

Goodpasture's Syndrome

Treatment With Nephrectomy and Renal Transplantation

Charles G. Halgrimson, MD; Curtis B. Wilson, MD; Frank J. Dixon, MD; Israel Penn, MD;
James T. Anderson, MD; David A. Ogden, MD; and Thomas E. Starzl, MD, PhD, Denver

Three young male patients developed acute glomerulonephritis and serious hemoptysis. All three had evidence of antiglomerular basement membrane (anti-GBM) antibodies in their serum and native kidneys. The pulmonary hemorrhages ceased after bilateral nephrectomy and splenectomy accompanied by irregular treatment with steroids and other immunosuppressants. Renal homotransplantation was success-

fully carried out from 95 to 162 days later, after circulating anti-GBM antibodies had disappeared. Two of the homografts were biopsied and the third was removed 20, 34, and 2 months posttransplantation, respectively, and contained little or no immunoglobulin. Therefore, Goodpasture's syndrome does not contraindicate renal transplantation under the stipulated conditions of staged therapy.

were ruled out in all three cases by the direct cross-match method of Terasaki.²⁷

Report of Cases

CASE 1.—A 30-year-old white man was admitted to the Denver Veterans Administration Hospital with a two-day history of hematuria. Within one week he developed hemoptysis, fluffy infiltrates throughout both lung fields, and oliguria (250 ml/24 hr). A closed renal biopsy revealed necrotizing glomerulitis. Prednisolone (120 mg/day) did not halt progressive renal failure (Fig 1), necessitating hemodialysis; however, the lung fields cleared rapidly. He was treated with variable daily doses (usually 2 mg/kg/day) of mercaptopurine between the 11th and 30th days following admission. In January 1968, 115 days after the onset of symptoms, elective splenectomy and bilateral nephrectomy were performed. A severe, crescent-forming, subacute glomerulonephritis was present histologically (Fig 4). Anti-GBM antibodies were present in the kidneys and in the circulation. Renal homotransplantation followed after an additional 95 days when circulating anti-GBM antibodies had disappeared. There were no rejection episodes, and the normally functioning homograft was biopsied 34 months posttransplantation. No glomerular abnormalities were present by light microscopy (Fig 5).

CASE 2.—A 29-year-old white man had recurrent "bronchopneumonia" in September and October of 1968, associated with dyspnea and hemoptysis. On Jan 8, 1969, he was hospitalized in another city for these pulmonary symptoms and gross hematuria. Laboratory studies disclosed the following values: hematocrit reading, 20%; blood urea nitrogen (BUN), 60 mg/100 ml; and antistreptolysin titer, 250 Todd units/100 ml (slightly elevated). Blood pressure was 160/80 mm Hg. Despite the maintenance of good urinary output, his BUN level rose to 152 mg/100 ml.

On Jan 20, 1969, he was admitted to

Antibodies detectable by immunofluorescence and by elution react with the glomerular basement membrane producing glomerular injury.¹⁻⁸ The subsequent glomerulonephritis often progresses rapidly and, when associated with pulmonary hemorrhage (sometimes fatal), is properly termed Goodpasture's syndrome.⁹⁻¹¹ The pulmonary manifestations are presumed to involve cross reaction of the antiglomerular basement membrane (anti-GBM) antibodies with the alveolar septal basement membrane.^{1,3-5,8,12-25} In patients, many of whom were diagnosed on clinical grounds only, chronic systemic steroid therapy, other immunosuppressive agents, and hemodialysis have been inconsistent or valueless in controlling either these renal or pulmonary symptoms.^{11,16-22}

This paper reports three patients with anti-GBM antibody mediated glomerulonephritis and pulmonary hemorrhage treated initially with

splenectomy and bilateral nephrectomy 7 to 37 months ago. After circulating anti-GBM antibodies could no longer be detected, each patient received a renal homograft.

Methods

General Care.—The surgical procedures and the general principles of postoperative care have been described elsewhere.²³ Immunosuppression with azathioprine, prednisone, and equine antilymphocyte globulin (ALG)²⁴ was begun two to four days before transplantation. The subsequent timing and dosage of the individual agents are shown in Fig 1 to 3. The recipients' ages, the timing of surgical interventions, and the source and match of kidney homografts are shown in the Table.

Detection of Renal Bound and Circulating Anti-GBM Antibodies.—Snap frozen renal nephrectomized and biopsied specimens were examined for glomerular-bound human immunoglobulins (IgG, IgA, and IgM), complement (C3), fibrin, albumin, and equine immunoglobulin by direct immunofluorescence.²⁵ Anti-GBM antibodies eluted from this renal tissue with hypotonic citrate buffer (pH 3.2) were detected by indirect immunofluorescence on normal human kidney sections.^{7,8} Circulating anti-GBM antibodies were sought by indirect immunofluorescence using normal human kidney sections.²⁶ Preformed cytotoxic antibodies against donor lymphocytes

Accepted for publication March 22, 1971.

From the Department of Surgery, Veterans Administration Hospital and University of Colorado School of Medicine, Denver; and the Department of Experimental Pathology, Scripps Clinic and Research Foundation, La Jolla, Calif.

Read before the 28th annual meeting of the Central Surgical Association, Minneapolis, March 5, 1971.

Reprint requests to Department of Surgery, University of Colorado, 4200 E Ninth Ave, Denver 80220 (Dr. Halgrimson).

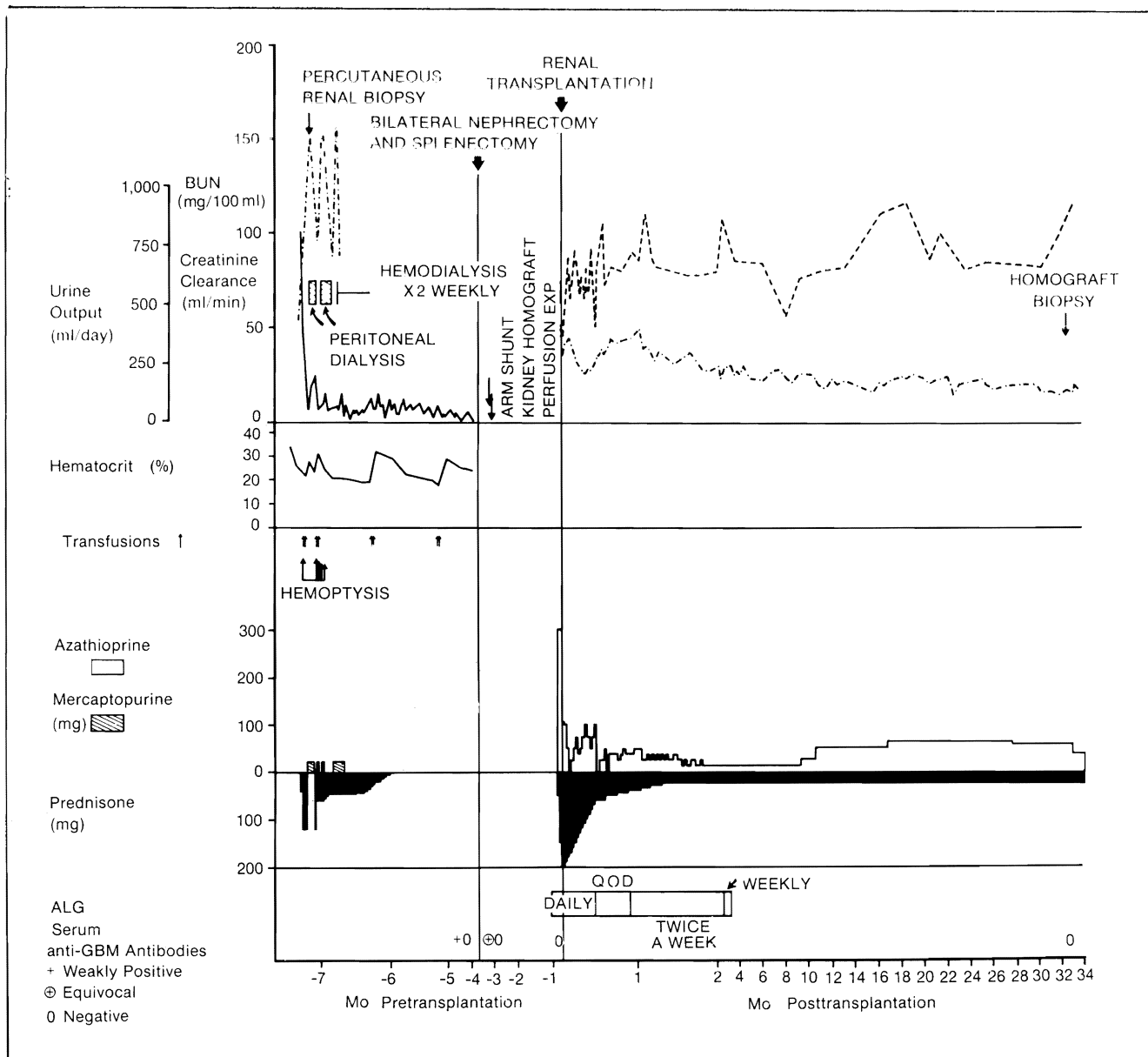


Fig 1.—Course of 30-year-old male patient (case 1).

the Denver Veterans Administration Hospital in acute respiratory tract distress with muscle cramps, chills, tremor, and malaise. His blood pressure was 142/90 mm Hg and he had 2+ pitting pretibial edema. His hematocrit reading was 25%; BUN, 170 mg/100 ml; and serum creatinine, 9.5 mg/100 ml. Creatinine clearance was 5 ml/min, and there was microscopic hematuria with 3+ albuminuria. Antistreptolysin titer was within normal limits; antinuclear antibody titers (ANA) and three LE preparations were negative. An x-ray film of the chest demonstrated bilateral interstitial infiltrates. On Jan 23 percutaneous renal biopsy revealed a severe, sub-

acute, crescent-forming glomerulonephritis.

Treatment was started with 60 mg of prednisone per day. Hemoptysis with inadequate oxygenation persisted, and on Feb 4, 1969, bilateral nephrectomy and splenectomy were carried out, even though significant renal function remained (serum creatinine, 13.5 mg/100 ml; creatinine clearance, 6 ml/min, BUN, 146 mg/100 ml; and daily urine volume of about 900 ml). The renal biopsy findings were confirmed (Fig 4) with anti-GBM antibodies detected in the nephrectomized kidneys and in the circulation (Fig 6 to 8).

After surgery, hemodialysis was

started and repeated three times a week, while the steroid dosage was gradually lowered. Hemoptysis recurred (Fig 2 and 9) with near death from an alveolocapillary diffusion defect. The pulmonary hemorrhage ceased with increased dosage of prednisone which was subsequently tapered from 105 to 10 mg/day. On July 3, 1969, a total of 149 days after nephrectomy and splenectomy, after the circulating anti-GBM antibodies had disappeared, he received a renal homograft from his brother, which has functioned normally since (Fig 2). He had serum hepatitis, Au-positive, in the early posttransplantation period. The homograft was biopsied 20

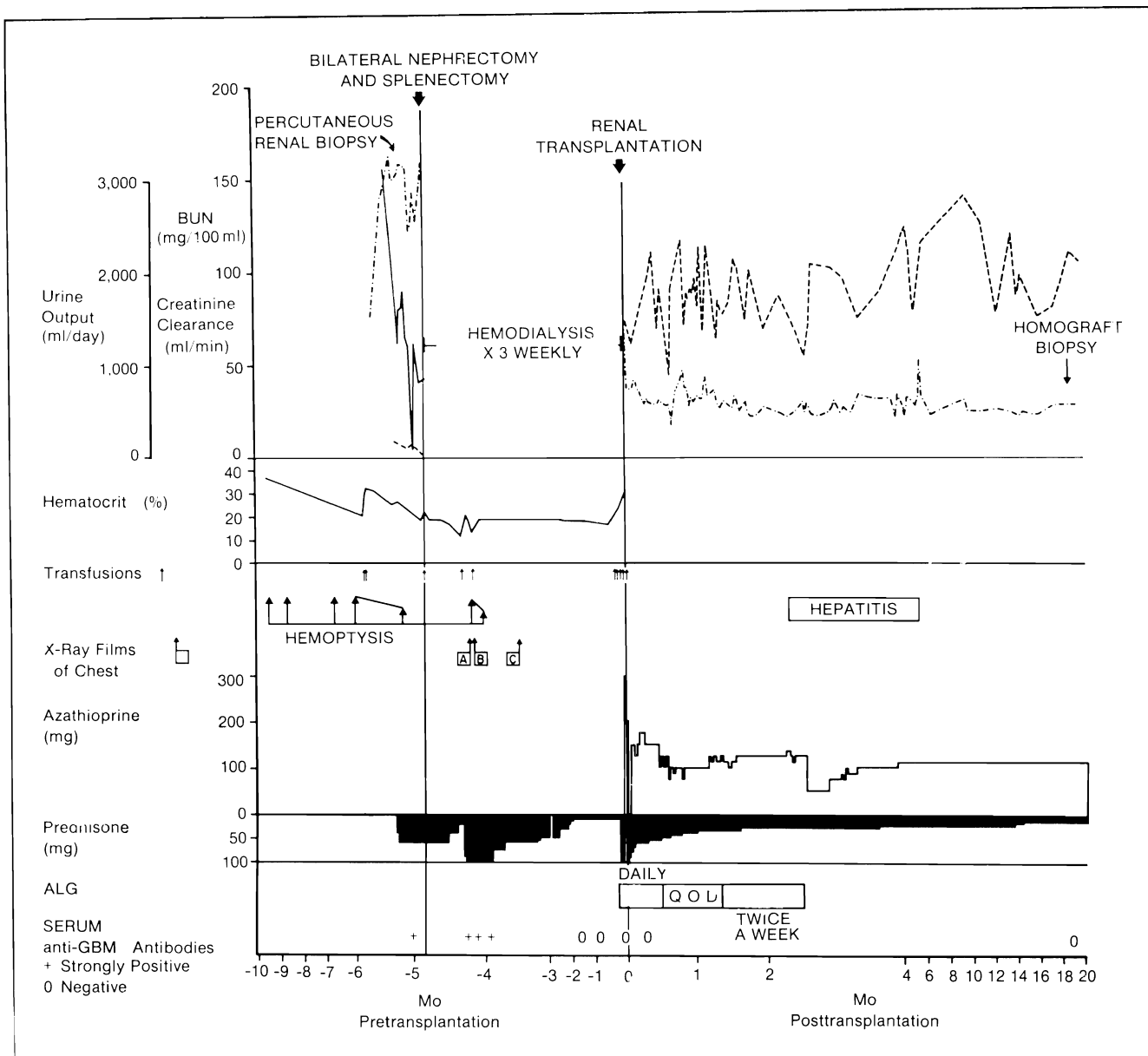


Fig 2.—Course of 29-year-old male patient (case 2).

months after transplantation and no glomerular abnormalities were found by light microscopy (Fig 5).

CASE 3.—A 35-year-old white man noted anorexia and vomiting as well as ankle edema in late May 1970. One week later, intermittent hemoptysis began with no other pulmonary symptoms. His local physician observed gross hematuria. Laboratory studies revealed the following values: blood pressure, 150/100 mm Hg; anemia with a hematocrit reading of 33%; BUN, 41 mg/100 ml; and serum creatinine, 3.1 mg/100 ml. Urinalysis showed 4+ protein, numerous granular casts, and gross blood. An x-ray film of the chest was normal except for

prominent bronchovascular marking of the hilum of the left lung.

He was admitted to the Denver Veterans Administration Hospital on July 1, 1970. The previous laboratory and physical findings were confirmed except that the hematocrit reading had fallen to 25% and the BUN and serum creatinine had risen to 85 mg/100 ml and 15.6 mg/100 ml, respectively. Rheumatoid factor, ANA, and three LE preparations were negative, and whole serum complement was normal. An x-ray film of the chest showed bilateral lower-lobe alveolar infiltrates. A needle biopsy of the kidney revealed acute glomerulonephritis with crescent formation.

Systemic heparinization and furosemide therapy were begun on July 3, 1970. Within three days he became oliguric and had severe hemoptysis and dyspnea (oxygen pressure [PO₂], 53 mm Hg, while receiving oxygen nasally, 4 liters/min). The alveolar infiltrates in both lung fields had extended. Intermittent hemodialysis was begun. With the presumptive diagnosis of Goodpasture's syndrome, azathioprine and prednisone therapy were started, provided no perceptible benefit, and were discontinued. After a complicated course during which emergency thoracentesis and periardiocentesis were required, splenectomy and bilateral nephrectomy were done on

Aug 19, 1970. Severe, crescent-forming subacute glomerulonephritis was present (Fig 4). Linear immunofluorescent deposits of human IgG and C3 were detected in the nephrectomized kidneys, and anti-GBM antibodies were present in the circulation.

A maternal kidney was transplanted after 162 days during which circulating anti-GBM antibodies had disappeared. After 18 hours of brisk diuresis, an apparent accelerated rejection took place with oliguria and azotemia, but not proteinuria. Adequate renal function returned (Fig 3) after one posttransplantation dialysis.

Results

Renal Bound and Circulating Anti-GBM Antibodies.—All three cases had direct immunofluorescent evidence of anti-GBM antibodies in the native kidneys, with linear deposits of IgG and C3 bound to the glomerular basement membrane (Fig 7). No deposits of IgA, IgM, fibrin, or albumin were identified. The presence of anti-GBM antibodies reactive with Bowman's capsule and to a portion of the tubular basement membranes in addition to GBM was confirmed by elution studies in cases 1 and 2 (Fig 7). Unfortunately, tissue was not available for elution in case 3.

Homograft biopsies at 34 months (case 1) and 20 months (case 2) did not contain unusual human IgG, IgA, IgM, fibrin, albumin, or equine immunoglobulin deposits. Moderate amounts of C3 were present in vessel walls, and trace amounts of irregular C3 deposits were seen in the mesangial stalk.

Circulating anti-GBM antibodies were present before or following nephrectomy, or both, in all three patients (Fig 8). In case 1, circulating anti-GBM antibodies were detected by both indirect immunofluorescence and by fixation to a normal infant kidney interposed in the patient's arteriovenous dialysis shunt 16 days following nephrectomy. The anti-GBM antibodies in the perfused kidney were detected by direct immunofluorescence and confirmed by elution studies. Anti-GBM antibodies absent prior to transplantation (95 to 162 days after bilateral nephrectomy) have not recurred.

Comment

Subsequent renal transplantation

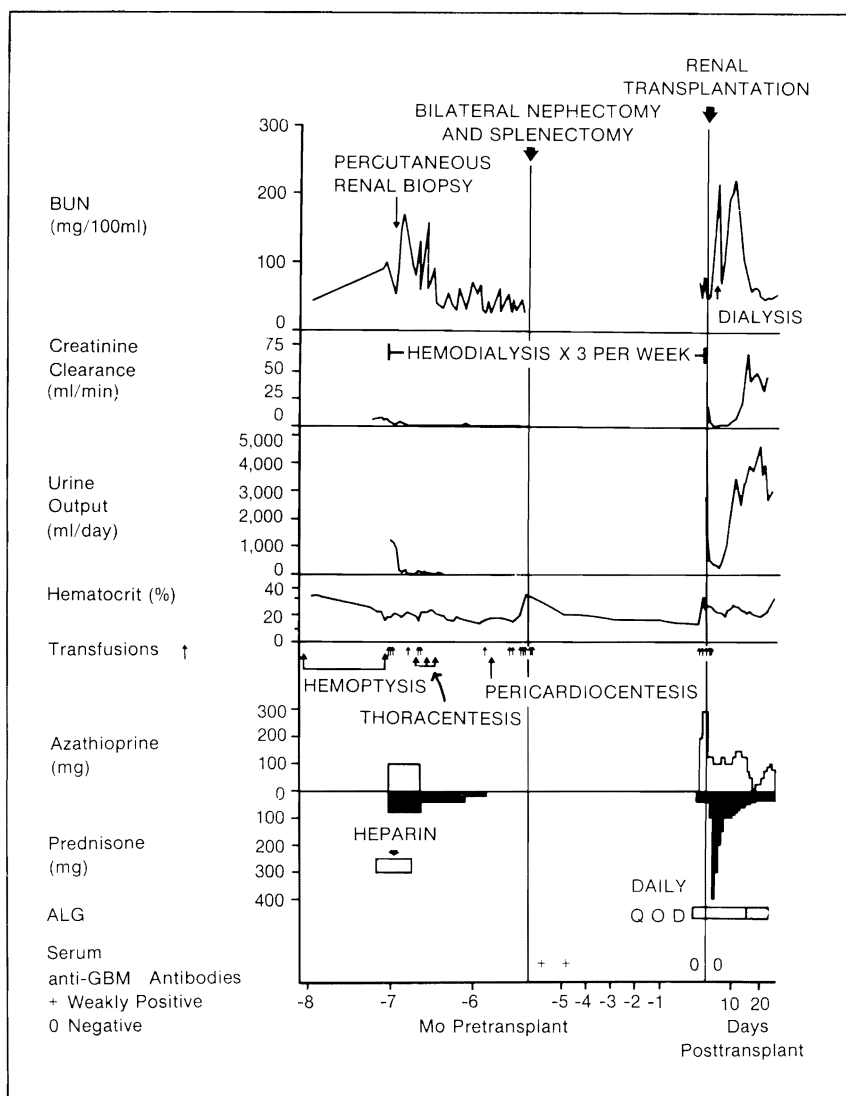


Fig 3.—Course of 35-year-old male patient (case 3).

Case Material

	Case 1	Case 2	Case 3
Date of onset	10/1/67	9/13/68	5/29/70
Age of patient, yr	30	29	35
Date of splenectomy and nephrectomies	1/24/68	2/4/69	8/19/70
Date of transplantation	4/29/68	7/3/69	1/28/71
Kidney donor	Brother	Brother	Sister
Terasaki match	A	A	D
Time of posttransplantation, mo	34	20	1

provided long-term success in two of these cases. Similar treatment has been reported associated with favorable results in five additional patients with clinical courses compatible with Goodpasture's syndrome.²⁸⁻³¹ In view of the limited number of patients and the complex therapeutic measures involving

surgery, anesthesia, dialysis, and intensive immunosuppression, it is difficult to determine definitely specific effects of any single measure. No doubt multiple factors influence most events, for example, the importance of pharmacologic immunosuppression is indicated by the exacerbation of hemoptysis follow-

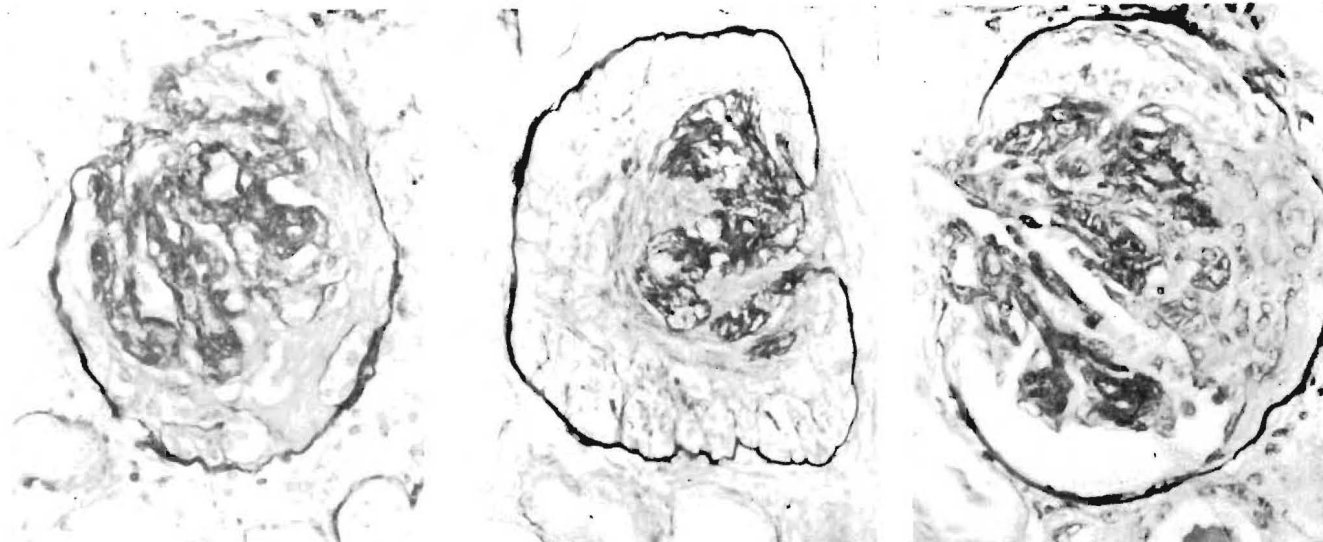


Fig 4.—Crescent forming subacute glomerulonephritis found in native kidneys of patients in case 1 (left), case 2 (center), and case 3 (right) (PAS, $\times 340$).

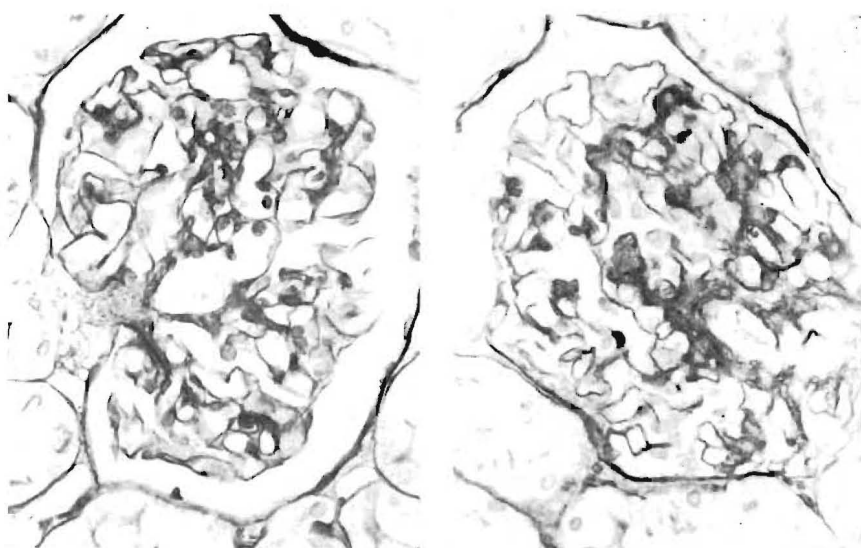
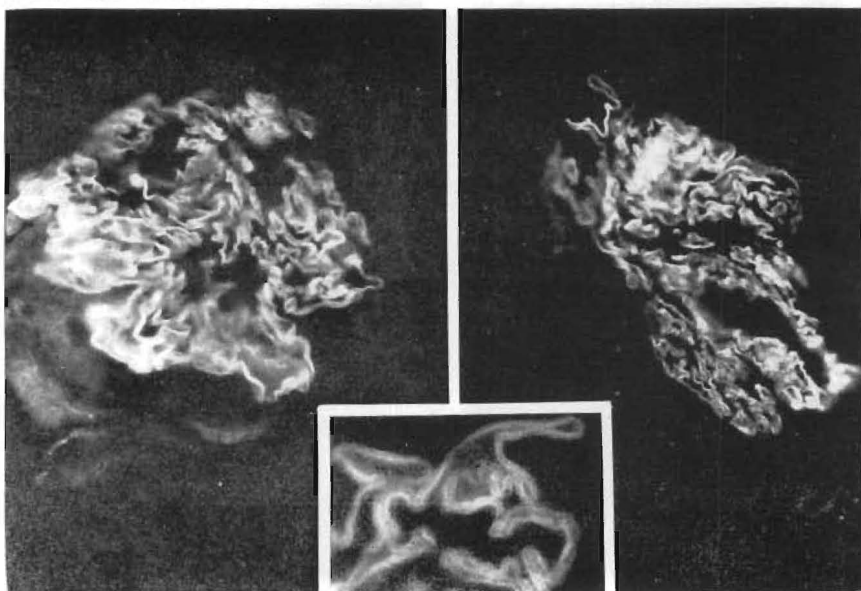


Fig 5.—Normal histologic appearance of representative glomeruli from renal homograft biopsies of case 1 (left) 34 months posttransplantation and case 2 (right) 20 months posttransplantation (PAS, $\times 340$).

Fig 6.—Smooth continuous linear deposits of human IgG found along glomerular basement membrane (case 2) (fluorescein isothiocyanate-conjugated rabbit anti-human IgG, $\times 250$; inset, $\times 1,000$).



ing reduction in prednisone dose in two of our patients. The dramatic improvement of pulmonary disease following nephrectomy in two of our patients is by no means a consistent finding. Further, it is even impossible to establish whether disappearance of circulating anti-GBM antibodies is an essential prerequisite for successful renal transplantation, but this certainly seems likely.⁷

There are a number of theoretical aspects of the surgery employed which led to its application and should be considered. At least three immunologic consequences of the surgery may have had beneficial effects. First, splenectomy may reduce antibody forming potential, thereby contributing to fall in anti-GBM antibodies. Second, nephrectomy by eliminating the GBM may be removing an antigenic stimulus. Third, nephrectomy by removing the normal route of excretion of nonrenal basement membrane antigens, which presumably are derived from turnover of basement membrane generally and which cross-react with glomerular basement membrane, might cause an increase in circulating basement membrane antigens which could combine with anti-GBM antibodies, thereby protecting the lungs.^{15,32} The postnephrectomy improvement of patients with little or no residual renal function could not be attributed to this third mechanism. Unfortunately, there is no available direct evidence

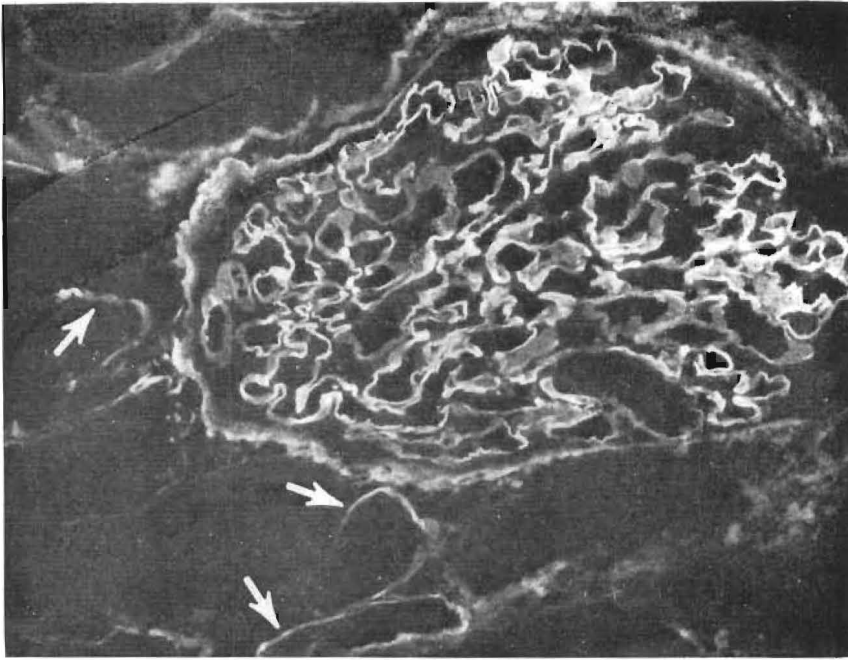


Fig 7.—Fixation of human IgG eluted (pH 3.2) from native kidney to normal human kidney section (case 2). Fixation is to glomerular basement membrane, Bowman's capsule, and to tubular basement membranes (**arrows**) (fluorescein isothiocyanate-conjugated rabbit anti-human IgG, $\times 250$).

Fig 8.—Fixation of IgG from immediate postnephrectomy serum of to a normal human kidney section (case 2). Fixation is to glomerular basement membrane, Bowman's capsule, and tubular basement membranes (**arrows**) (fluorescein isothiocyanate-conjugated rabbit anti-human IgG, $\times 250$).

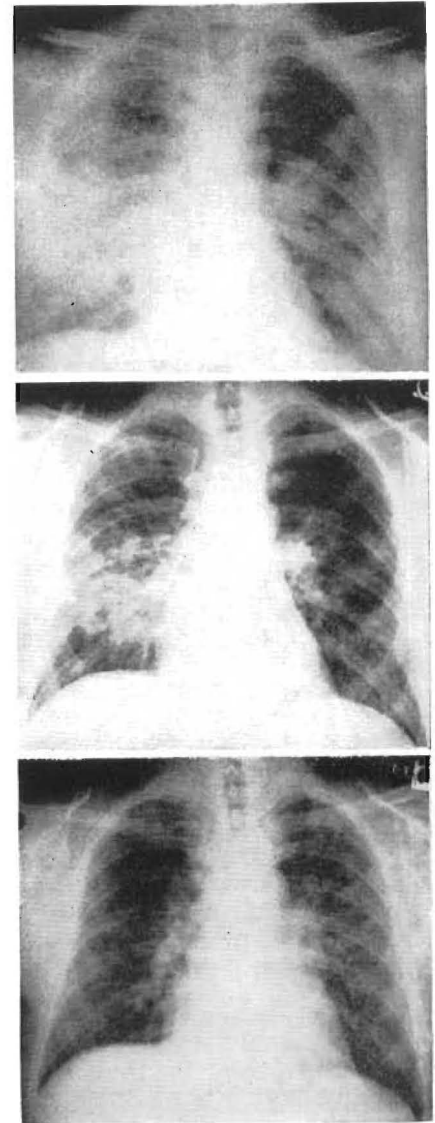
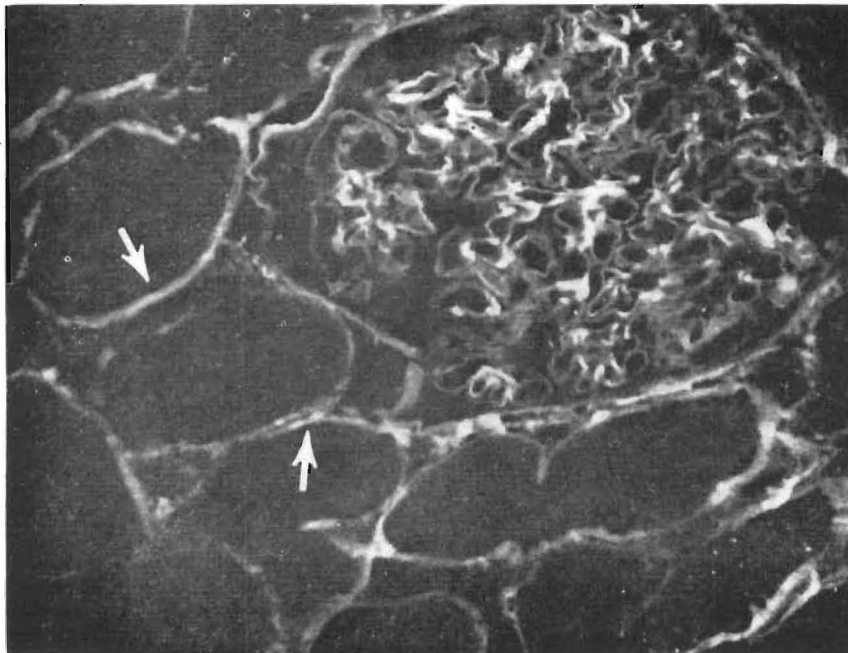


Fig 9.—X-ray films of the chest 19, 21, and 41 days following bilateral nephrectomy and splenectomy. Diffuse pulmonary infiltrate (**top**) was associated with massive hemoptysis and severe alveolar-capillary diffusion defect. Two days later, after increase in dosage of prednisone the hemoptysis diminished, diffusion block improved, and infiltrate began to clear (**center**). Twenty days later, x-ray film was normal (**bottom**) and patient was asymptomatic (case 2).

to support any of these possibilities; however, de Oliveira et al³³ observed in rats that prior termination of renal excretion greatly lessened the pneumotoxic effect of heterologous nephrotoxic sera. This might have resulted in part from increased circulating basement membrane antigens or from the anti-inflammatory effects of uremia or both. At least two theoretical disadvantages associated with nephrectomy did not seem to be important in these patients. The removal of the GBM did not appear to terminate any significant protective immuno-absorbent action. The accumulation, if any, of nonrenal basement membrane antigens in the circulation did not appear to serve as an immunogenic stimulus.

In the absence of more decisive evidence, we have adopted the following policies. Nephrectomy and splenectomy are performed following stabilization of the clinical course with dialysis and steroid therapy. Circulating anti-GBM antibodies are monitored. Immunosuppression is not provided during the waiting period unless circulating anti-GBM antibodies persist or pulmonary hemorrhage recurs. When circulating anti-GBM antibodies disappear, usually within six months, renal transplantation may proceed. If circulating anti-GBM antibody remains, chronic immunosuppression should be considered.

Subsequent to the preparation of this paper, the patient in case 3 developed a staphylococcal wound abscess and severe bilateral bronchial pneumonia which led to his death 69 days following transplantation. Prior to death, immunosuppressive therapy was withdrawn and his kidney was removed after being in residence for 62 days. Postmortem examination revealed necrosis and abscess formation in both lungs due to infection with multiple organisms, including *Pseudomonas aeruginosa*, *C albicans*, *Aspergillus*, and *cytomegalovirus*. Histologic examination of the excised homograft revealed scant focal interstitial mononuclear cell accumulation. Focal glomerular hypercellularity was present with some cells containing intranuclear inclusion bodies. No conclusive evidence of anti-GBM antibodies in the homograft was found by immunofluorescence and acid elution

studies of the 50 gm of tissue available for study.

This investigation was supported by Public Health Service research grants A1-04152, A1-07007, A1-AM-08898, AM-12148, AM-06344, AM-07772, RR-00051, RR-00069, and HE-09110; Public Health Service contract PH-43-68-621; and Atomic Energy Commission contract AT(04-3)-410.

Elution studies on cases 1 and 2 were performed by Richard A. Lerner, MD, and John J. McPhaul, Jr., MD, respectively.

Nonproprietary and Trade Names of Drugs

Azathioprine—*Imuran*.

Furosemide—*Lasix*.

References

1. Sheer RL, Grossman MA: Immune aspects of the glomerulonephritis associated with pulmonary hemorrhage. *Ann Intern Med* 60:1009-1021, 1964.
2. Duncan DA, Drummond KN, Michael AF, et al: Pulmonary hemorrhage and glomerulonephritis: Report of six cases and study of the renal lesion by fluorescent antibody technique and electron microscopy. *Ann Intern Med* 62:920-938, 1965.
3. Sturgill BC, Westervelt FB: Immunofluorescence studies in a case of Goodpasture's syndrome. *JAMA* 194:914-918, 1965.
4. Markowitz AS, Battifora HA, Schwartz F, et al: Immunological aspects of Goodpasture's syndrome. *Clin Exp Immun* 3:585-591, 1968.
5. Beirne GJ, Octaviano GN, Kopp WL, et al: Immunohistology of the lung in Goodpasture's syndrome. *Ann Intern Med* 69:1207-1212, 1968.
6. Poskitt TR: Immunologic and electron microscopic studies in Goodpasture's syndrome. *Amer J Med* 49:250-257, 1970.
7. Lerner R, Glasscock RJ, Dixon FJ: The role of anti-glomerular basement membrane antibody in the pathogenesis of human glomerulonephritis. *J Exp Med* 126:989-1004, 1967.
8. McPhaul JJ Jr, Dixon FJ: Characterization of human anti-glomerular basement membrane antibodies eluted from glomerulonephritic kidneys. *J Clin Invest* 49:308-317, 1970.
9. Goodpasture EW: The significance of certain pulmonary lesions in relation to the etiology of influenza. *Amer J Med Sci* 158:863-870, 1919.
10. Benoit FL, Rulon DB, Theil GB, et al: Goodpasture's syndrome: A clinicopathologic entity. *Amer J Med* 37:424-444, 1964.
11. Proskey AJ, Weatherbee L, Easterling RE, et al: Goodpasture's syndrome: A report of five cases and review of the literature. *Amer J Med* 48:162-173, 1970.
12. Steblay RW, Rudofsky U: Autoimmune glomerulonephritis induced in sheep by injections of human lung and Freund's adjuvant. *Science* 160:204-206, 1968.
13. Koffler D, Sandson J, Carr R, et al: Immunologic studies concerning the pulmonary lesions in Goodpasture's syndrome. *Amer J Path* 54:293-305, 1969.
14. Hagadorn JE, Vazquez JJ, Kin-

ney TR: Immunopathologic studies of an experimental model resembling Goodpasture's syndrome. *Amer J Path* 57:17-30, 1969.

15. Willoughby WF, Dixon FJ: Experimental hemorrhagic pneumonitis produced by heterologous anti-lung antibody. *J Immun* 104:28-37, 1970.

16. Rusby NL, Wilson C: Lung purpura with nephritis. *Quart J Med* 29:501-511, 1960.

17. Fairley KF, Kincaid-Smith P: Goodpasture's syndrome. *Brit Med J* 2:1646, 1961.

18. Johnson JR, McGovern VJ: Goodpasture's syndrome and Wegner's granulomatosis. *Aust Ann Med* 11:250-259, 1962.

19. Lunberg GD: Goodpasture's syndrome: Glomerulonephritis with pulmonary hemorrhage. *JAMA* 184:915-919, 1963.

20. Walker JM, Joekes AM: Survival after haemoptysis and nephritis. *Lancet* 2:1199-1201, 1963.

21. Holman RE, Hutt MP, Brittain RS, et al: Goodpasture's syndrome: Treatment failure with azathioprine. *JAMA* 196:31-32, 1966.

22. Freeman RM, Vertel RM, Easterling RE: Goodpasture's syndrome: Prolonged survival with chronic hemodialysis. *Arch Intern Med* 117:643-647, 1966.

23. Starzl TE: *Experience in Renal Transplantation*. Philadelphia, WB Saunders Co, 1964.

24. Starzl TE: *Experience in Hepatic Transplantation*. Philadelphia, WB Saunders Co, 1969.

25. Wilson CB, Dixon FJ: Antigen quantitation in experimental immune complex glomerulonephritis. *J Immun* 105:279-290, 1970.

26. McPhaul JJ Jr, Dixon FJ: The presence of anti-glomerular basement membrane antibodies in peripheral blood. *J Immun* 103:1168-1175, 1969.

27. Patel R, Terasaki PI: Significance of the positive crossmatch test in kidney transplantation. *New Eng J Med* 280:735-739, 1969.

28. Cleveland AJ, Lee HM, Prout GR, et al: Preservation of the cadaver kidney for renal homotransplantation in man. *Surg Gynec Obstet* 119:991-996, 1964.

29. Maddock RK Jr, Stevens LE, Reemtsma K, et al: Goodpasture's syndrome: Cessation of pulmonary hemorrhage after bilateral nephrectomy. *Ann Intern Med* 67:1258-1264, 1967.

30. Shires DL, Pfaff WW, DeQuesada A, et al: Pulmonary hemorrhage and glomerulonephritis: Treatment of two cases by bilateral nephrectomy and renal transplantation. *Arch Surg* 97:699-703, 1968.

31. Siegel RR: The basis of pulmonary disease resolution after nephrectomy in Goodpasture's syndrome. *Amer J Med Sci* 259:201-213, 1970.

32. McPhaul JJ Jr, Dixon FJ: Immunoreactive basement membrane antigens in normal human urine and serum. *J Exp Med* 130:1395-1409, 1969.

33. de Oliveira HL, Laus-Filho JA, Sarti W: Prevention of acute immunological lung change by previously induced acute uremia in rats. *Int Arch Allerg* 29:384-392, 1966.