infection. In January 1978, he had a respiratory infection with a temperature of 102 F; he was treated with penicillin and recovered uneventfully. In October 1978, his WBC count was $1650/\text{mm}^3$ with 27% polymorphonuclear leukocytes. Splenomegaly was noted for the first time. The RA was still quiescent and he had no history of leg ulcer-

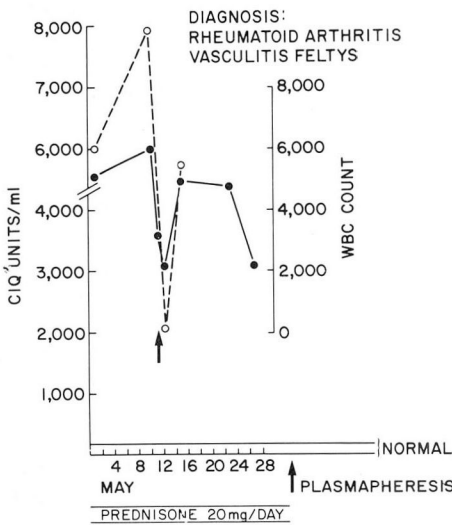


Fig. 5. Effect of therapy on CIC and WBC (patient 4).

ations. He was admitted to the hospital in November 1978 and underwent three 2-L plasma exchanges. Although the CIC levels fell promptly, there was no consistent change in the WBC count. In light of the paucity of symptoms associated with the lowered WBC count, observation rather than further treatment was planned.

He remains asymptomatic although the CIC has rebounded to pretreatment levels.

Comment. Plasmapheresis had no effect on the WBC count in this patient with Felty's syndrome. This is in distinction to patient 4, whose leukopenia improved transiently with plasma exchange therapy.

Case 7. A 61-year-old white man was admitted for evaluation of advancing renal failure. He had been well until approximately 4 weeks before admission when he began to experience flu-like symptoms with a nonproductive cough. Physical examination on admission revealed that he was mildly short of breath but not in acute distress. Aside from bilateral, coarse inspiratory rales, the examination was unremarkable. A chest roentgenogram revealed five-lobe interstitial-alveolar infiltrates. On the 12th hospital day, he was transferred to the medical intensive care unit because of increasing respiratory difficulty. Serum creatinine level had risen from 3.5 mg/dl on admission to 6.1 mg/dl. During the next several days, mechanical ventilation was required and hemodialysis was begun. An open lung biopsy revealed an acute pneumonia superimposed upon chronic interstitial pneumonitis. All cultures for bacteria, fungi, and opportunistic organisms were negative. On the basis of markedly elevated CIC levels and severely depressed serum complement (total hemolytic complement, 44 units/ml; normal, 70 to 190 units/ml), a regimen of high-dose prednisone, 80 mg daily, and a course of plasmapheresis were begun. Reduction of CIC levels and normalization of serum complement were observed during therapy. However, no change was noted in his progressively downhill course. Prompt rebounding of the CIC levels was observed after plasmapheresis (*Fig. 6*). He died 10 days later.

Comment. Autopsy revealed a healing widespread arteritis. Plasmapheresis had no effect on the clinical course of this patient, but both respiratory and renal failure were well established before treatment. Our experience and that of others suggest the need for early institution of therapy in immunologically mediated renal disease.

Case 8. A 71-year-old white woman was admitted to the hospital for treatment of immune complex-mediated vasculitis. The principal manifestation of disease was mononeuritis multiplex with glove and stocking paresthesias and a right-sided carpal tunnel syndrome. Neurologic symptoms had progressed during the preceding 8 months. She had lost considerable weight. On physical examination, she was cachectic with severe atrophy of the right thenar eminences. Sensory examination revealed decreased pin, temperature, and vibratory sensation in the lower extremities. She was treated with three 2-L plasma exchanges followed by IVMP. Prompt serologic improvement was noted; however, there was no change in her neurologic symptoms. She was discharged from the hospital with a return appointment in 2 weeks but has since been lost to follow-up.

Comment. This patient had no clinical improvement in the immediate post-therapy period; however, it is possible that the neurologic damage was irreversible. Alternatively, since she has been lost to follow-up, delayed improvement would not have been detected.

Case 9. A 29-year-old white woman was referred for evaluation of systemic lupus erythematosus (SLE). In the past year she had experienced constant migratory arthralgias and recently began to experience photosensitivity and Raynaud's phenomenon. She described a recent episode of pleurisy. She had taken no medication.

Physical examination revealed some patchy alopecia and a faint erythematous rash over the malar area. The remainder of the examination was unremarkable. Laboratory tests revealed a hemoglobin of 11.4 g/dl; WBC, 9300/mm³; ANF, 1:320; DNA binding, 50%; Clq binding capacity, 315 units (normal < 120 units); total hemolytic

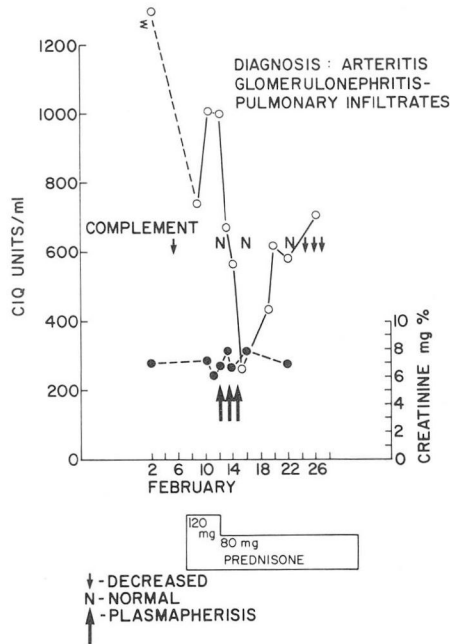


Fig. 6. Effect of therapy on CIC, creatinine and complement (patient 7).

complement (CH_{50}), 45 units (normal 70 to 180 units); and negative rheumatoid factor. Urinalysis showed 3 to 5 red blood cells per high power field, creatinine level was normal, and the 24-hour urine protein was 250 mg; no casts were seen.

One month later she came to the emergency room complaining of scintillating scotoma followed by loss of vision in the right eye that morning, all of which lasted 20 minutes. Later that day, she experienced the same phenomenon, came again to the emergency room, and was admitted to the hospital. Physical examination was unremarkable except for some blurring of the right optic disc. The neurological consultant believed that the attacks were consistent with either migraine or lupus cerebritis. Computed tomography (CT) of the head and lumbar puncture were performed and were unremarkable. A regimen of 40 mg of prednisone per day was begun. The patient's neurologic status remained unchanged, but she felt extremely weak until the fifth hospital day when she awoke feeling nauseated

and experienced diplopia, which was worse on left gaze. Cyclophosphamide (Cytosan), 150 mg daily, was started and the prednisone was increased to 80 mg daily. Two-liter plasma exchanges were performed daily for 3 consecutive days. During this period minor symptoms, i.e., weakness, and dull headache continued, but beginning 2 days after plasmapheresis and until discharge on the 20th hospital day, improvement continued and she felt stronger and free of neurologic symptoms.

She has been seen twice in the outpatient department and has remained in complete serologic and clinical remission on a regimen of prednisone, 60 mg/day, and azathioprine, 150 mg daily.

Comment. The clearing of neurologic symptoms and the prompt correction of serologic abnormalities soon after plasma exchange (Fig. 7) suggest that plasmapheresis was beneficial for this patient. Clinical and serologic remission has been maintained for 4 months following therapy with a combination of corticosteroid and cytotoxic drug (azathioprine).

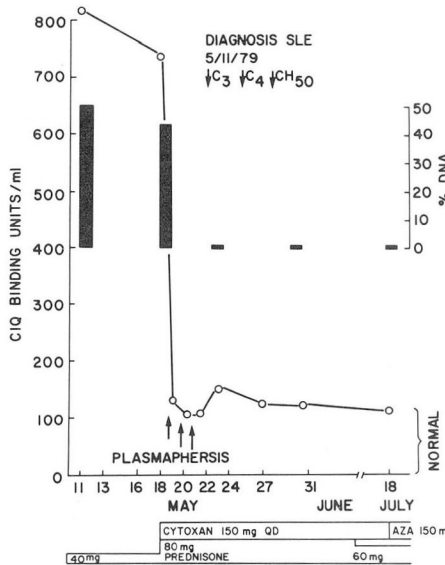


Fig. 7. Effect of therapy on CIC and anti-DNA antibody (patient 9).

Discussion

We have treated nine patients with diseases associated with CIC with plasmapheresis. Clinical improvement was observed in six of the nine. These preliminary data must be interpreted with caution because there was no control group and, in addition, each patient was also treated with some form of additional immunotherapy. Even with these reservations, it can be argued from these data that plasmapheresis contributed to the clinical improvement. First, the majority of patients treated had difficult therapeutic problems; treatment with conventional therapy had failed, and symptomatic improvement was observed only after plasmapheresis was added to the therapeutic regimen. Second, the improvement in clinical parameters followed the clearing of immune complexes, which presumably can be attributed to the effects of plasmapheresis. Furthermore, in selected cases failure to respond to plasma exchange may be explained on an individual basis. For example, patient 7 had well-established renal failure before plasmapheresis was instituted. Since that time, in a similar report, Lockwood et al⁵ have shown that prompt initiation of plasmapheresis is necessary if improvement of immunologically mediated renal disease is to be expected. Alternatively, it may be argued that although immune complexes are present in all patients, they may not be of primary pathogenic importance.

It is difficult to interpret with confidence the clinical effects of plasmapheresis in our study group, but the ability of plasma exchange to lower CIC levels was dramatic. Those patients receiving two or more exchanges had prompt lowering of CIC levels from a mean of 970 units/ml to a level of 190 units/ml (*Table 1*).

In five of these eight patients, CIC levels became normal (<140 units/ml) following plasma exchange alone, and in the remaining three patients (patients 6 through 8), CIC levels were reduced but not to normal levels. It is interesting that the three patients in whom the CIC levels did not become normal were the same three who experienced the least clinical improvement from the treatment regimen. Factors that might contribute to the failure of plasmapheresis to normalize CIC levels in these patients include rapid resynthesis of CIC or decreased endogenous clearance mechanisms, i.e., reticuloendothelial blockade or both. With regard to the dynamic effect of plasma exchange upon ongoing immune complex disease, the results of our study are in accord with the experimental work of others in that plasma exchange alone is ineffective and is routinely followed by a rebound of CIC.^{6,7} This effect was not blocked by steroids as can be seen graphically in *Figure 6*. In those patients followed up 16 weeks, only patient 9, who was treated with full-dose cytotoxic therapy, sustained normalization of CIC levels. IVMP, low-dose methotrexate, and conventional doses of oral corticosteroids had a delaying effect, at best, in affecting the rebound of CIC levels.

We attempted to compare the actual clearance rate of CIC with a calculated value based upon equation 2.

To apply these results to clinical practice, certain conditions must be met; these constitute the assumptions implicit in the use of this calculation.

1. Synthesis and endogenous clearance of CIC must be slow compared to the rate of exchange.
2. Exchange between intravascular and extravascular immune complex pools must be slow compared to the rate of plasma exchange.

3. Concentration of the CIC must not affect their physical properties in such a way that the efficiency of their detection might be reduced.
4. There must be instantaneous mixing of the replacement fluid throughout the intravascular pool.
5. Plasma volume must be accurately determined.

It is clear that not all of these assumptions may be valid; moreover, assumptions that may be valid in one clinical setting, e.g., low rate of endogenous complex formation and clearance, may be invalid in another. Even with these reservations, *Figure 2* shows that with the exception of patient 2, the clearance rates of the remaining patients equaled or exceeded the predicted rates in every case. Several explanations of this phenomenon are possible. First, the dilutional effect of the replacement fluid (immunoglobulin-free, complement-free plasma protein fraction) may alter the physical properties of the remaining CIC, reducing the efficiency of their detection. This explanation is probable in at least some instances since we have found that when diluted, CIC from different patients will react with different Clq binding than would be predicted from undiluted sera (unpublished data). This phenomenon is independent from protein concentration and is being investigated in our laboratory. A second explanation is that plasmapheresis enhances endogenous clearance mechanisms possibly by "unblocking" the reticuloendothelial system. Results of recent studies have indicated that such a "block" exists in several immune complex disease states;⁸ Lockwood et al⁹ have demonstrated that plasmapheresis can potentially unblock this system.

Review of literature

Technique. The proliferation of stud-

ies utilizing plasmapheresis can be attributed in large part to the advances in technique during the past decade. In early experience, plasma exchange was performed manually by withdrawing a unit of blood, separating the cells from plasma by centrifugation, and returning the red blood cells to the donor. Since the late 1960s, plasma exchange has been more commonly performed by one of an increasing number of models of cell separators.^{10, 11} These machines can now separate plasma, red cells, white cells, and platelets in large volumes. The technique is rapid, replaces up to 4 L of plasma in a 2-hour period and causes little discomfort or risk to the patient who requires only percutaneous venous cannulation. At these high rates of exchange, it is necessary to replace the patient's plasma with an isoosmotic solution such as fresh frozen plasma, purified protein fraction or albumin to avoid a hyposmotic state with subsequent edema formation.¹² The procedure can be performed with few short- or long-term adverse effects. Prolonged (one year or more) intensive plasmapheresis of normal volunteers had no detectable effect on delayed hypersensitivity as assayed by lymphocyte count, skin testing, and mitogen stimulation, but did significantly reduce the serum concentration of immunoglobulin, C3, and albumin.¹³

Rationale. The procedure of removing a patient's plasma and replacing it with another physiologic solution could be potentially beneficial in any condition in which a humoral phase would be important in pathogenesis. In theory, two broad categories of immunologic injury would be most responsive to such therapy: those that mediated by antibody or those that mediated by CIC.

Disease states mediated by circulating antibody may be subclassified into two

categories: cytotoxic and blocking. Cytotoxic antibodies generally involve the combination of IgG or IgM antibody with an antigenic determinant on a cell membrane or other surface. These antibodies frequently fix complement leading to cell lysis or immunologic damage of the target surface in the case of a noncellular antigen, i.e., glomerular basement membrane (GBM). Examples of this type of reaction are listed in *Table 3*. Blocking antibody is a second type of antibody-mediated process. In general these antibodies do not fix complement and do not lead to immunologic damage of their targets, but rather lead to an alteration in their function. Either suppression or stimulation can be observed, depending on the conditions. An example of stimulation resulting from antibody is Graves' disease²² in which immunoglobulins capable of displacing thyrotropin have been identified. Diseases in which antibody brings about inhibition of biologic function include insulin-resistant diabetes with anti-insulin receptor immunoglobulins²³ and myasthenia gravis with antiacetylcholine receptor antibody.²⁴ Other examples of this type of reaction are listed in *Table 3*.

A detailed discussion of immune complex disease is beyond the scope of this paper, but it has been the subject of several recent reviews.²⁶⁻²⁸ With regard to the therapeutic potential of plasma exchange in disease mediated by CIC, several points deserve consideration. The mere presence of CIC in the circulation does not necessarily bring about immunologically mediated disease. A complex interaction of many factors must exist before immunologic damage is observed. These factors include the ratio of antibody to antigen, ability of the CIC to fix complement, presence of

Table 3. Conditions characterized by circulating antibody

Cytotoxic antibody
Immune hemolytic anemia ¹⁴
Immune thrombocytopenia ¹⁵
Immune neutropenia, Felty's ^{16, 17}
Immune lymphopenia ^{18, 19}
Anti-GBM disease ^{20, 21}
Blocking antibody
Graves' disease ²²
Insulin resistant diabetes ²³
Myasthenia gravis ²⁴
Malignancy with "blocking factors" ²⁵

vasoactive amines to enhance vascular permeability, and localization of CIC to the target organ. Aside from the above factors that primarily affect the deposition of CIC, other factors important in CIC formation and elimination, such as the nature and timing of the antigenic exposure and the integrity of the reticuloendothelial system, are critical in determining the extent of the resultant immunologic disease. The mere elimination of a given quantity of CIC is no assurance that clinical benefit will result. Furthermore, plasmapheresis could theoretically have deleterious effects on immune complex-mediated disease by such mechanisms as adversely altering the ratio of antibody to antigen or by causing release of vasoactive amines by a similar mechanism as has been demonstrated during hemodialysis.²⁹

Plasma exchange is not in itself helpful in most immunologic disease states for which it has been employed, as demonstrated by experiments in both animals and man. Bystryn et al⁶ showed that removal of specific antibody by plasma exchange invariably resulted in a rapid rebound of antibody to levels above those in the pretreatment period. In further experiments, it was demonstrated that this rebound could be

blocked by the administration of cyclophosphamide.³⁰ When humans undergo plasmapheresis without concomitant immunosuppression, a similar rebound in antibody levels has been described. Examples of this phenomenon include insulin-resistant diabetes³¹ with anti-insulin receptor antibodies and severe Rh disease in women.³² Plasmapheresis combined with adjuvant corticosteroid and cytotoxic therapy have been successful in suppressing levels of anti-GBM antibodies in patients with Goodpasture's syndrome. Furthermore, rebound of antibody to pretreatment levels was observed in one patient when cytotoxic therapy was discontinued.³³ In certain situations, plasma exchange alone may be sufficient to eliminate an unwanted antibody. Branda et al⁷ have demonstrated in immunized dogs that plasmapheresis may permanently suppress antibody produced by a secondary but not a primary immunization. Accordingly, they recommended that plasmapheresis alone be considered only for patients in whom multiple intermittent stimulations leading to unwanted antibody are suspected. This concept would theoretically apply to any condition in which pathogenic antibody is stimulated in a secondary fashion, i.e., hemophilia with anti-Factor VIII antibodies. However, adjunctive corticosteroid or cytotoxic therapy or both have traditionally been employed to control such an immunologic response.^{34, 35}

Plasmapheresis has also been applied in disease states characterized by CIC and hypocomplementemia. Several interesting questions regarding the kinetics of immune complex formation and removal have been raised. Jones et al³⁶ in treating patients with acute SLE postulated that plasma exchange, in addition to removing immune complexes on

a purely volume basis, somehow enhanced endogenous reticuloendothelial function, attempting to explain a disproportionate fall in serum anticomplementary activity, which was observed in several patients. Recently, in a detailed study of splenic function in patients with various conditions characterized by CIC, Lockwood et al^{5, 9} demonstrated impaired reticuloendothelial function that was "unblocked" by plasma exchange. This is in agreement with our data that actual clearance rates equaled or exceeded predicted rates in all but one patient. Additional explanations of the potential benefit of plasmapheresis in immune complex-mediated disease include depletion of mediators, such as complement and coagulation factors brought about by the substitution of purified protein fraction (PPF) (immunoglobulin-free, complement-free) for plasma.

Treatment

Plasmapheresis in antibody-mediated disease

Myasthenia gravis. Strong evidence exists of pathogenic antibody activity in this condition. Antiacetylcholine receptor antibodies have been identified in 87% of patients with myasthenia gravis, but not in patients with other neurologic or autoimmune diseases.²⁴ This antibody crosses the placenta and is believed responsible for the appearance of transient neonatal myasthenia gravis. Furthermore, a disease similar to myasthenia can be produced in animals by immunization with acetylcholine receptor.³⁷

Traditionally, patients who fail to respond to medications that directly facilitate neuromuscular transmission have

been treated by some form of immunologic intervention such as steroid, cytotoxic drugs, or thymectomy. Plasmapheresis has been reported to be successful in the treatment of myasthenia gravis.^{38, 39} Studies by Dau et al⁴⁰ have shown the increased strength of patients treated with plasma exchange to be concurrent with falling titers of acetylcholine receptor antibody; moreover, clinical relapses were associated with a rebound in titer.

Antiglomerular basement membrane disease. Goodpasture's syndrome is a combination of glomerulonephritis and pulmonary hemorrhage, which is believed to be mediated by antibody directed against glomerular and alveolar basement membranes. The natural course is characterized by progressive deterioration culminating in death from intractable pulmonary hemorrhage or renal failure.⁴¹ Treatment with steroids or immunosuppressive drugs or both has met with varying success. Nephrectomy has been considered to be of benefit in some patients with life-threatening pulmonary hemorrhage;⁴² however, the results have not been consistent.²¹

In 1976, Lockwood et al³³ described seven patients with anti-GBM-induced Goodpasture's syndrome, treated with plasmapheresis and immunosuppressive therapy. Since then, additional reports of such therapy have appeared.⁴³⁻⁴⁹ Recent review of the literature concluded that plasmapheresis and immunosuppressive therapy may reverse the renal lesion in some patients with Goodpasture's syndrome.⁴⁹ In the 24 cases of anti-GBM disease reported by Lockwood et al,⁵ they emphasized the need for early institution of therapy.

Rh disease. Plasmapheresis via the cell separator combined with intrauterine transfusion has been claimed by sev-

eral workers to improve fetal survival in women immunized by the Rh isoantigen.^{12, 29, 50, 51} Treatment must be started early and frequent large volume exchanges appear necessary.

Hematologic disease. A wide variety of hematologic conditions mediated by pathologic antibodies have been treated by plasma exchange. Anti-factor VIII antibodies develop in about 10% of classic hemophiliac antibodies; this presents a major problem in management of these patients. Plasma exchange with or without immunosuppressive therapy has successfully extended the half-life of subsequently administered factor VIII.^{32, 34, 52}

Posttransfusion purpura is a rare but serious condition that develops in persons who lack the PIA1 platelet antigen, or who have become immunized to it through pregnancy or blood transfusion. When these patients have received transfusions, profound thrombocytopenia develops in approximately one week, occasionally associated with life-threatening hemorrhage. Plasma exchange has been reported to be successful in the management of this condition.⁵³

Idiopathic thrombocytopenic purpura is mediated by a plasma antiplatelet factor widely believed to be an antibody.¹⁵ Corticosteroids and immunosuppressive drugs control the disorder in the majority of patients albeit after days or weeks. Plasmapheresis has been used successfully in several patients for whom conventional therapy was not satisfactory, either because of life-threatening hemorrhage or when such therapy was considered ineffective or dangerous.^{51, 52, 54}

Branda⁵⁵ has also reported plasma exchange to be effective in the treatment of hemolytic anemia mediated by anti-

e antibody. Finally, Tursz et al⁵⁶ have reported removal of anti-B-cell antibodies by plasmapheresis in a patient with hypogammaglobulinemia who had a subsequent rise in B-cell numbers; the effect was only transient.

Endocrine disorders. Muggeo et al³¹ have recently reported the success of plasmapheresis in treating an insulin-resistant diabetic who had autoantibodies directed against the insulin receptor. In a highly provocative recent report, Dandona et al⁵⁷ have treated a patient with Graves' disease who had acute progressive exophthalmos and pretibial myxedema. Clinical improvement was noted after plasma exchange treatment and was thought to coincide with decreasing IgG and specific thyroid-stimulating immunoglobulin levels. The results suggested that plasmapheresis may be useful in treating such conditions.

Skin conditions. Plasmapheresis as yet has had limited use in few skin conditions.^{58, 59} The serum of patients with pemphigus contains an antibody directed against an antigen in the epidermal intercellular space. At present, the use of plasma exchange in this condition remains controversial.

Immune complex-mediated disease

Systemic lupus erythematosus. SLE is one of the prototypes of immune complex-mediated disease. Many of its clinical manifestations, especially renal involvement, appear to be directly related to immune complex-mediated injury.⁶⁰⁻⁶² Accordingly, on theoretical grounds, active SLE should potentially benefit from removal of immune complexes via plasma exchange.

Jones et al,^{63, 64} in a preliminary report and recently in a series of 14 patients, have presented evidence that

plasmapheresis is beneficial in the treatment of certain patients with SLE. Of their group of 14 patients, eight had evidence of either clinical improvement or clinical and serologic improvement at the time of plasmapheresis. Three patients showed no improvement and the conditions of three patients were considered unevaluable. Three patients with high levels of CIC preplasmapheresis had sudden falls in CIC levels greater than could be accounted for on the basis of amount removed. Jones et al explained this observation on the basis of unblocking of the reticuloendothelial system, thus enhancing endogenous clearance. Our one patient with SLE also had a sudden fall in CIC, in excess of that calculated on the basis of amount removed. Clinically, our one patient who was extremely active serologically (i.e., CIC ten times normal, depressed hemolytic complement and DNA binding of 50%) had total clearing of central nervous system symptoms within 5 days of treatment. Several other reports have also suggested plasma exchange may be beneficial in treatment of this disorder.^{36, 65}

Vasculitis. Necrotizing arteritis is a final pathologic expression for a wide variety of pathogenic mechanisms. In recent years, many disease states believed to be of widely differing etiologies have been thought to induce injury through an immune complex process. Some of the more clearly defined disease states in which immune complex-mediated vasculitis plays a role include Hb_sAg positive arteritis, hypersensitivity vasculitis, vasculitis associated with endocarditis, essential mixed cryoglobulinemia, vasculitis associated with some malignancies, rheumatoid vasculitis, and serum sickness. Immune complexes have also been identified in some

cases of Wegener's granulomatosis; however, their role in pathogenesis is not clear at this time.⁶⁶

When vasculitis is not secondary to a treatable cause such as endocarditis, current conventional therapy has centered about the use of steroids and cytotoxic drugs and has met with varying degrees of success.^{67, 68} Therefore, when the success of plasmapheresis is examined in combination with these modalities, it is difficult to evaluate the results without the benefit of any prospective randomly controlled trials. Lockwood et al⁹ have treated a large series of patients with nephritis secondary to polyarteritis and Wegener's granulomatosis with a combination of plasmapheresis and immunosuppressive therapy and demonstrated considerable improvement in the majority of patients as shown by fall in serum creatinine levels and disappearance of CIC. Goldman et al⁶⁹ have recently reported the successful use of limited plasmapheresis in three of four patients with rheumatoid vasculitis. Two of their successfully treated patients received full-dose cytotoxic drugs in addition to plasma exchange. The other two including the therapeutic failure received D-penicillamine. In the present study three patients with rheumatoid vasculitis and two patients with necrotizing arteritis were treated. The results were interpreted as possibly effective in the two RA patients with leg ulcerations and probably effective in the RA patient with ischemic gangrene of the forefoot. In patient 7 with necrotizing arteritis, plasmapheresis had no effect on established pulmonary renal insufficiency; furthermore, this patient had the dramatic rebound of CIC levels (days) apparently unaffected by prednisone, 80 mg/day. Plasmapheresis has also been helpful in treating the im-

mune complex, mediated complications of subacute bacterial endocarditis⁷⁰ and cryoglobulinemia.⁷¹

Rheumatoid arthritis. RA is a systemic disease in which immune complexes have long been thought responsible for many of the articular and non-articular manifestations. Recently, Wallace et al.⁷² have treated 12 patients with either plasmapheresis or lymphopheresis or both. Ten of 12 patients had remission periods averaging 4 months. Clinical remissions appeared to be sustained even when serologic parameters such as immunoglobulins, sedimentation rate, and CIC had returned to prepheresis levels. In the present study only two patients were treated for severe refractory RA. Both patients received different postexchange treatment regimens. One patient treated with methotrexate has remained in remission more than 4 months; the patient treated with penicillamine relapsed in 2 weeks. Although additional studies are in progress, the present experience is too limited to draw any conclusions.

Disease state of presumed immunologic origin

Thrombotic thrombocytopenic purpura (TTP). Bukowski et al^{73, 74} and later others⁷⁵⁻⁷⁷ have reported success in the treatment of TTP by plasmapheresis using fresh frozen plasma as a substitute. Although immune complex formation has been postulated as an etiologic mechanism, none has been identified for this disorder.

Raynaud's disease. The pathogenesis of Raynaud's disease is not well defined, but the frequent association of the phenomenon with a wide variety of connective tissue disorders makes the proposition of an immunologic etiology tempt-

ing. Talpos et al⁷⁸ have reported treating five patients with severe Raynaud's disease who were refractory to other therapy with plasmapheresis and claimed striking improvement in both clinical parameters and ultrasonic velocimetry of digital arteries.

Acute polyneuropathy. Evidence exists for a myelinotoxic IgM antibody in the sera of patients with "acute infective polyneuritis."⁷⁹ Controlled trials have demonstrated steroids to be ineffective.⁸⁰ Brettle et al⁸¹ recently reported dramatic results in the treatment of one patient with plasmapheresis.

Asthma. Gartmann et al⁸² have reported improvement in one patient with severe asthma treated with plasmapheresis. Clinical improvement lasted several months only to relapse, but promptly responded to reinstitution of plasmapheresis.

Transplantation. Plasmapheresis has been used in several areas in clinical organ transplantation. Cardella et al⁸³ have successfully managed five of seven episodes of renal rejection with plasmapheresis. Graze and Gale⁸⁴ have reported unsuccessful attempts to treat several patients with chronic graft versus host reactions following bone marrow transplantation.

Paraproteinemia. The use of plasma exchange in removal of paraproteins was the earliest clinical experience with this tool.⁸⁵ Although the hyperviscosity syndrome has been the most commonly treated complication, others have also been treated.⁸⁶ Ibster et al⁸⁷ have reported the success of plasma exchange in three patients with malignant paraproteinemia who developed hemostatic complications. Misiani et al⁸⁸ have also recently reported excellent recovery of renal function in three patients in whom acute renal failure developed during the

course of multiple myeloma.

Plasmapheresis is an exciting new therapeutic modality with great potential in a wide variety of immunologic disorders. Early experience with this tool has been encouraging, with many reports demonstrating clinical and serologic improvement with little significant morbidity.

A word of caution must temper this optimism, for virtually all trials of this therapy to date have been uncontrolled. Since it is apparent that plasmapheresis alone is sufficient to control only a few immunologic disorders, the exact role of adjuvant immunotherapy needs to be defined. In addition, the beneficial effects attributable to the plasmapheresis itself as opposed to the associated immunotherapy have not in many instances been clearly definable. Apart from these reservations, the cautious application of this modality adds a new dimension to the immunopharmacologic armamentarium.

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