Is Complement Alone Capable of Inducing Glomerular Injury in Passive Heymann Nephritis?

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Dear Sir,

A popular concept envisages complement activation by subepithelial glomerular immune deposits, without cellular involvement, as a potent mechanism of glomerular injury [1, 2]. Formation of the membrane attack complex (MAC) on the surface of the glomerular epithelial cells is thought to be the decisive event [3, 4]. We report that deposition of complement (C3) and MAC in the absence of inflammatory cells is not sufficient to induce proteinuria in passive Heymann nephritis (PHN). PHN was induced in Wistar rats by intravenous injection of sheep anti-brush border antigen (F $\times$ 1A, 60 mg Ig/100 g body weight); onset of proteinuria was seen on day 3. A group of 8 rats was simultaneously depleted of peripheral monocytes (M) and polymorphonuclear leucocytes (PMN) by injecting rabbit anti-cell antiserum twice daily intraperitoneally (20 mg Ig/injection). This anti-cell (M + PMN) antiserum had been raised in rabbits by immunizing with rat peritoneal M. It was absorbed with rat erythrocytes, thymic cells and lymphnode cells. Depletion was commenced 12 h before induction of nephritis and continued for 4 days. The nephritic control consisted of 8 rats given normal rabbit globulin instead of anti-cell globulin. The results are summarized in table I. Highly effective M and PMN depletion was achieved without reduction of serum C3 levels.

Immunofluorescent studies on day 4 revealed no differences in deposition of sheep IgG, rat C3 and MAC. Proteinuria was significantly decreased by cell depletion. We interpret these findings to mean that besides complement monocytes/macrophages are essential for inducing glomerular injury in PHN. This latter conclusion appears justified as, although PMN depletion was also achieved, it has been convincingly demonstrated that PMN are not involved in PHN [1]; whereas M have not been adequately studied until now. Participation of lymphocytes

Table I. Effect of PMN and M depletion in passive Heymann nephritis

Peripheral blood cell count, cells/mm³

Control nephritic (n = 8) PMN, M depleted (n = 8)

PMN M Ly PMN M Ly

(Ly) is unlikely because (1) the time interval studied is too short for induction of a cell-mediated Ly response; (2) specific anti-PMN antiserum alone also transiently lowers the number of

peripheral Ly [5], and (3) cyclosporine A treatment had no effect in PHN [Dr. Thaïss, personal communication].

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In another nephritis model hallmarked by subepithelial deposits inflammatory cells were also clearly shown to be involved, although the influx of cells in glomeruli was very low [6]. Studies in the early stages of membranous nephropathy in humans have shown that proteinuria is independent of the presence or absence of MAC in immune deposits [7]. Taking all these findings together, the idea of a sole role for complement in glomerular immune injury involving subepithelial deposits should be reconsidered. 7

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