Immunopathogenesis of crescentic glomerulonephritis and lung purpura

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Case presentation

A 61-year-old white woman was referred to the University Hospital for management of rapidly progressive glomerulonephritis and pulmonary hemorrhage. One week prior to admission, she developed a cough productive of a small amount of bloody sputum; the cough and hemoptysis became worse over the succeeding week. Chest x-ray showed bilateral pulmonary infiltrates in a “butterfly” pattern. She was admitted to another hospital, where she was found to be hypoxic. Arterial blood gas analysis (with the patient breathing room air) showed pH, 7.42; PCO₂, 36 mm Hg; and PO₂, 58 mm Hg. At this time she was coughing up about one-quarter cup of bright red blood per hour. Urinalysis showed 3+ proteinuria, microscopic hematuria, and many granular and red blood cell casts/high-power field. The BUN and serum creatinine were 38 and 2.5 mg/dl respectively. Three months earlier (at the time of an elective cholecystectomy) the BUN had been 20 mg/dl; the creatinine were 3.5 mg/dl, a white blood cell count of 5600/mm³, and a clear urine output exceeded 1 liter/day. Chest x-ray confirmed the presence of bilateral alveolar-interstitial infiltrates more marked on the left (Fig. 1).

The serum creatinine level rose over 6 days to a peak of 5.4 mg/dl while the pulmonary infiltrate improved. Urine output remained normal, and the serum creatinine level eventually began to decline. Urine protein excretion was 470 mg/24 hr. Discharge was delayed because of progressive neutropenia (2400/mm³) and anemia. The patient was discharged after 3 weeks with microscopic hematuria, a serum creatinine of 3.5 mg/dl, a white blood cell count of 5600/mm³, and a clear chest x-ray (Fig. 1). The following laboratory investigations were either negative or normal: antinuclear antibody, radioimmunoassay for antiglomerular basement membrane antibody, serum complement, hepatitis Bs, cryoglobulins, and peripheral eosinophil count. The patient’s serum contained IgG antibodies that stained the cytoplasm of normal human leukocytes to a dilution of 1:20 (control < 1:10).

We have followed this patient for almost 2 years since her acute illness. Two months after onset of the illness, prednisone was switched
Crescentic glomerulonephritis and lung purpura

Fig. 1. Chest x-ray before (A) and two weeks after (B) treatment was started with cyclophosphamide and prednisone. Note the alveolar-interstitial infiltrate in the left upper zone and right mid zone in A, which has completely resolved in B.

to an alternate-day regimen and was then discontinued over the course of 4 months. The dose of cyclophosphamide at discharge was 100 mg daily, but was reduced within 4 months to 50–75 mg daily because of neutropenia. Serum creatinine declined progressively and stabilized at 2.2 mg/dl after approximately 10 months. Microscopic hematuria also resolved after about 10 months. Urine protein excretion remains at 400–700 mg/24 hours. The long-term course was complicated by a bout of herpes zoster and an episode of diverticulitis with bacteremia. The latter resolved without further complications after a short course of intravenous antibiotics. Cyclophosphamide was continued for 15 months after complete resolution of all symptoms. The dose was then tapered and finally discontinued after a total duration of 20 months. At last followup, the serum creatinine was 2.0 mg/dl, blood pressure was normal, and the urine sediment showed only occasional red blood cells.

Discussion

DR. DAVID J. SALANT (Associate Professor of Medicine, Evans Department of Clinical Research at University Hospital, Boston University Medical Center, Boston, Massachusetts): Each new case of rapidly progressive glomerulonephritis (RPGN) presents the clinician with a diagnostic and therapeutic challenge. This patient’s presentation—rapidly declining renal function, hematuria with red blood cell casts, and mild proteinuria—was entirely compatible with a diagnosis of RPGN. In managing such a patient one must specifically diagnose the underlying illness and initiate therapy without delay for two important reasons. First, the type of treatment selected depends on the diagnosis of the primary disease, because no one form of therapy is effective for all causes of RPGN [1]. Second, unless appropriate therapy is instituted promptly, the prognosis of RPGN is poor. Patients who receive ineffective or no treatment have a 2-year renal survival rate of less than 30% [2].

To diagnose a specific disease from the broad differential diagnosis of this syndrome (Table 1), one generally relies on a combination of features that include the clinical renal manifestations, extrarenal symptoms and signs, serologic abnormalities, and renal immunopathology. Clinical renal manifestations are relatively “soft” criteria on which to base a diagnosis but, in the patient under consideration, the absence of nephrotic-range proteinuria and hypertension tended to favor anti-glomerular basement membrane (anti-GBM) nephritis, idiopathic RPGN without immune deposits, or vasculitic syndromes such as microscopic polyarteritis nodosa (PAN) or Wegener’s granulomatosis (WG) rather than the immune-complex glomerulonephritides shown in Table 1.

Extrarenal manifestations of a systemic disease are important clues to the diagnosis in RPGN, especially when they display a typical spectrum of abnormalities as in systemic lupus erythematosus (SLE), Henoch-Schönlein purpura (HSP), and essential mixed cryoglobulinemia (EMC) [1], or characteristic features such as the upper respiratory tract destruction that can occur with WG. Pulmonary hemorrhage, as in this patient, can be of considerable diagnostic help in narrowing the differential diagnosis to one of the specific pulmonary-renal syndromes listed in Table 2. Several nonspecific pulmonary manifestations can occur with similar or greater frequency in any patient with RPGN, however, and these should be excluded first. Any patient with oliguric acute renal failure is at risk of volume overload and pulmonary edema. Pulmonary infection may be incidental or causally related to a proliferative glomerulonephritis [1], and minor hemoptysis or transient pulmonary infiltrates are seen in about 30% of cases early in the course of “depositt free” idiopathic RPGN [3]. Right-sided infective endocarditis is an important cause of multilobar septic pulmonary emboli and can cause RPGN [1, 4]. After excluding these nonspecific disorders in the patient described, we had to determine whether she had anti-GBM disease (Goodpasture’s syndrome), SLE, or vasculitis (particularly WG, as there were no atopic features to suggest allergic granulomatosis). On purely clinical grounds we might have excluded Goodpasture’s syndrome because it occurs more often in young men, and because of the patient’s history of sinusitis and arthralgia. But these features are merely demographic or too subjective to be firm diagnostic criteria.

Serologic studies could have been of considerable diagnostic
Table 1. Immunopathologic classification of crescentic and/or necroizing glomerulonephritis

<table>
<thead>
<tr>
<th>Linear immune deposits (anti-GBM nephritis)</th>
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<tr>
<td>Goodpasture’s syndrome</td>
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<td>Nephritis without pulmonary hemorrhage</td>
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<tr>
<td>Granular immune deposits (immune-complex nephritis)</td>
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<td>Systemic diseases</td>
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<td>Henoch-Schönlein purpura</td>
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<td>Essential mixed cryoglobulinemia</td>
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<td>IgA nephropathy</td>
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<tr>
<td>Idiopathic immune-complex RPGN</td>
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<td>No immune deposits</td>
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<tr>
<td>Idiopathic RPGN</td>
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<tr>
<td>Systemic vasculitis</td>
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<tr>
<td>Wegener’s granulomatosis</td>
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<td>Polyarteritis nodosa</td>
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Table 2. Major causes of lung purpura in association with RPGN

<table>
<thead>
<tr>
<th>Pulmonary-renal syndromes</th>
<th>Nonspecific</th>
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</thead>
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<td>Goodpasture’s syndrome</td>
<td>Pulmonary edema</td>
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<td>Wegener’s granulomatosis</td>
<td>Infection</td>
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<td>Allergic granulomatosis</td>
<td>Pulmonary embolism</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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</tbody>
</table>

Fig. 2. Renal biopsy findings. A Immunofluorescent micrograph showing staining for fibrin/fibrinogen-related antigens. B Light micrograph of a crescentic glomerulus. Note compression and distortion of the glomerular tuft (large arrows) by a large, pleomorphic cellular crescent (arrow heads); periglomerular infiltrate of mononuclear cells; and disruption of Bowman’s capsule (small arrows). C Electron micrograph of a glomerular capillary showing mononuclear cells in the capillary lumen (small arrowhead) and urinary space (large arrowhead). No electron-dense deposits were visible on higher magnification of this or several other fields. Ep, visceral epithelial cell.

formed in a matter of hours and have good specificity for anti-GBM nephritis, albeit less sensitivity than a good radioimmunoassay [2, 5, 6]. Unfortunately, these studies are not available to most clinicians as emergency procedures.

In the patient we are discussing, the three most likely diagnoses and their treatments were: plasma exchange for Goodpasture’s syndrome [6], high-dose steroids, possibly with immunosuppressive agents, for SLE [7], and cyclophosphamide with low-dose steroids for WG [8]. Considering that serologic confirmation of the diagnosis was not immediately available, that therapy should be instituted immediately, and that the appropriate form of therapy is different for each of the diagnoses [9], the most expeditious diagnostic procedure was a renal biopsy. This served three major purposes. First, the immunofluorescent findings were obtained within hours, enabling us to classify the patient’s illness into one of the three categories shown in Table 1. The absence of linear or granular immunoglobulin deposits in this patient unequivocally excluded Goodpasture’s syndrome and SLE (or any other form of immune-complex glomerulonephritis). Second, light microscopy confirmed the diagnosis of crescentic glomerulonephritis. Third, light microscopy showed the crescents to be mainly cellular without extensive scarring of glomeruli and with good preservation of tubulointerstitial architecture. Although a definite diagnosis of WG, or most other forms of vasculitis, cannot be made on the basis of a renal biopsy, the immunopathologic findings and extrarenal manifestations in this patient were sufficient to suggest that disease, and we instituted cyclophosphamide therapy. The patient’s excellent response to treatment and gratifying “medium-term” outcome further suggest that she had Wegener’s nephritis and pulmonary disease.
Open lung biopsy is the most reliable means of establishing the diagnosis of WG and distinguishing it from deposit-free, idiopathic, crescentic glomerulonephritis associated with non-specific lung disease. Several independent observers have found that the serum of patients with active WG and closely related vasculitic syndromes contains IgG antibodies that react with granulocyte cytoplasmic antigens [10–12]. Antibody titers correlate with disease activity, and binding is independent of Fc [11]. The test is quickly and easily done and if, as the first three published reports suggest, it is specific for active WG and negative for SLE, it will be of considerable diagnostic value.

The nature of the cytoplasmic antigens has not been determined; nor has it been established whether this reactivity is the same as that described with Ro (SS-A), a cytoplasmic nucleoprotein identified by certain lupus sera and sera of some patients with active WG [13]. It is noteworthy that the serum of the patient under discussion contained anticytoplasmic antibodies.

The predominantly cellular nature of the crescents in this patient’s biopsy (Fig. 2) and her relatively well-preserved renal function at the onset of treatment probably contributed to her favorable response. Fibrous scarring of crescentic glomeruli can develop rapidly [14], as recently illustrated in rat [15] and rabbit [16] models of crescentic glomerulonephritis induced by accelerating the autologous phase of anti-GBM nephritis. These experiments showed that crescents evolve from a fibrin cast in Bowman’s space, through a predominantly cellular phase, to an organized fibrocellular scar containing cross-linked interstitial collagens, in as brief a period as 3 to 4 weeks [15–17]. The level of renal dysfunction and likelihood of reversal with treatment therefore reflect not only the extent of glomerular involvement but also the point along this continuum at which therapy is started. Inflammatory cell infiltration and endogenous parenchymal cell proliferation are potentially reversible events but fibrosis is not. Cellular crescents sometimes resolve, leaving small fibrotic scars, which allows improvement in the inflammatory and hemodynamic alterations [1] affecting renal function.

Large fibrous crescents that compress and collapse the glomerular tuft are unlikely to resolve; these generally lead to glomerular obsolescence, tubular atrophy, and permanent renal dysfunction. This difference probably explains why, in patients with RPGN—especially those with anti-GBM nephritis—the probability of recovery, or at least stabilization, is highest in those with relatively well-preserved renal function (6, 18–20). For example, Savage and colleagues noted that patients with anti-GBM nephritis whose serum creatinine exceeded 600 μmol/liter (6.5 mg/dl) did not respond to plasmapheresis [6]. In contrast, the prognosis was good in nonoliguric patients whose serum creatinine was below 600 μmol/liter (6.5 mg/dl) when treatment was started [6]. The same is generally true for other forms of RPGN [18], although even dialysis-dependent patients with lupus nephritis, WG, postinfectious glomerulonephritis, and idiopathic RPGN have been known to recover some renal function with appropriate treatment [2, 19]. Long-term renal survival in such patients with these other forms of RPGN tends to be worse than in those whose renal function is well preserved when treatment is begun, however [18–22].

This patient’s renal biopsy (Fig. 2) also illustrates certain points of pathogenetic importance, which I will discuss later. The crescents appeared to be composed of a pleomorphic collection of cells together with a hyaline stroma that stained positively on immunofluorescent examination with antiserum to fibrin-related antigens. Staining for fibrin also was evident within the glomerular tuft. In some areas, a striking periglomerular infiltrate of mononuclear cells appeared to merge with the crescent through breaks in Bowman’s capsule. This is a well-recognized finding in both clinical [14, 18, 23, 24] and experimental [15, 25] proliferative glomerulonephritis, but only recently have investigators begun to examine the role these mononuclear cells, which are derived from interstitial vessels, might play in the development of periglomerular fibrosis [26], disruption of Bowman’s capsule [15], and perhaps even crescent formation.

Several reviews have dealt extensively with therapy of idiopathic RPGN [2], vasculitis [27], and lupus nephritis [8]. Except for a controlled, prospective, collaborative study of severe lupus nephritis, which showed no beneficial effect of plasma exchange on multiple outcome variables [28], no major therapeutic advances have occurred since publication of those articles. I therefore shall not reiterate their contents here and will defer discussing the management of RPGN. Instead, the rest of this discussion will emphasize recent discoveries that enhance our understanding of the clinical and pathologic manifestations of RPGN. I shall focus on the immunopathogenesis of crescentic glomerulonephritis because it is only by understanding the fundamental pathobiology of the glomerular lesion that we will be able to proceed from empiric to rational treatment.

**Lung purpura with RPGN**

*Goodpasture’s syndrome.* Pulmonary hemorrhage occurs in approximately two-thirds of patients with anti-GBM nephritis (Goodpasture’s syndrome) [29–31] and is due to deposition of anti-basement membrane (BM) antibodies on the alveolar BM [32]. The remaining one-third of patients without symptomatic lung disease might have lung deposits of weakly pathogenic antibody [31] but, on the basis of experimental data [33, 34], it appears more likely that anti-BM antibodies fail to bind to the alveolar BM in such cases. Although antibodies from patients with Goodpasture’s syndrome (GP) and those from patients with non-GP anti-GBM nephritis can differ in their ability to bind extraglomerular BMs [33], recent experimental observations suggest that alveolar capillary anatomy and the chemistry of the GP antigen are also important factors.

In contrast to the highly fenestrated glomerular endothelium, alveolar (and most other) capillary endothelia do not have open fenestrae and provide a very effective barrier to the passage of anti-BM antibodies. If this barrier is disrupted, antibodies can gain access to antigens in the alveolar BM and cause injury. Jennings and coworkers injected rats with anti-alveolar BM antiserum and exposed some of the animals to toxic concentrations of inhaled oxygen. All rats developed GBM deposits of antibody as well as nephritis, but only those exposed to 100% oxygen developed alveolar BM deposits of antibody and fatal pulmonary injury [34]. A similar outcome was not observed in rats exposed to hydrocarbon vapors and anti-GBM antibody [35]; additional factors therefore might be important for alveolar BM binding.

Advances in basement membrane biochemistry have led to the identification, isolation, and characterization of the GP
antigen [36-38]. Further, this work has revealed features that might help explain why extraglomerular capillaries are less susceptible than are glomeruli to injury by circulating anti-BM antibodies. For several years it has been known that antisera from patients with anti-GBM nephritis bind to collagenase-resistant components of the GBM [5, 39]. In fact, successful immunoassays for anti-GBM antibodies, which employ collagenase-solubilized GBM as substrate [5, 6, 40], have depended on this property. Type IV (basement membrane) collagen is a heterotrimer composed of two $\alpha 1$(IV) and one $\alpha 2$(IV) chains arranged in a triple helix interrupted by two non-collagenous (NC1 and NC2) regions [41] (Fig. 3). Type IV collagen differs from interstitial collagens in that it is laid down as a three-dimensional lattice of procollagen molecules containing both collagenous and noncollagenous domains: this arrangement imparts strength and flexibility to the BM. The supramolecular organization is still uncertain, but it is known that four adjoining molecules of type IV collagen are associated via their amino terminals (7S domain), and that each molecule is also linked through its carboxyterminal NC1 (globular) domain to another type IV collagen molecule [41] (Fig. 3). Lateral associations between adjacent collagen chains, or through the junctions described above, complete the three-dimensional structure.

Using gel fractionation of collagenase digests of human GBM, Wieslander and colleagues showed that antisera from patients with anti-GBM nephritis (GP antisera) react exclusively with a 26 kD noncollagenous monomeric peptide (and 48 kD dimeric aggregates thereof) [37]. Antisera from patients with GP also reacted with a similar collagenase-resistant molecule from bovine GBM and bovine type IV collagen [42]. This molecule from bovine GBM proved to be one (M2) of the three noncollagenous monomeric peptides (M1, M2, M3) in the globular domain at the carboxyterminal end of type IV collagen, each representing the NC1 of the two $\alpha 1$(IV) chains and one $\alpha 2$(IV) chain [38, 43–45] (Fig. 3). Sera from patients with a variety of immunologic renal diseases (such as SLE, IgA nephropathy, PAN) react with other extracts of GBM [46], but only patients with anti-GBM nephritis have antibodies reactive with collagenase digests of GBM [46] and the ~28 kD M2 monomer or 42–50 kD M2 dimers contained within NC1 [38, 43].

Whereas GP antisera and glomerular eluates are unquestionably nephritogenic [47], the GBM reactivity in the other diseases is of doubtful significance.

The location of the GP antigen in type IV collagen also might explain why only some patients with circulating anti-GBM get pulmonary disease. Despite the ubiquitous distribution of type IV collagen (and hence the GP antigen) in all BMs, specific anti-GP antisera do not readily bind to extraglomerular BMs even when the endothelial barrier is abrogated by sectioning of the tissue [48]. Yet if the molecule is dissociated by treatment with 6 M guanidine [44] or with acid-urea [48], increased binding can be demonstrated, probably because the GP epitope is normally ensfolded within the tertiary structure of the hexameric NC1 complex formed by adjacent type IV collagen molecules in tissue [44, 45].

Tissue-damaging agents therefore might facilitate the binding of anti-GBM antibodies to GP antigen within the alveolar BM, either by damaging the alveolar capillary endothelium or by exposing GP epitopes hidden within the globular domain of type IV collagen (Fig. 4). This hypothesis might explain the increased frequency of pulmonary hemorrhage in cigarette smokers [49], as well as the sporadic association between Goodpasture’s syndrome and exposure to volatile solvents [30, 50] and viral infections [51]. An alternate, and once popular, notion—that anti-BM antibody production is triggered by solvent-induced alveolar injury [50]—has not been supported by epidemiologic data [52]. Possibly, in some cases, cryptic GP antigens in nonrenal BMs might be exposed by injurious agents and lead to autoantibody production. If this were true, GBM would be expected to bear the brunt of injury because of the anatomic and biochemical characteristics I have discussed.

Other causes of lung purpura with RPGN. Hemoptysis, sometimes massive and life-threatening, also can occur in WG [9, 21, 53, 54], and SLE [55–57]. In WG, scant evidence suggests that humoral immunity plays any role in pulmonary injury, but the presence of necrotizing granulomatous and vasculitic lesions, accompanied by a prominent infiltrate of T lymphocytes and macrophages [58], suggests that cell-mediated immune mechanisms might be important in the pathogenesis. This belief is supported by the responsiveness of the pulmonary lesions in WG to cyclophosphamide. Pulmonary involvement in SLE is less common than is pleuritis and most often is infectious and secondary to immunosuppression [55–57]. However, “lupus pneumonitis” has been documented [57] and, although the primary lung pathology is often obscured by secondary
processes, some evidence indicates that alveolitis, interstitial edema, and hyaline membranes might result from immune-complex deposition [56].

In essence, the immunopathogenesis of pulmonary injury in pulmonary-renal syndromes is similar to that in the kidney, with evidence for anti-BM, immune-complex, and possibly cell-mediated mechanisms. The effector systems that mediate tissue damage in the lung have been studied extensively [59, 60] and will not be reviewed here. However, insights gained from such studies have aided our understanding and investigation of glomerular injury, especially with regard to the role of oxidants and proteases.

Immunopathogenesis of crescentic glomerulonephritis

Injury to the glomerular capillary wall (GCW) is an important initiating event in the formation of a glomerular crescent. The events that follow the injury are similar to those involving capillary injury and wound healing elsewhere in the body, except that these occur in Bowman’s space instead of in the perivasculary connective tissue. An immunologically mediated inflammatory insult is responsible for GCW injury in most forms of crescentic glomerulonephritis, but similar processes may follow GCW disruption from any cause and probably account for the occasional crescents seen in other noninflammatory glomerular diseases [14].

Humoral immunity. The pathogenetic role of anti-GBM antibodies in human RPGN was unequivocally established 20 years ago when Lerner and colleagues induced linear GBM deposits and nephritis in subhuman primates by passively transferring antibodies eluted from the kidneys of patients with Goodpasture’s syndrome [47]. Studies in animal models induced by active immunization with GBM (Steblay’s nephritis) [61] or passive infusion of heterologous anti-GBM antiserum (Masugi’s or nephrotoxic serum nephritis) also demonstrated the nephritogenic role of anti-GBM antibodies [31], and subsequent studies of anti-GBM nephritis helped to elucidate the mechanisms of GCW injury [31, 62]. Similarly, the injurious effect of immune complexes has been well established in animal models [31, 62, 63] and most likely accounts for the proliferative, exudative, and sometimes crescentic glomerular lesions in postinfectious GN, lupus nephritis, and the other ‘‘immune-complex’’ glomerulonephritides shown in Table 1.

None of the established “humoral” models adequately explains the pathogenesis of glomerular injury in the 40% or more of patients with crescentic glomerulonephritis in which deposits are absent. Morphologic abnormalities, including focal glomerular tuft necrosis and interruptions in the continuity of the GBM [3], suggest that GCW injury is also an important precondition for crescent formation in “deposit-free” crescentic glomerulonephritis, either idiopathic or secondary to vasculitis [64, 65]. Some authors have suggested that cases of “deposit-free” crescentic glomerulonephritis represent examples of transient immune-complex nephritis in which the immunoglobulin deposits are no longer evident at the time of biopsy [66]. An alternate view is that cell-mediated immunity might play a role in the absence of a humoral response.

Cell-mediated immune mechanisms. Although few good models of deposit-free crescentic glomerulonephritis exist, several clues have led investigators to examine the possible role of cell-mediated immune mechanisms. Mononuclear cells can be demonstrated in the hypercellular glomerular tufts and crescents of diseased glomeruli, and macrophages can be grown from such glomeruli obtained from patients and experimental animals with crescentic glomerulonephritis (Table 3). Lymphocytes also have been found in crescentic glomeruli [26, 67], and lymphocyte reactivity to a range of putative antigens has been demonstrated in patients with various types of proliferative glomerulonephritis [68]. Evidence for the participation of T cells in proliferative glomerulonephritis is derived from studies on the autologous phase of experimental anti-GBM nephritis. Although the presence of infiltrating mononuclear cells in glomeruli suggested a delayed-type hypersensitivity reaction, more direct evidence was required because macrophages bear receptors for complement C3b (CR1) and immunoglobulin Fc [69] and can be recruited to an inflammatory focus via the immune adherent and chemotactic properties of C3b and C5a [25, 70] and by adhesion to Fc [71]. To examine this issue, Bhan and colleagues “planted” subepithelial immune complexes containing rabbit anti-GBM IgG or immune complexes containing rabbit anti-BSA IgG in the glomeruli of rats. Endogenous glomerular cell proliferation and macrophage infiltration occurred only after rats received T cells passively transferred from donors specifically sensitized to rabbit IgG [72, 73]. Although these and similar studies [74] showed the potential ability of sensitized T cells to participate in glomerular injury, the model systems were designed to maximize the chances of eliciting a T-cell effect; nonetheless, glomerular damage was modest and did not resemble the severe lesions and functional derangements seen in rats with accelerated autologous-phase anti-GBM nephritis [15, 75, 76]. Also one cannot exclude a synergistic injurious effect of the so-called
lymphocytes from immunized bursectomized chickens migrated to the glomeruli of normal chickens after passive transfer. The same workers subsequently produced glomerular lesions in normal chicks by transferring sensitized lymphocytes derived from the kidneys or spleens of syngeneic chicks immunized with heterologous or isologous GBM in adjuvant [83]. Although the aforementioned studies provide strong circumstantial evidence that cell-mediated immune mechanisms participate in deposit-free crescentic glomerulonephritis, an important question remains. Given that sensitized T cells can only ‘‘see’’ antigen if it is presented by accessory cells bearing the appropriate class-II histocompatibility phenotype, what cells presented the relevant endogenous or exogenous antigens in the studies I have described? Possible candidates might include resident or infiltrating macrophages or activated endothelial cells [84].

In most cases of crescentic glomerulonephritis, the triggering stimulus to the immune response, whether humoral, cellular, or both, is unknown. An exogenous antigen, as in postinfectious glomerulonephritis, can be implicated in some patients, and a history of ‘‘viral-like’’ illness is not uncommon in the other apparently cryptogenic varieties. Such infections might play a role in initiating an autoimmune humoral or cellular reaction, or might contribute an exogenous antigen for immune-complex formation. These questions have been most critically examined in SLE with respect to autoreactivity against DNA and other self antigens, and are reviewed in detail elsewhere in another Nephrology Forum [85].

**Mediation of glomerular capillary wall injury in crescentic glomerulonephritis**

Studies in experimental anti-GBM and immune-complex glomerulonephritis have elucidated several mechanisms by which GCW injury might occur (Fig. 5). These mediation systems have been discussed in detail elsewhere [62, 63] and include: a direct effect of antibody; antibody-directed, complement-mediated injury through the action of leukocytes or the membrane attack complex (MAC); and antibody-directed, complement-independent injury mediated by leukocytes. These systems will be reviewed here only in the context of glomerular inflammation and crescent formation.

**Role of complement and neutrophils.** Complement-mediated chemotaxis and immune adherence of neutrophils are important in acute, exudative glomerulonephritis, in which hypercellularity is limited to the glomerular tuft. This hypercellularity is

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### Table 3. Role of the monocyte/macrophage in crescentic glomerulonephritis (GN)

<table>
<thead>
<tr>
<th>Observation</th>
<th>Disease or model</th>
<th>References</th>
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<tr>
<td>Monocytes infiltrate glomerular tuft</td>
<td>Anti-GBM nephritis</td>
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<td>Serum-sickness nephritis</td>
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<td></td>
<td>Other experimental GN</td>
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<td></td>
<td>Human proliferative GN</td>
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<td>Macrophages comprise up to 30% of cells in crescents</td>
<td>Autologous anti-GBM nephritis</td>
<td>154</td>
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<td>Macrophages grow from explanted glomeruli in increased numbers</td>
<td>Human crescentic GN</td>
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<td>Macrophage depletion abrogates proteinuria and proliferative GN</td>
<td>Experimental and human crescentic GN</td>
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<td>Macrophage depletion inhibits glomerular fibrin deposition</td>
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### Table 4. Response of normal (N) or bursectomized (Bsx) chickens to immunization with bovine GBM

<table>
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<th>Circulating anti-GBM Titer</th>
<th>Linear GBM deposits</th>
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<tr>
<td>Positive (%)</td>
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<td>N</td>
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<td>&gt;2000</td>
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<tr>
<td>Bsx</td>
<td>32</td>
<td>&lt;1000</td>
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</table>

*From Ref. 82; only mean values are shown.

*Average glomerular size in unimmunized chicks; N = 13.6, Bsx = 14.9.

In Bsx the presence of glomerular proliferation and crescents did not correlate with anti-GBM titers or glomerular deposits.
observed in the heterologous phase of anti-GBM nephritis in rabbits and rats [31, 62, 63, 86], and in certain forms of acute, experimental, immune-complex glomerulonephritis [25, 70]. Inflammatory-cell influx and immune adherence are favored when the immune reaction in the GCW occurs in close proximity to the circulation, as in the subendothelial space [25]. Studies of heterologous anti-GBM nephritis in C6-deficient rabbits by Groggel et al showed that complement also can directly injure the GCW through its membranolytic action [87]. This report indicates that the MAC in glomeruli of patients with anti-GBM [88], lupus [89], and poststreptococcal nephritis [90] might have a pathogenetic role. Although neutrophils also have been implicated in autologous anti-GBM nephritis in rabbits (a model of crescentic glomerulonephritis [91]), most clinical and experimental evidence indicates that macrophages play a central role in the GCW injury that leads to crescentic glomerulonephritis, irrespective of whether the initial immune response is predominantly humoral or cellular. This evidence is summarized in Table 3.

Role of macrophages. Increased numbers of blood-borne mononuclear cells, with features of monocytes/macrophages, have been identified in the hypercellular glomerular tufts of patients with proliferative glomerulonephritis [92–94] and in animals with anti-GBM [76, 95–97] and serum sickness [98–100] nephritis. A functional role for macrophages in GCW injury was documented in two studies. Holdsworth et al showed that specific depletion of macrophages prevented both the accumulation of macrophages in glomeruli and the development of proteinuria in a passive, autologous-phase model of anti-GBM nephritis and in acute serum sickness [101]. In contrast to the heterologous phase of anti-GBM nephritis, depletion of complement and neutrophils had no effect in these models [101]. Schreiner and colleagues obtained similar results in rats with accelerated autologous anti-GBM nephritis [75]. In this model x-irradiation prevented glomerular hypercellularity, glomerular influx of mononuclear cells, and proteinuria in the autologous phase, but did not influence heterologous injury. The factors that direct an influx of leukocytes appear to vary according to the model employed. Thus, as I said, cell-mediated immune mechanisms might be important in certain circumstances [72–74, 81, 82], whereas Fc-dependent [71, 102] or complement-mediated [25, 70] immune adherence appears to operate in others. It is also possible, but is as yet unproven in glomerulonephritis, that immune adherence properties of activated endothelial cells [103], or the chemotactic effects of locally produced platelet-activating factor (PAF) [104] and leukotrienes [105] could contribute to the glomerular localization of macrophages.

The mechanisms by which macrophages damage the GCW have not been defined but might be similar to those employed by neutrophils, as shown in acute inflammatory models of glomerular [62, 86] and pulmonary injury [59]. Neutrophil-derived reactive oxygen species, especially hydrogen peroxide, have been implicated in the pathogenesis of proteinuria in experimental glomerulonephritis mediated by polymorphonuclear leukocytes [106, 107]. This effect appears to be at least partly due to the halogenation of glomerular structures by hypohalous acids generated from the reaction of hydrogen peroxide with halide; this reaction is catalyzed by neutrophil-derived myeloperoxidase that binds to the GCW by charge interactions [108]. Macrophages are also an abundant source of toxic oxygen metabolites [59]. Macrophages can also elaborate neutral proteinases [69, 109] capable of digesting GBM matrix components in vitro [110], and can produce a variety of potent inflammatory mediators that have chemotactic and vasoactive properties, such as PAF, thromboxane A₂, and leukotrienes [69, 104, 111]. Activated macrophages therefore are armed to breach the integrity of the GCW; they allow leakage of plasma proteins and clotting factors, including fibrinogen, into the urinary space. Whatever the mechanisms, leukocyte-dependent
GCW injury leads to disruption of the endothelium, breaks in the continuity of the GBM, and the appearance of GBM degradation products in the urine [31, 62].

Considering that intra- and extracapillary fibrin deposition is prominent in crescentic glomerulonephritis [14–16, 112], it is relevant that activated macrophages can produce tissue factor, a phospholipid cofactor that activates the extrinsic coagulation cascade [113, 114], and prothrombinase, a prothrombin-cleaving enzyme or enzyme complex [115]. Hancock and Atkins used this property to identify tissue factor-positive macrophages, together with fibrin, in the hypercellular glomerular tufts and crescents of patients with proliferative GN [116]. I shall discuss the functional importance of this observation in a moment. Although it is not known what stimuli induce macrophage-procoagulant activity (PCA) in glomerulonephritis, in-vitro studies have shown that immunoglobulins, immune complexes, endotoxin, and complement components can fulfill this function [114, 115, 117, 118], especially in cooperation with helper T cells [118].

The role of activated endothelial cells. Activated macrophages also produce interleukin 1 (IL-1) and tumor necrosis factor (TNF, cachectin) [119, 120]. These cytokines stimulate leukocyte migration and adhesion [119–121], and they activate cultured human umbilical vein endothelial cells to express tissue factor-like PCA, leukocyte-adhesion properties [103, 121–123], and a unique activation antigen [124]. However, cultured human endothelial cells also can be activated by other, macrophage-independent, stimuli such as endotoxin [103, 122], as well as by immune complexes and antibodies from patients with SLE [125]. The expression of tissue factor and an endothelial activation antigen was demonstrated recently in endothelia of normal human glomeruli exposed in vitro to IL-1 and endotoxin [126]. Tissue factor also was detected in an endothelial distribution (as well as in macrophages) in glomeruli of patients with proliferative glomerulonephritis; this finding correlated with the presence of fibrin [126]. Certain endothelial cells also manufacture PAF [104, 127], which might provide an additional stimulus for leukocyte aggregation. Thus, in glomerulonephritis, immune reactants might directly trigger endothelial cells to express PCA and leukocyte-adhesion properties, or this might occur in sequential fashion through macrophage-derived IL-1 or TNF. The proposed relationships are shown in Figure 5.

The role of mesangial cells. “Endocapillary” proliferation, that is, hypercellularity of the glomerular tuft, is due in part to mesangial hypertrophy, and possibly hyperplasia, and occurs in several forms of crescentic glomerulonephritis, especially in those associated with mesangial immune deposits, such as SLE and Henoch-Schönlein nephritis. In culture, rat mesangial cells can be activated by several stimuli, including macrophage IL-1, complement, endotoxin, and PAF [128–131]. These cells respond by proliferating [128] and/or by releasing potent inflammatory mediators that include prostaglandins [130–132], reactive oxygen species [129], and mesangial IL-1 [133]. These cells also can produce PAF [134], as well as a neutral protease capable of digesting GBM [135], and a growth factor that resembles platelet-derived growth factor (PDGF) [136]. In addition, mouse mesangial cells in culture produce a cytokine that stimulates macrophages to secrete an IL-1–like factor [137]. Such mediators have several potential effects. Aside from the hemodynamic and tissue-damaging effects of prostanooids, PAF, and toxic oxygen radicals produced by mesangial cells, mesangial IL-1 might stimulate endothelial cells to express PCA and leukocyte-adhesion properties. Also, PDGF-like activity could promote the proliferation of glomerular cells. Thus mechanisms exist by which immune and nonimmune stimuli such as bacterial endotoxin, affecting primarily the mesangium, ultimately could lead to hypercellularity, GCW injury, and local activation of the extrinsic coagulation cascade.

The role of fibrin in crescent formation. I would now like to discuss the long-recognized observation, so graphically illustrated by the case in point (Fig. 2), that fibrin deposition in glomerular vessels and urinary space is common to all forms of necrotizing and crescentic glomerulonephritis [14, 112]. As illustrated in the accelerated autologous anti-GBM model, the earliest indication of impending crescent formation is the appearance of fibrin in Bowman’s space [15, 16]. Careful sequential analysis does reveal, however, that fibrin-related antigens are first detectable within the glomerular tuft [15]. The importance of fibrin deposition in the genesis of a crescent was convincingly shown by Naish, Thomson, and colleagues, who found that defibrination with ancred (a fibrinogen-splitting enzyme from viper venom) effectively prevented the development of crescents and abrogated the decline in renal function in autologous anti-GBM and serum sickness nephritis [138, 139] without inhibiting proteinuria [140] (Table 5). This finding suggests that intraglomerular coagulation does not contribute to GCW injury but is an important signal for the accumulation in Bowman’s space of cells that constitute a crescent. How fibrin thrombi (or other products of coagulation or fibrinolysis) stimulate the formation of a cellular crescent is still unknown, but thrombin is known to be an effective chemotaxin for monocytes [141].

Several counterbalancing procoagulant and anticoagulant factors normally interact to maintain integrity of the vessel wall while preventing formation of a fibrin thrombus on the endothelial surface [142]. Endothelial cells synthesize various procoagulants in vitro, including Factor VIII antigen (von Willebrand factor), Factor V, thrombospodin, and tissue factor, and they can bind Factors IX/IXa and X. They also synthesize anticoagulants such as prostacyclin, heparin-like proteoglycans, and thrombomodulin, as well as fibrinolytic and antifibrinolytic agents such as tissue plasminogen activator (PA) and PA inhibitor. Although there is still much to be learned about the state of individual procoagulant and anticoagulant components in glomerulonephritis, new insights have been gained into some of the stimuli that lead to glomerular fibrin deposits.

The first appearance of fibrin in the glomerular tuft coincides with the influx of tissue factor-positive macrophages in patients with crescentic glomerulonephritis [116] and with the occurrence of measurable PCA in the glomeruli and urine of nephritic rabbits [16]. The nature of the glomerular PCA is complex but, at least initially, the PCA appears to include tissue factor [15, 16, 143]; this finding suggests that coagulation proceeds mainly via the extrinsic cascade. Further evidence that macrophages are important for the development of glomerular fibrin deposits was provided by Holdsworth and Tipping in a passive-autologous model of anti-GBM nephritis in rabbits [144] (Table 6). Glomerular fibrin deposition and PCA could be diminished by...
monocyte depletion and partly restored by monocyte repletion [144]. Cole and colleagues found increased expression of prothrombinase in circulating monocytes of patients with severe proliferative lupus nephritis but not in those of patients with nonrenal lupus or end-stage nephritis [145]. Together, these studies suggest that infiltrating macrophages, in addition to damaging the GCW and allowing the passage of plasma proteins into Bowman’s space, initiate intravascular fibrin deposition by activating the extrinsic coagulation pathway, either directly by producing tissue factor or prothrombinase, or indirectly by activating endothelial cells to express PCA (Fig. 5). The source of PCA responsible for activating extrinsic coagulation pathway components that leak into the urinary space is not yet known (Fig. 6). It could be derived from macrophages that infiltrate Bowman’s space but, if the chemo
tactic stimulus for such migration originates from the fibrin cast, an alternate source of PCA must exist in the urinary space prior to macrophage influx. The source might be tissue factor, released as phospholipid vesicles from injured glomerular cells.

Defective anticoagulant or fibrinolytic mechanisms also might exist in certain forms of glomerulonephritis, and these mechanisms might allow the formation of glomerular micro-
thrombi. Kant et al [146] and Glas-Greenwalt et al [147] have described a subgroup of patients with severe lupus nephritis who have glomerular microthrombi, depressed plasma levels of vascular PCA, and increased levels of PCA inhibitor. Several such patients had reversal of these abnormalities and stabilization of renal function when treated with ancord; the authors attribute this outcome to improved fibrinolysis [147]. Failure of some patients to improve correlated with elevated plasma levels of α2-antiplasmin [146, 147]. In addition, inhibitors of fibrinolysis appear to exacerbate glomerular injury in experimental crescentic glomerulonephritis [76, 148].

Platelets, platelet antigens, and platelet-derived inflammatory products all have been identified in proliferative and exudative glomerulonephritides [149–151]. However, despite the gamut of potential and established means by which platelets might provoke or exacerbate the local inflammatory process and contribute to GCW injury [152, 153], no direct evidence has yet confirmed that platelets participate in crescent formation.

Composition and morphogenesis of glomerular crescents

The composition of a glomerular crescent varies during its metamorphosis. Beginning as a fibrin cast in Bowman’s space, it passes through a predominantly cellular phase to become a fibrous scar (Fig. 6). As late as 1974, it was believed that crescents were composed entirely of parietal epithelial cells undergoing proliferation in response to fibrin in the urinary space [14, 112]. Data summarized in Table 3 later suggested that macrophages comprise the major cellular component of crescents. Current evidence indicates, however, that early crescents contain cells of mixed origin [93, 154–157] together with fibrin, fibronectin and, in some cases, type IV collagen [158], and that these cells are progressively replaced by interstitial-type collagen.

In general, no more than 30% of the cells in a cellular crescent are blood-derived mononuclear cells that have assumed the properties of macrophages. This has been quantitatively shown in human crescentic glomerulonephritis by histochemical staining for nonspecific esterase [156], by analysis of Y-body-positive mononuclear cells in kidneys transplanted from females into male recipients [155], and by the use of monoclonal antibodies that identify macrophage-phenotypic antigens [116, 157]. In contrast, macrophages are prominent in the hypercel-
lar glomerular tufts in diseases in which there is marked endocapillary proliferation, for example, lupus nephritis [159] and essential mixed cryoglobulinemia [94]. These findings are in accord with those of Cattell and Jamieson, who performed experiments in which nephritie kidneys were transplanted into recipient rabbits whose peripheral blood monocytes were pulse-labeled with [3H]thymidine [154]. These authors found that blood-derived monocytes contributed considerably to the early hypercellularity of the glomerular tuft, but their studies showed relatively few labeled monocytes in crescents [154]. In contrast, in separate experiments they demonstrated substantial replication of intrinsic, presumably epithelial, cells [154]. These results were supported by those of Magil, who examined human crescentic glomeruli and found that up to 50% of cells stained positively for cytokeratin, an intermediate filament found exclusively in the cytoskeleton of epithelial cells [156]. In addition, the eventual appearance of interstitial collagen in fibrocel-
lar and fibrous crescents [158] suggests either that local cells acquire the ability to secrete types I and/or III collagen, or that fibroblasts also infiltrate the crescent through breaks in Bowman’s capsule [15, 24].

Factors responsible for stimulating the proliferation of pari-
etal epithelial cells and fibroblasts have not been identified, but again, the macrophage is a prime candidate. Macrophages can produce a variety of growth factors and cytokines that stimulate fibroblast proliferation and collagen synthesis [160]. Although numerically in the minority in crescents, macrophages might exert a major local influence on crescent morphogenesis by
providing the signals for cell replication and collagen synthesis (Fig. 6). Additional factors must be considered, however, because proliferation of intrinsic glomerular cells may occur prior to the influx of monocytes in accelerated anti-GBM nephritis in rats [161].

**Conclusion**

I have attempted to review much, although by no means all, of the relevant data pertaining to the inflammatory response that culminates in GCW injury, crescent formation, and the clinical syndrome of RPGN. While one hesitates to take experimental results painstakingly gathered by others, assemble them according to one’s own point of view, and present them as a model, I believe that the schemes depicted in Figures 4 through 6 serve three main purposes. First, they summarize a large body of clinical and experimental information, and allow us to integrate clinical and experimental observations in crescentic glomerulonephritis and antibody-induced lung injury with certain recent research advances in inflammation and matrix chemistry. Second, they clarify the deficiencies in our current knowledge. Finally, these schemes might help us in identifying points along the inflammatory pathway that are amenable to pharmacologic or immunologic manipulation. Hopefully this information will lead us to devise more specific ways than the use of high-dose corticosteroid or cytotoxic drugs to prevent the activation of macrophages and other inflammatory cells, and perhaps it even will yield the means of neutralizing the effects of soluble mediators released by already activated cells.

**Questions and answers**

**DR. JOHN T. HARRINGTON (Chief, Department of Medicine, Newton-Wellesley Hospital, Newton, Massachusetts):** What is your specific diagnosis in this patient and on what grounds did you make it?

**DR. SALANT:** Clinical information combined with a renal biopsy showing necrotizing and crescentic glomerulonephritis without immune deposits led me to believe that the patient had early Wegener’s granulomatosis. Should the patient have had an open lung biopsy? The clinical spectrum suggested a multisystem disease sufficiently for us to exclude idiopathic deposit-free, crescentic glomerulonephritis and to begin therapy with cyclophosphamide. Had her extrarenal symptoms not resolved so quickly, a lung would have been biopsied. Considering the rapid resolution of this patient’s hemoptysis and pulmonary infiltrate, it seems unlikely that a lung biopsy on presentation would have demonstrated granulomata. At best we might have found necrotizing vasculitis, and I therefore wonder at the diagnostic utility of lung biopsy in such “early” cases. Let me emphasize, however, that open lung biopsy is still the only definitive way to diagnose Wegener’s granulomatosis and, because the treatment is prolonged and hazardous, a biopsy should be performed in all patients in whom the diagnosis is in doubt or when adequate therapy fails to produce a prompt improvement.

**DR. JEROME P. KASSIRER (Associate Chairman, Department of Medicine, Tufts University School of Medicine, Boston):** How would you have proceeded if you had been unable to carry out a renal biopsy? How much did the biopsy results contribute to this particular patient’s management?

**DR. SALANT:** I would have obtained a serum anti-GBM antibody as quickly as possible to exclude Goodpasture’s syndrome. If the antibody test had been positive, we would have promptly treated the patient with plasmapheresis because she fell into the “good prognostic” category of patients with nonoliguric anti-GBM nephritis whose serum creatinine is less than 6.5 mg/dl (Fig. 7). At the same time I would have measured the ANA, serum complement, anti-streptolysin titer, cryoglobulins, and hepatitis Bs because, if the anti-GBM were negative, we would have had to rely on clinical and serologic features to
exclude the systemic immune-complex diseases shown in Table 1. If these tests had been negative, we then could have decided, according to the presence or absence of extrarenal symptoms, whether the patient had vasculitis or idiopathic RPGN (immune-complex or deposit-free) (Table 1, Fig. 7). The problem with the “noninvasive” approach is the delay in obtaining the results of serologic studies. This is especially true of anti-GBM assays. Few nephrologists have access to an indirect immunofluorescence assay, and the shortest turnaround time we have been able to find in a commercial laboratory that runs radioimmunoassays for anti-GBM is 4 to 7 days. As I mentioned before, the nature of the antigen substrate used in the radioimmunoassay is also critically important for achieving the reliability reported by those who have developed these assays [5, 6, 40]. Because of the need for prompt action, and because the need for, efficacy of, and type of treatment varies in each disease (Fig. 7), I believe that renal biopsy, where possible, is the most efficacious procedure in RPGN. In this particular patient, immunofluorescent study of the renal biopsy allowed us to distinguish among the three main causes of pulmonary-renal syndrome (Table 2) and institute specific therapy within hours of her admission.

DR. HARRINGTON: It seems to me that you are using the renal biopsy primarily to exclude the possibility of anti-GBM disease. Assuming that one had a rapid, sensitive, and specific serum assay for anti-GBM antibodies, could you then not eliminate the renal biopsy? Your treatment protocol for immune-negative and immune complex-induced RPGN is identical.

DR. SALANT: Your question is most easily answered by Figure 7. It is true that patients with idiopathic RPGN are treated the same way whether or not they have immune deposits; but most other diseases are treated differently. One should also preface any remarks on the treatment of RPGN with the disclaimer that most recommendations are based on largely uncontrolled data [1, 6–9]. Further, we should moderate our therapeutic aggressiveness according to the extent of renal scarring shown on biopsy. Plasma exchange plus immunosuppressive drugs and steroids are recommended for nonoliguric patients with anti-GBM nephritis who have well-preserved renal function [6, 9], although some might argue that such patients fare equally well with drug therapy alone [20]. Pulmonary hemorrhage usually can be controlled with pulse steroids [1, 29] or plasma exchange [6] irrespective of the level of renal function, and nephrectomy is now rarely, if ever, indicated. Unless the renal biopsy shows only cellular crescents without fibrosis or scarring, dialysis-dependent patients with anti-GBM nephritis who are oliguric are best treated conservatively with dialysis followed by transplantation when anti-GBM titers are no longer detectable by radioimmunoassay.

In patients with granular immune deposits, clinical symptoms and serology usually help distinguish those with systemic forms of immune-complex nephritis from those with primary renal disease complicated by crescentic glomerulonephritis (Table 1). The primary glomerulonephritides can be distinguished from each other by the nature of the deposits on immunofluorescent examination and electron microscopy. Eradication of the infection and supportive care are all that is needed in postinfectious GN, whereas oral steroids, with or without immunosuppressives [7] or initial pulse steroid therapy [1], are the mainstay of treatment in lupus nephritis. Crescentic glomerulonephritis complicating primary immune-complex glomerulonephritis generally responds poorly to treatment, but pulse therapy sometimes is effective. The results with plasma exchange are similar. Pulse steroids and plasma exchange (plus immunosuppressive drugs) are equally effective in idiopathic RPGN without immune deposits [1, 9]. We favor pulse therapy because of its familiarity, simplicity, and cost. In crescentic glomerulonephritis without immune deposits, most patients with extrarenal symptoms have a form of vasculitis such as Wegener’s granulomatosis or microscopic polyarteritis nodosa. These patients are best treated with cyclophosphamide and low-dose steroids [8, 27].

### Table 1: Systemic Immune-Complex Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Biochemical Manifestations</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>hypocomplementemia</td>
<td>rash, arthritis, renal</td>
</tr>
<tr>
<td>Systemic vasculitis</td>
<td>hypocomplementemia</td>
<td>rash, infarcts, renal</td>
</tr>
<tr>
<td>Postinfectious glomerulonephritis</td>
<td>hypocomplementemia</td>
<td>postinfectious symptoms</td>
</tr>
<tr>
<td>Crescentic glomerulonephritis and lung purpura</td>
<td>hypocomplementemia</td>
<td>lung hemorrhage, renal</td>
</tr>
</tbody>
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### Figure 7: Algorithm for the management of rapidly progressive glomerulonephritis

DR. NICOLOAS E. MAIDIAS (Chief, Division of Nephrology, New England Medical Center Hospitals, Boston): We have seen patients who have anti-GBM nephritis but no lung purpura early in their presentation. Later in their course, when the plasma level of anti-GBM antibody has decreased or even become undetectable, lung purpura has become apparent. The question is, what is the relationship between the level of anti-GBM antibody and the development of lung purpura?

DR. SALANT: There is no simple relationship between circulating levels of anti-GBM antibodies and the occurrence or severity of pulmonary hemorrhage. The absence of such a relationship suggests that the nature of the antibody and local factors also are important determinants of lung injury [20, 31]. The phenomenon you describe has been recognized for some time, but its cause is unknown [31]. In some cases the onset of lung purpura has been attributed to superimposed infection or fluid overload in patients with otherwise asymptomatic pulmonary disease [31]. It is also worth noting that pulse steroids are as effective as plasma exchange in controlling lung purpura despite the more rapid disappearance of circulating anti-GBM antibodies with plasmapheresis [20].

DR. DAVID B. BERNARD (Director of Clinical Nephrology, Boston University Medical Center, Boston): It is intriguing that certain therapies work better for some conditions than others, as morphologically similar crescents can develop either in the presence or absence of immune deposits. For example, does the fact that cyclophosphamide is best for Wegener’s granulomatosis and steroids for some forms of idiopathic RPGN allow us to define the most important component of the pathologic process leading to crescent formation in these diseases? Also, what is the current thinking about the place of anticoagulant or thrombolytic therapy in these conditions?

DR. SALANT: In answer to your first question, treatment for crescentic glomerulonephritis remains largely empiric. It is tempting to oversimplify the issue and speculate that pulses of steroids and cyclophosphamide are effective and rational therapy in deposit-free idiopathic RPGN and vasculitis, respectively, because they inhibit cell-mediated immunity. The truth is, high-dose steroids and immunosuppressives are also effective antinfiammatory agents capable of influencing several leukocyte functions, which may be equally or more important in limiting tissue damage than in suppressing an already activated immune response. Accelerated removal from the circulation of pathogenetically important antibodies and inflammatory mediators is probably the main reason why plasma exchange works in some cases of anti-GBM nephritis. However, improvement of mononuclear-phagocyte function and enhanced clearance of circulating immune complexes [162] is a clue that other, less direct, effects of plasmapheresis also might be important. Unfortunately, clinical experience in SLE nephritis indicates that these effects are not of great therapeutic benefit to patients with severe immune-complex nephritis [28].

You asked about anticoagulant therapy. Despite the importance of fibrin deposition in the formation of crescents, anticoagulants, with or without oral steroids and immunosuppressives, have proved much less effective and more harmful than simpler therapy with pulses of steroids and rapidly tapered oral prednisone [1, 9], possibly because fibrin acts early in the pathogenetic pathway. As I noted earlier, initial results in patients with severe lupus nephritis and glomerular thrombi who were treated with ancred are encouraging [146, 147] and merit more controlled studies.

DR. HARRINGTON: You mentioned the results of an anticytoplasmic antibody titer early in this patient’s course. Can that test be used sequentially to determine the efficacy of treatment in patients with Wegener’s granulomatosis?

DR. SALANT: Yes. In one study that looked at this sequentially, anticytoplasmic antibodies were present only during active Wegener’s granulomatosis and not during the inactive phase [11]. The test also proved to be a more sensitive prospective maker of disease activity than did other acute-phase reactants. I should stress, however, that the number of reports and cases is still small.

DR. JOHN DONOHUE (Consultant Nephrologist, The National Renal Unit, The Charitable Infirmary, Jarvis Street Hospital and the Mater Misericordiae Hospital, Dublin, Ireland): What is the presented patient’s prognosis now that she has recovered from the acute episode? Alternatively, what would you have done had she gone on to end-stage renal failure as a result of crescentic glomerulonephritis? Would you have considered her a candidate for transplantation? Finally, is she likely to have a recurrence of her disease at some later stage?

DR. SALANT: An update on 85 patients from the National Institutes of Health (NIH) who were treated with chronic low-dose cyclophosphamide reports a 93% overall remission rate, with an average followup of 4 years [8]. Moreover, about one-third of the NIH patients in remission were followed for an average of 3 years after all treatment was discontinued [8]. Unfortunately, not all long-term studies of treated patients have demonstrated the same degree of success. In series with a high proportion of patients presenting with acute renal failure [54] or advanced renal disease [21], mortality rates of 44% at 3 years [54] and 50% after an average of 5 years [21] were recorded. Relapse on withdrawal of cyclophosphamide occurs in up to 30% of cases, and it is therefore recommended that treatment be continued for 12 to 15 months after induction of complete remission [8]. An attempt should then be made to taper the drug over about 6 months to limit the risk of long-term complications such as hemorrhagic cystitis, leukopenia, leukemia, and lymphoma. Patients with Wegener’s granulomatosis, or any other form of crescentic glomerulonephritis, also are at risk for long-term deterioration of renal function without the recurrence of acute disease [21, 22].

Good results have been reported in several renal transplant recipients maintained on conventional posttransplant therapy (azathioprine and prednisone) [8, 22, 163]. Respiratory symptoms occurred in isolated cases but resolved when azathioprine was replaced with cyclophosphamide [8, 164]; delay in changing therapy was followed in one case by recurrence of Wegener’s nephritis and graft loss [165]. It is premature to formulate strict guidelines for posttransplant therapy, but the following are suggested. Patients should be in stable remission before undergoing transplantation and preferably should not be receiving therapy; the choice of immunosuppressive drugs should be guided by antirejection considerations; cyclophosphamide need be included initially only if it was required before transplantation, but it should be introduced at the first evidence of recurrent Wegener’s granulomatosis. Experience with cyclosporine A in transplant recipients with WG is even more
limited. Dr. Bernard, would you like to describe our recent encounter with such a patient?

Dr. Bernard: We recently had an interesting experience with a patient with Wegener’s granulomatosis who underwent renal transplantation. She had been maintained for some years on chronic hemodialysis, continuously received low-dose cyclophosphamide, and apparently was in remission. At the time of transplantation, cyclophosphamide was discontinued, and prednisone and cyclosporine were used as standard immunosuppressive therapy. About 3 weeks after successful transplantation with normal graft function, a vigorous recurrence of pulmonary hemorrhage occurred, which fortunately responded promptly to reinstitution of cyclophosphamide.

Dr. Madias: Glomeruli of patients with Alport’s syndrome do not react with anti-glomerular basement membrane antibodies. Does the specific defect in the glomerular basement membrane of these patients, which recently was identified by Kleppel et al [166], correspond to the Goodpasture antigen?

Dr. Salant: Yes. The study you mentioned showed that patients from certain cohorts with X-linked dominant familial nephropathy (Alport’s syndrome) lack one of the 3 NC1 glycopeptides (28 kD) that make up the globular domain of type IV collagen in normal human GBM. The epitopes that make up the Goodpasture antigen appear to reside on that peptide [38, 43], and its absence in Alport’s syndrome accounts for the lack of staining of basement membranes by Goodpasture antisera, and for the risk of anti-GBM nephritis developing in normal kidneys transplanted into recipients who have Alport’s syndrome.

Dr. Geetha Narayan (Director, Tri-City Dialysis Center, Medford, Massachusetts): How do you approach patients who have idiopathic disease clinically, but in whom renal biopsy reveals crescentic glomerulonephritis with immune deposits?

Dr. Salant: If a thorough clinical and serologic search for systemic disease, including occult infection, is negative, the patients should be treated the same way as those with idiopathic RPGN without immune deposits (Fig. 7).

Dr. Harrington: Are there any experimental studies using specific antibodies directed against some of the fundamental components important in the genesis of crescents, such as anti-IL-2 receptor antibodies?

Dr. Salant: I know of no studies that have directly examined the effect of such agents on crescent formation, but Kelly and Strom recently inhibited the development of murine lupus by treating young lupus-prone mice with anti-IL-2 receptor antibodies [167]. This treatment probably worked more proximally in the immune response than the events shown in Figures 5 and 6, by inhibiting the proliferation of autoreactive lymphocytes.

Dr. Michael P. Madaio (Division of Nephrology, New England Medical Center Hospitals): In many patients, periglomerular infiltrates of mononuclear cells are prominent. Do these cells have a specific pathogenetic role? Do they have prognostic significance?

Dr. Salant: Not much is known about the role and prognostic significance of periglomerular mononuclear infiltrates. In recent experimental observations by Eldredge and Wiggins, the cells, as though responding to a chemotactic stimulus, appeared to arise from interstitial venules and migrate towards glomeruli at about the same time as the earliest crescents began to appear.

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