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Treatment of Goodpasture's disease by plasma exchange and immunosuppression

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SUMMARY

Three cases of Goodpasture's disease are described who were treated with intensive plasma exchange and immunosuppression. There was no improvement in renal function and the patients required chronic haemodialysis, but renal function did recover with treatment for recurrence of disease in a transplanted kidney. Anti-GBM antibody levels were not controlled and substantial reductions in fibrinogen and complement were only achieved with daily treatment. A controlled trial of this regime is urgently required.

INTRODUCTION

Goodpasture's disease is an uncommon disorder characterized by glomerulonephritis and pulmonary haemorrhage. It is associated with circulating antibody to human glomerular basement membrane antigens (anti-GBM antibody) and the binding of this antibody to both kidney and lung, with the consequent inflammatory reaction involving white cells, complement and the coagulation system, is believed to be responsible for the pathological consequences (Wilson & Dixon, 1973).

The renal lesion is usually severe and rapidly progresses to chronic renal failure (Benoit *et al.*, 1964; Proskey *et al.*, 1970). The pulmonary lesions range from mild haemopytsis to fatal haemorrhage.

A recent report (Lockwood *et al.*, 1976) described the success of plasma exchange and immunosuppression in the treatment of this illness, and we wish to add our own experience of treating a small number of patients.

MATERIALS AND METHODS

Patients. We have treated three patients on a total of five occasions. The clinical presentations and initial laboratory data are in Table 1.

Case histories. (a) R.McG. was a 22 year old dairyman who first noted mild haemoptysis in August 1975, but did not present to the hospital until November 1975, with profuse haemoptysis and nephrotic syndrome. He was a moderate cigarette smoker. Although not oliguric, the endogenous creatinine clearance was 15 ml/min and the urine contained 12 g protein/24 hr, with an unselective pattern. He was anaemic and hypoxic breathing air. The chest radiograph (see Fig. 1a) showed bilateral alveolar opacities consistent with alveolar haemorrhage.

A renal biopsy performed the following morning demonstrated discontinuous linear staining of IgG along the glomerular capillary walls and large epithelial cell crescents greatly compressing 75% of the glomeruli. There was a heavy polymorphonuclear cell infiltrate, but little mesangial cell proliferation.

(b) W.A. was a 56 year old civil servant who presented with a 3 week history of haematuria, ankle swelling and a single episode of frank haemoptysis in April 1976. On admission, the endogenous creatinine clearance was only 2 ml/min, he was oliguric and the urine contained 9 g protein/24 hr, with an unselective pattern. He too was markedly anaemic with a low plasma iron (5 μmol/l) and hypoxic breathing air (Table 1). The lung volumes were normal, but the transfer factor for carbon monoxide (T_{CO}) was 10·15 mmol/min/kPa, which is elevated in relation to the anaemia. The chest radiograph showed patchy basal alveolar opacities, consistent with haemorrhage.

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Renal biopsy within 24 hr showed florid crescents compressing 70% of the tufts and a heavy polymorphonuclear cell infiltrate, but without mesangial cell proliferation. There was heavy fibrin deposition in the crescents but no linear staining of the GBM with either IgG or C3.

(c) M.N. was a 64 year old civil servant who was admitted after 3 days anuria. This followed a mild gastrointestinal illness lasting 24 hr and she never had any loin pain, haematuria or haemoptysis. Although she was slightly hypoxic the chest radiograph was normal.

Renal biopsy the following day revealed a florid rapidly progressive glomerulonephritis, with linear staining of the GBM by complement and immunoglobulins and a polymorphonuclear cell infiltrate.

Treatment schedules. An arteriovenous Scribner shunt was inserted providing access for both haemodialysis and plasma exchange.

R.McG. was initially treated with seven plasma exchanges in 8 days and thereafter thrice weekly for 2 weeks (see Fig. 2). After a further 2 weeks of no treatment, plasma exchange was resumed thrice weekly for 2 weeks and combined with oral prednisolone, 60 mg, and cyclophosphamide, 200 mg, daily for about 3 weeks. His second course of treatment (see below) was of daily plasma exchange for 5 days followed by twelve exchanges in the next 3 weeks with chemotherapy given from the outset (see Fig. 3).

His third course of treatment was ten plasma exchanges over 2 weeks, with prednisolone, 20 mg, and azothiaprine, 150 mg, daily and a course of dexamethasone, 100 mg i.v., daily for 3 days.

W.A. was treated with steroids and cyclophosphamide immediately (as above) for 6 weeks. After two initial exchanges, plasma exchange was performed daily for 7 days and then thrice weekly for 2 weeks (see Fig. 4).

M.N. received steroids and cyclophosphamide for 6 weeks. Plasma exchange was performed for 10 consecutive days and then thrice weekly for 2 further weeks (see Fig. 5).

Regular haemodialysis was required in all the patients.

Plasma exchange. An Aminco continuous flow blood cell separator (American Instrument Co., Silverspring, U.S.A.) was used with a blood warmer on the return line. Using a centrifuge speed of 1500 rev/min and a total blood flow of 100 mg/min, the procedure was usually completed within approximately 1·5 hr. Heparinization was achieved with 2000–5000 u intravenously at the start followed by an infusion of 40–100 u/min. At the end this was usually reversed by 20–50 mg of protamine sulphate diluted by slow infusion into the return line.

Plasma was exchanged for, initially, 5·2 litres of plasma protein solution (PPS, Protein Fractionation Centre, Edinburgh) supplemented with calcium gluconate, but this was later reduced to 4·0 litres. Fresh plasma (FFP) was used when PPS was unavailable. The only side effects noted were two episodes of mild bronchoconstriction when using FFP.

Histology. Renal tissue obtained by percutaneous biopsy was stained for immunofluorescence and light microscopy by standard techniques.

Fibrinogen, complement and immunoglobulins. Plasma fibrinogen was measured by the method of Ellis & Stransky (1961) and IgG and C3 by radial immunodiffusion using monospecific antisera.

Anti-GBM antibody. Serum anti-GBM antibody was kindly measured by Dr C. Wilson, Department of Immunopathology, Scripps Research Clinic and Foundation, La Jolla, California, U.S.A., by a double antibody radioimmunoassay using radiolabelled, collagenase-solubilized human GBM. Results are expressed as the percentage binding of the radiolabelled antigen which is less than 1% in patients without anti-GBM disease.

RESULTS

Clinical

R.McG. showed rapid resolution of pulmonary haemorrhage after 3 days using plasma exchange alone. The chest radiograph dramatically improved (Fig. 1b), all haemoptysis ceased and he could maintain a pA_{O_2} of 10·0 kPa breathing air.

W.A. also showed rapid improvement in the chest radiograph; the pA_{O_2} improved to normal values and the T_{CO} fell to 5·4 mmol/min/kPa, a value consistent with the anaemia.

No patient showed any improvement in renal function and all have been subsequently treated by regular haemodialysis.

Repeat renal biopsies showed marked reduction or absence of linear staining of the GBM with complement and immunoglobulins, but complete hyalinization of many glomeruli and severe damage to the remainder. There was improvement in the inflammatory features of the lesion.

In May 1976 R.McG. received a cadaver kidney graft and standard immunosuppression with oral prednisolone, 100 mg, and azothiaprine, 100 mg, daily. An episode of rejection associated with an *E. coli* urinary infection and bacteraemia was treated with methylprednisolone (1·0 g i.v. for 3 days) and gentamycin. 24 hr later he developed profuse pulmonary haemorrhage and red cell casts in the urine. A chest radiograph showed extensive, bilateral alveolar changes and he was hypoxic breathing air (Table 1).

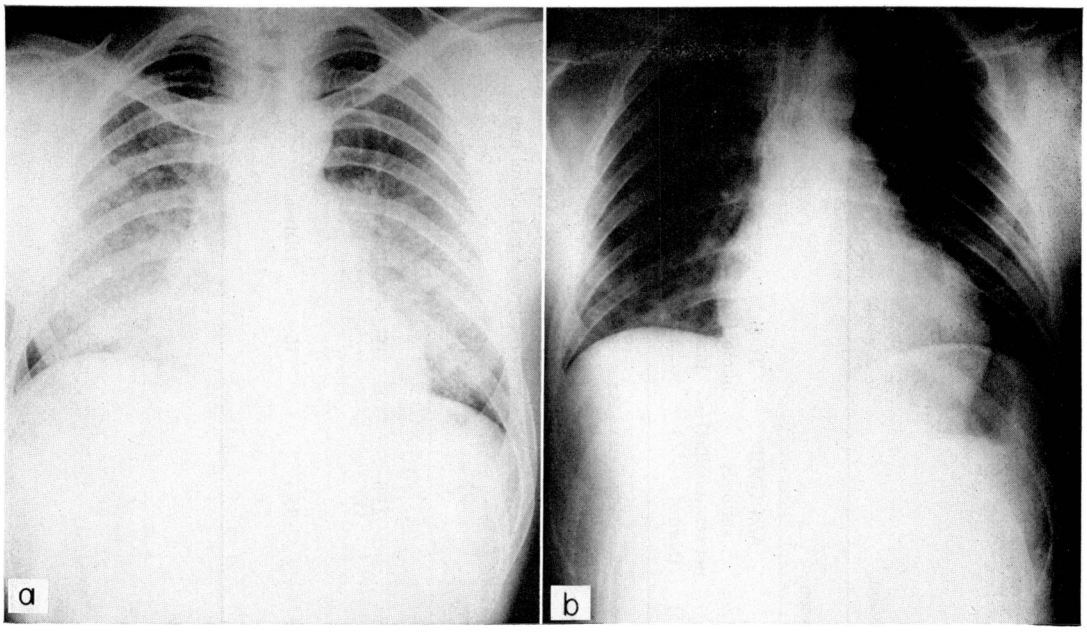

FIG. 1. R.McG.'s chest radiographs, (a) before treatment, and (b) after 3 days plasma exchange alone.

A biopsy of the transplanted kidney showed linear deposition of IgG along glomerular capillary walls and an acute tubular necrosis with lymphocyte infiltration of the interstitium.

Plasma exchange, steroids and cyclophosphamide were used as detailed above. The haemoptysis stopped and the chest radiograph cleared within 72 hr, but haemodialysis was also used to remove extracellular fluid. The pA_{O_2} improved more slowly. A second transplant biopsy showed only mild mesangial cell proliferation and a lymphocyte infiltrate. He subsequently recovered renal function and was discharged with a creatinine clearance of 35–40 ml/min. The graft continued to function well for 6 months, but heavy proteinuria and a further drop in creatinine clearance led to a biopsy. This showed recurrence of an active proliferative glomerulonephritis with heavy linear staining of the GBM by IgG. The chest radiograph was clear and the T_{CO} not elevated. Plasma exchange and immunosuppression were given as previously detailed. There was no improvement in renal function or protein excretion and renal function gradually declined. Dialysis was started in June 1977.

Anti-GBM antibody, immunoglobulin, complement and fibrinogen

Figs 2–5 show the effects of treatment on serum anti- GBM titres, total IgG, C3 and plasma fibrinogen. The diagnosis was confirmed in each instance by the finding of high levels of anti-GBM antibody. There was no reduction in antibody level in R.McG. with plasma exchange alone or with immunosuppression, despite striking improvement in the pulmonary lesions. During his second course of treatment he and W.A. show an initial fall, followed by a slow rise towards the end of the first month of treatment, in spite of continuing plasma exchange combined with immunosuppression. The data for M.N. is unavailable.

Fig. 6 shows the gradual decline in anti-GBM antibody over 450 days in R.McG., which seems to be typical of the natural history of this disease. Although the steep fall between days 203–240 could be related to the azothiaprine, the various intensive treatment periods have not produced sustained reductions in the serum level. Two patients were mildly hypogammaglobulinaemic at presentation (4·0 and 6·9 g/l respectively). The total serum IgG was markedly decreased and maintained below 2·0 g/l during periods of daily exchanges. IgG was used as a readily measurable, day-to-day index of the effectiveness of treatment. There is considerable divergence, however, between the pattern of reduction of the anti-GBM antibody and total IgG during treatment.

TABLE 1. Clinical and laboratory data on admission

Patient	Clinical presentation	Laboratory data on admission: Haemoglobin (g/dl)	Creatinine (μmol/l)	pA_{O_2} (kPa) (normal 12–15)	Anti-GMB antibody per cent binding) (normal < 1%)	Total number of plasma exchanges	Results
R. McG. (aged 22 years)	Haemoptysis and nephrotic syndrome with alveolar oedema on chest X-ray (November 1975).	8·1	480	8·6	30·7	19	Dialysis T/P June 1976
	Recurrence of haemoptysis and acute rejection with *E. coli* infection 1 week after transplant.	5·1	560	7·3	16·7	17	Recovery Cr.cl. 36 ml/min
	Further recurrence with nephrotic syndrome	12·3	270	12·8	4·7	10	Cr. 230 Proteinuria (20 g/day)
W.A. (aged 56 years)	Haemoptysis and haematuria with minimal X-ray changes (April 1976)	6.5	803	9·6	23·0	15	Dialysis
M.N. (aged 64 years)	Anuria for 3 days following mild G.I. illness.	10·0	1300	10·6	35·5	16	Dialysis

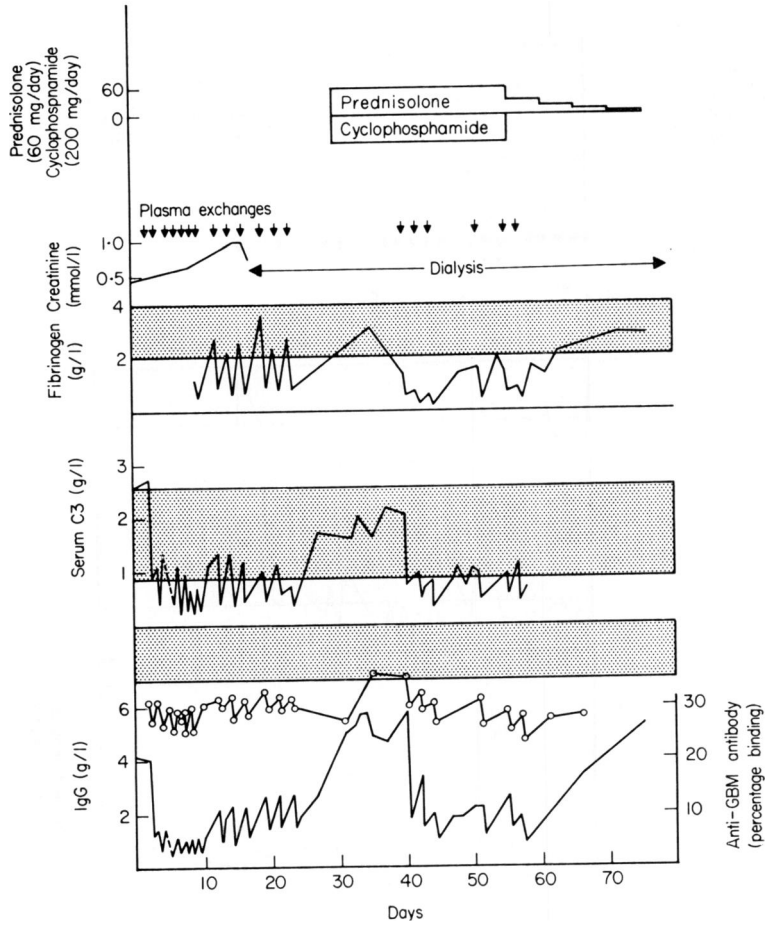

FIG. 2. Serum IgG, C3, anti-GBM antibody and plasma fibrinogen and creatinine concentrations during treatment of R.McG. For bottom graph, (——) IgG, (○) anti-GBM antibody. (⊠) Normal values for any of the parameters

Although both fibrinogen and C3 are effectively removed by plasma exchange, the concentrations rapidly return towards pre-treatment values and a sustained reduction in these two important mediators of inflammation could only be achieved during periods of daily exchange (Keller & Urbaniak, 1977). Steroids and cyclophosphamide did not appear to influence the levels of either C3 or fibrinogen, as these were very similar during R.McG.'s first course of treatment.

DISCUSSION

Goodpasture's disease is a severe form of human anti-GBM disease, but as our third patient illustrates there may be no clinically detectable lung involvement even when anti-GBM antibody levels are high and the renal lesion correspondingly severe. Many factors may affect the lung-damaging properties of the antibodies measured, not least that they may be heterogeneous and differ between patients in their avidity for lung basement membrane antigens or complement fixation. The suspected diagnosis is usually confirmed by finding linear immunofluorescence of IgG along the glomerular capillary basement membrane, but this is not always reliable as case 2 illustrates. The quickest method of confirming the presence of circulating anti-GBM antibody is by indirect immunofluorescence (Wilson & Dixon, 1973) and this can later be confirmed and quantified by the specific radioimmunoassay. Recurrence in the

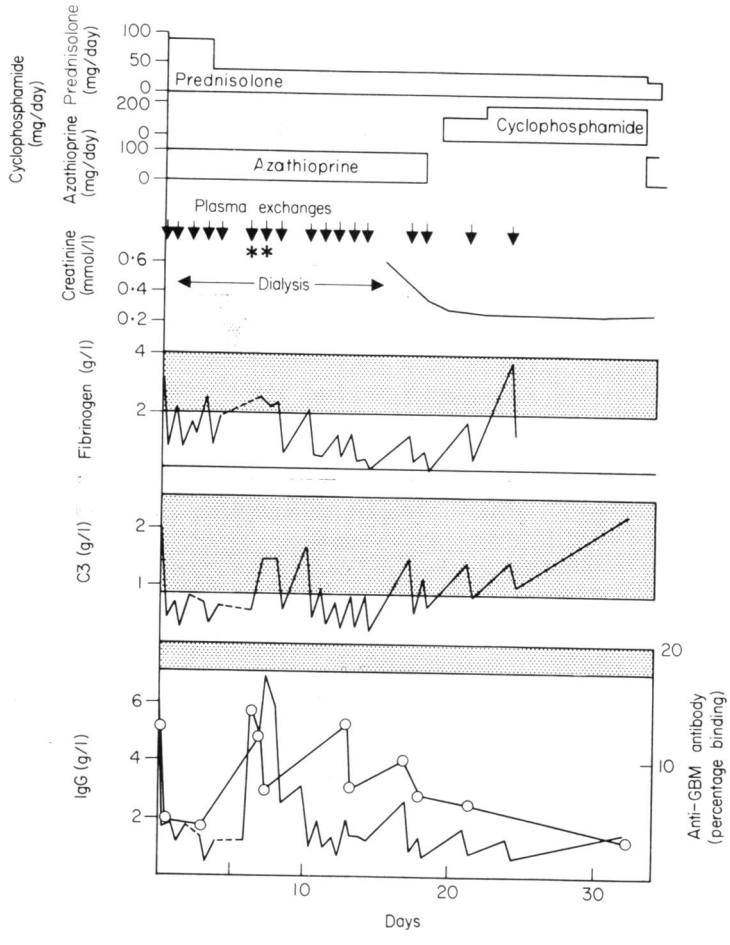

FIG. 3. R.McG. after recurrence of disease after transplant. Legend as for Fig. 2. *FFP.

transplant, despite falling serum levels, may mean that the actual level measured is not a good indicator of the severity of the disease.

The aims of our treatment were (i) to remove anti-GBM antibody, (ii) to prevent the synthesis of fresh anti-GBM antibody and (iii) to remove some important mediators of inflammation, namely complement and fibrinogen.

At the time of treating our first patient (November 1976) Lockwood *et al.* (1975) had shown a dramatic recovery and reduction in anti-GBM antibody levels using only seven plasma exchanges and immunosuppression. The evidence that cytotoxic drugs suppress the immune response in man is controversial (Steinberg *et al.*, 1972), and plasma exchange results in a rebound rise of antibody only after primary immunization, not after an on-going secondary response where a permanent fall is seen (Branda *et al.*, 1975). It therefore seemed reasonable to assess the effect of plasma exchange initially alone, and then with immunosuppression. Intensive plasma exchange alone did not reduce anti-GBM antibody levels (Fig. 2), but some reduction was achieved when it was combined with immunosuppression. This was not, however, sustained. The dosages of steroid and cyclophosphamide chosen were based on Lockwood *et al.* (1976), and do not appear to have been effective in completely suppressing the production of anti-GBM antibody. The disparity between the reduction in total IgG and anti-GBM antibody probably reflects autonomy of the antibody-producing clone of lymphocytes and stimulation of a primary immune response. These data suggest that such production may continue for a long period.

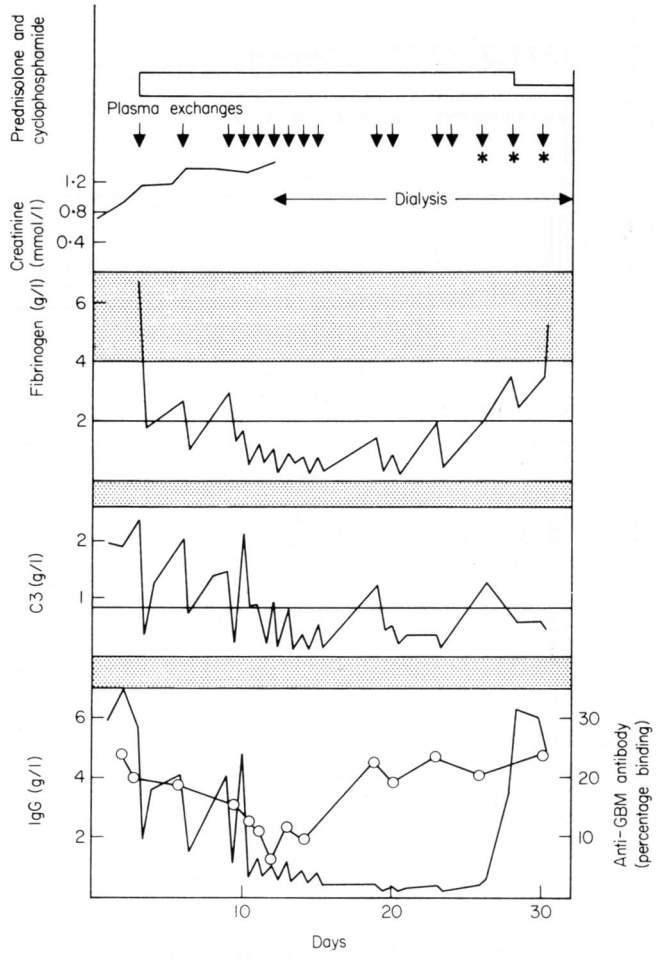

FIG. 4. Patient W.A. Legend as for Fig. 3.

A rebound rise in anti-GBM antibody following periods of plasma exchange is well illustrated by these patients, and is similar to the phenomenon observed in mice (Bystryn, Schenkein & Uhr, 1971) or in rabbits after primary immunization (Branda *et al.*, 1975). This may partly account for our failure to reverse the renal disease, but it is surprising that the lung haemorrhage did not recur. Total IgG did not show such a rebound and it is likely that the immunosuppression used prevented this. An actively secreting clone of lymphocytes may require much larger doses, and a single large dose of cyclophosphamide (e.g. 50 mg/kg) may be more successful than daily therapy. Prednisolone may have been useful in controlling some of the inflammatory features of the disease and in preventing further damage by leucocytes.

Plasma exchange is only effective in substantially reducing the circulating amounts of complement or fibrinogen when performed on consecutive days. The rapid rise in concentrations after each exchange reflects rapid turnover and redistribution from extravascular pools.

The clinical spectrum and natural history of Goodpasture's syndrome are variable. Spontaneous resolution of lung haemorrhage is described (Azen & Clatanoff, 1964; Bloom, Wayne & Wrong, 1965; Cohen, Wilson & Freeman, 1976; Duncan *et al.*, 1965; McCall, Harris & Hatch, 1965; Teichman *et al.*, 1976; Wilson & Smith, 1972), and so is recovery from renal failure, even when dialysis is required (Munro, Geddes & Lamb, 1967), but reported long-term survivors are few. Recovery has been reported with steroids alone (Azen & Clatanoff, 1964; Benoit *et al.*, 1964; Bloom *et al.*, 1965; Proskey *et al.*,

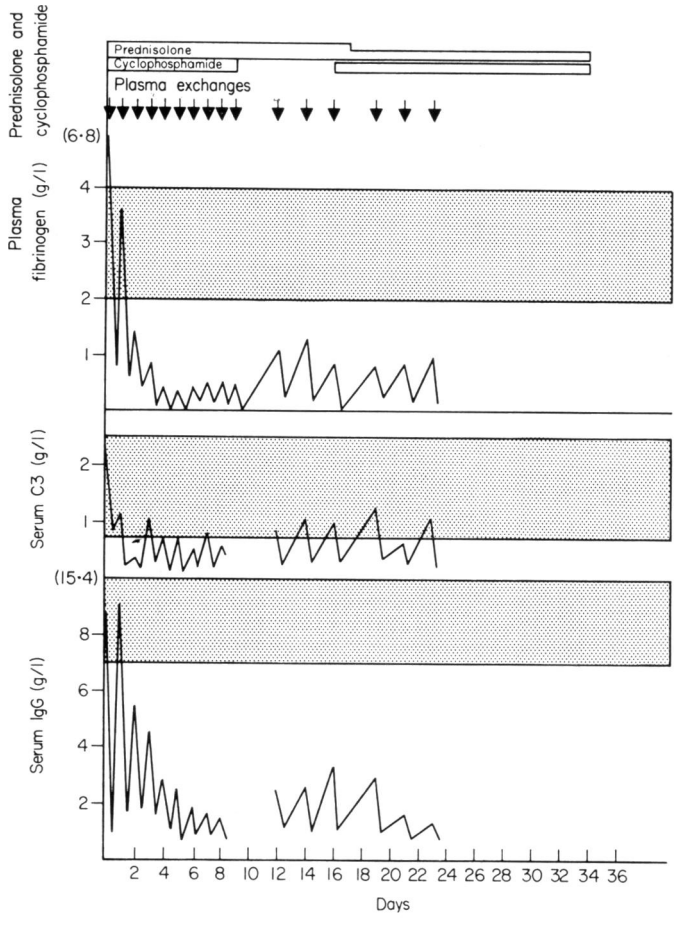

FIG. 5. Patient M.N. Legend as for Fig. 2.

1970; Rusby & Wilson, 1960), or in combination with azothiaprine (Hayslett, Berte & Kashgarian, 1971) and other immunosuppressive agents (Cohen *et al.*, 1976); conversely, these drugs have had no apparent effect except in delaying death from either pulmonary haemorrhage or uraemia (Azen & Clatanoff, 1964; Benoit *et al.*, 1964; Bloom *et al.*, 1965; Duncan *et al.*, 1965; Randall, Glazier & Liggatt, 1963). Nor is there evidence to support bilateral nephrectomy (Eisinger, 1973; Maddock *et al.*, 1967). It is probably unwise to transplant in the presence of high titres of anti-GBM antibody, but there may be a long delay in obtaining results. A high serum value partly explains the recurrence of R.McG.'s disease, despite adequate immunosuppression, and the role of an acute bacterial infection has been recently emphasized (Rees, Lockwood & Peters, 1977). The renal disease progressed in the transplant, however, despite a steadily falling circulating antibody level, which may reflect tissue binding to the kidney. Fig. 6 illustrates how the anti-GBM antibody declines slowly over 460 days, and it is difficult to relate any of the periods of treatment to a specific sustained decline in antibody levels. It is possible that there is an initial period of continuing antibody production because of persistent antigenic stimulation from damaged sites in the basement membrane. This gradually subsides as the GBM is covered in antibody and complement reacting at these sites and thereafter the circulating level gradually declines.

Plasma exchange is useful in the early treatment of severe forms of this disease, with high anti-GBM antibody levels, to control pulmonary haemorrhage and prevent irreversible renal damage. However, the removal of anti-GBM antibody after the patient has already developed renal failure does not lead to recovery of renal function. There seems to be considerable variation in the response of the anti-GBM

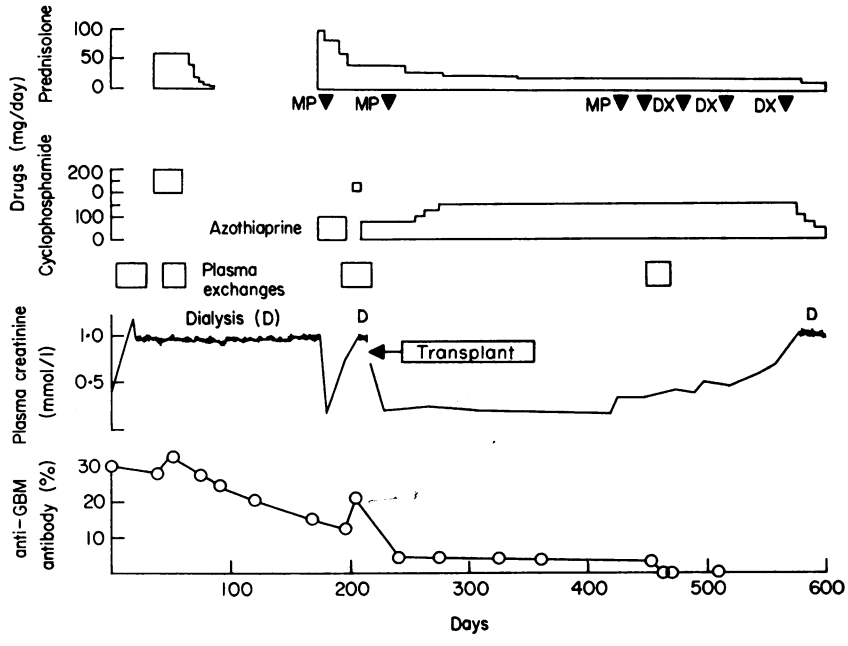

FIG. 6. Changes in circulating anti-GBM antibody and plasma creatinine in relation to therapy. MP = 3 day course of methylprednisolone, 1 g i.v.; DX = 3 day course of dexamethasone, 100 mg i.v.

antibody level in the serum to serial plasma exchange and immunosuppression. Lockwood *et al.* (1975), in their first successful treatment, reduced anti-GBM antibody into the normal range with only seven exchanges. In their subsequent series there was considerable variation, but none of their patients had levels as high as these and in general the patients with highest levels had the poorest response to plasma exchange. It may be that for such patients intensive daily exchange needs to be maintained for several weeks. We agree that patients must be treated early, but to justify the considerable expense of intensive plasma exchange, a controlled clinical trial is urgently needed before its wider use is encouraged.

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