J Am Soc Nephrol 10: 664–665, 1999

Sensitized Cells Come of Age: A New Era in Renal Immunology with Important Therapeutic Implications

WILLIAM G. COUSER
Division of Nephrology, University of Washington, Seattle, Washington

This article is the first in a new effort by the editors of *JASN* to translate results of basic research published in the Journal into information of relevance to the clinical nephrologist. So why should the clinician be interested in the observations of Cunningham *et al.* in this issue, that a small series of patients with anti-neutrophil cytoplasmic antibody (ANCA)-positive crescentic rapidly progressive glomerulonephritis (RPGN) exhibit features of delayed-type hypersensitivity in their biopsies (T cells, macrophages, tissue factor, and fibrin)? Let me explain.

It is axiomatic in clinical medicine that better treatment only follows improved understanding of the mechanisms that cause disease. We would all agree that nowhere in nephrology is there a greater need for improved treatment than in that most frightening of nephrologic emergencies, RPGN—a group of diseases for which modern biotechnology still has not found an effective remedy. "Breakthroughs," as the media like to call them, have been few and far between in the treatment of RPGN. In 1999, we still subject these patients to intravenous infusions of highly noxious alkylating agents such as cyclophosphamide, a therapy first used in nephrology in the 1930s (1), and we employ pulse steroids, which have been on the scene now for more than 20 years (2). The observations of Cunningham *et al.* do not so much provide new information we did not know before about RPGN; however, they bring that information together in the context of recent experimental findings to refocus our thinking about the mechanisms that cause RPGN in a way that is likely to significantly change our approach to therapy of these patients.

When I encountered my first patient with RPGN (Goodpasture's syndrome) as an intern in 1966, we stared through the newly acquired fluorescence microscope in amazement at the bright, linear staining for IgG that lighted up every glomerulus in the biopsy, and we had absolutely no idea what it represented. The seminal studies of Lerner, Glassock, and Dixon published a year later finally identified anti-glomerular basement membrane (GBM) antibody as a cause of this disease (3), and thereby connected several decades of previous work by Masugi, Steblay, Dixon, and others to a human renal disease (4–6). Thus dawned the era of renal immunopathology, and with it the systematic search in every biopsy for the deposition of immunoglobulins and complement components which, because they were so readily detectable (even measurable in the serum sometimes), focused all of our attention on the role of the humoral immune system in the pathogenesis of glomerulonephritis. Indeed, the ability to reproduce in animal models most of these patterns of deposits, and to some extent the clinical and histologic features of the human diseases associated with them, supported the view that *only* the humoral component of the immune response was relevant to human glomerulonephritis (7).

Although it had been recognized for more than 50 years that the immune response to most antigens involved cellular as well as humoral immunity, there had been little interest in the renal immunology world in pursuing this mechanism. *In vitro* assays of cell-mediated immunity were few, and far more complex than antibody measurements, and whatever the markers of delayed hypersensitivity were in the biopsy, they did not have the instant appeal of the bright, apple-green deposits of antibody and complement. In 1970 when Rocklin, Lewis, and David used one of the first *in vitro* assays of cell-mediated immunity (the release of macrophage inhibitory factor, or MIF, by lymphocytes in response to a specific antigen) to document the presence of T cells specifically sensitized to GBM antigen in anti-GBM nephritis (8), their suggestion that these cells might play a role in the pathogenesis of this disease was greeted with intense skepticism (7). When we first reported the observation that most patients with idiopathic RPGN lacked antibody deposits and suggested that cell-mediated immunity might be involved (9), a similar skepticism prevailed. In this climate, only the most diligent of an intrepid group of investigators continued to pursue the topic—Bhan, Bolton, and Schreiner among them (10–12). Their findings, largely that glomerular hypercellularity could be induced by sensitized T cells without much functional compromise, were positive but not persuasive. Most textbooks of the 1990s give little or no attention to cell-mediated immunity as a pathogenetic mechanism in glomerular disease while pages are occupied discussing antibody-related mechanisms.

But now we have entered a new and exciting era in renal immunology, and the article by Cunningham *et al.* connect the beginnings of that era to human disease. In the past 4 years, compelling evidence has emerged, much of it from this same group in Melbourne, that sensitized cells—totally independent of antibody—can cause severe glomerular injury and are likely

Received December 3, 1998. Accepted December 19, 1998.
Correspondence to Dr. William G. Couser, UW Division of Nephrology, Box 356521, BB1265 Health Sciences Building, 1959 NE Pacific Street, Seattle, WA 98195. Phone: 206-543-3792; Fax: 206-685-8661; E-mail: wgc@u.washington.edu

1046-6673/1003-0664$03.00/0
Journal of the American Society of Nephrology

the principal mediators of crescent formation. In 1994, Rennke showed that granulomatous, crescentic glomerulonephritis (like that seen in ANCA-positive patients) could be induced by T cells sensitized to an otherwise benign antigen planted in the glomerulus (13). Other studies have shown that crescents can be eliminated by T cell depletion without effects on antibody production (14), and that mice with intact cell-mediated immunity but absent humoral immunity develop crescentic glomerulonephritis equivalent to that seen in normal animals (15,16). Taken together, these studies more than fulfill Koch's postulates and firmly establish the role of cell-mediated immune mechanisms in the pathogenesis of experimental crescentic glomerulonephritis.

Do the observations of Cunningham *et al.* prove that cell-mediated immunity alone is responsible for glomerular injury in ANCA-positive RPGN in humans? Obviously not, and evidence that ANCA antibodies themselves play a role certainly exists (17). However, the markers of antibody-mediated disease such as immunoglobulin and complement deposits are entirely absent in these patients, whereas the markers of cell-mediated immunity, as Cunningham's article clearly documents, are very prominently present. If it looks like a duck and walks like a duck . . .

But back to the clinician. Does it make any difference clinically which arm of the immune response causes RPGN? Perhaps not today, but it certainly will tomorrow. Consider the dramatic beneficial effects that have now been documented in experimental glomerulonephritis with treatments that selectively suppress the cell-mediated response without altering antibody deposition. Examples include the infusion of interleukin-4 (IL-4) and IL-10 (18), inhibition of MIF (19), and use of agents such as deoxyspergualin, which selectively inhibits cell-mediated immunity (20). Other agents with effects primarily on the cell-mediated immune response are now available or nearly so—for example, IL-2 receptor antagonists and CD40 ligand—but have not yet been tried in glomerular disease. Even T cell pheresis may have promise (21).

As someone who has worked on mechanisms of glomerular disease for a long time, it is frankly embarrassing to discuss the treatment of RPGN in 1999 and confront the fact that the current therapies are not only toxic and relatively ineffective but largely relics of the rather ancient past. But as the century closes, I believe the era of IV cyclophosphamide and pulse steroids is drawing to an end as well. On the horizon is a battery of new, less toxic, and likely more effective therapies that derive from the recognition that some of the most severe forms of glomerulonephritis are probably mediated largely by cells and not by antibodies. That is why the article by Cunningham *et al.* is important. Read it, and think about it. The concept it addresses is truly a long-overdue breakthrough.

References

1. Baldwin DS, McLean PG, Chasis H, Goldring W: Effect of nitrogen mustard on clinical course of glomerulonephritis. *Arch Intern Med* 92: 162–167, 1953
2. Bolton WK, Couser WG: Intravenous pulse methylprednisolone therapy of acute crescentic rapidly progressive glomerulonephritis. *Am J Med* 66: 495–502, 1979
3. Lerner R, Glassock R, Dixon F: The role of anti-glomerular basement membrane in the pathogenesis of human glomerulonephritis. *J Exp Med* 126: 989–1004, 1967
4. Masugi M, Sato Y, Murasawa S, Tomizuka Y: Über die experimentelle Glomerulonephritis durch das spezifische anti-Nierenserum. *Trans JPN Pathol Soc* 22: 614–628, 1932
5. Steblay R: Glomerulonephritis induced in sheep by injections of heterologous glomerular basement membrane and Freund's complete adjuvant. *J Exp Med* 116: 253–272, 1962
6. Hammer D, Dixon F: Experimental glomerulonephritis II immunologic events in the pathogenesis of nephrotoxic serum nephritis in the rat. *J Exp Med* 117: 1019–1031, 1963
7. Dixon FJ: What are sensitized cells doing in glomerulonephritis? *N Engl J Med* 283: 536–537, 1970
8. Rocklin R, Lewis E, David J: *In vitro* evidence for cellular hypersensitivity to glomerular basement membrane antigens in human glomerulonephritis. *N Engl J Med* 283: 497–501, 1970
9. Stilmant MM, Bolton WK, Sturgill BC, Couser WG: Crescentic glomerulonephritis without immune deposits: Clinicopathologic features. *Kidney Int* 15: 184–195, 1979
10. Bahn AK, Schneeberger EE, Collins AB, McCluskey RT: Evidence for a pathogenic role of a cell-mediated immune mechanism in experimental glomerulonephritis. *J Exp Med* 148: 246–260, 1978
11. Bolton WK, Tucker FL, Sturgill BC: New avian model of experimental glomerulonephritis consistent with mediation by cellular immunity. *J Clin Invest* 73: 1263–1267, 1984
12. Unanue ER, Schreiner GF, Cotran RS: A role of mononuclear phagocytes in immunologically induced glomerulonephritis. In: *Immune Mechanisms in Renal Disease*, edited by Cummings N, New York, NY, Plenum, 1983, pp 443–451
13. Rennke HG, Klein PS, Sandstrom DJ, Mendrick DL: Cell-mediated immune injury in the kidney: Acute nephritis induced in the rat by azobenzenearsonate. *Kidney Int* 45: 1044–1056, 1994
14. Huang XR, Holdsworth SR, Tipping PG: Evidence for delayed type hypersensitivity mechanisms in glomerular crescentic formation. *Kidney Int* 46: 69–78, 1994
15. Huang XR, Tipping PG, Shuo L, Holdsworth SR: Thy1 responsiveness to nephritogenic antigens determines susceptibility to crescentic glomerulonephritis in mice. *Kidney Int* 51: 94–103, 1997
16. Li S, Holdsworth SR, Tipping PG: Antibody-independent crescentic glomerulonephritis in μ-chain deficient mice. *Kidney Int* 51: 672–678, 1997
17. Jennette JC, Falk RJ: Pathogenesis of the vascular and glomerular damage in ANCA-positive vasculitis. *Nephrol Dial Transplant* 13[Suppl 1]: 16–20, 1998
18. Tipping PG, Kitching AR, Huang XR, Mutch DA, Holdsworth SR: Immune modulation with interleukin-4 and interleukin-10 prevents crescent formation and glomerular injury in experimental glomerulonephritis. *Eur J Immunol* 27: 530–537, 1997
19. Lan HY, Bacher M, Yang N, Mu W, Nikolic-Paterson DJ, Metz C, Meinhardt A, Bucala R, Atkins RC: The pathogenic role of macrophage migration inhibitory factor in immunologically induced kidney disease in the rat. *J Exp Med* 185: 1455–1465, 1997
20. Nikolic-Paterson DJ, Kerr PG, Lan HY, Tesch GH, Atkins RC: Deoxyspergualin: A new immunosuppressive drug for the autoimmune disease. *Nephron* 70: 391–396, 1995
21. Furata T, Hotta O, Yusa M, Horigome I, Chiba S, Taguma Y: Lymphocytopheresis to treat rapidly progressive glomerulonephritis: A randomized comparison with steroid-pulse treatment. *Lancet* 352: 203–204, 1998