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EDITORIAL REVIEW

Macrophages in acute glomerular inflammation

Blood monocytes migrate into tissues to form a system of phenotypically diverse macrophages, whose functions range from degradation of biological debris to mediation of aggressive inflammation [1]. Macrophages are frequently present in glomeruli in acute proliferative types of human and experimental glomerulonephritis (GN). This article will focus on recent developments in our understanding of macrophage involvement in acute GN, with emphasis on *in vivo* studies on mechanisms of macrophage infiltration, the phenotype of macrophages, and the role of macrophages in acute glomerular inflammation. Earlier studies which demonstrated the presence of macrophages in glomerular lesions, and those more recently advocating a role for macrophages in chronic glomerular scarring will not be discussed.

Mechanisms of macrophage infiltration

Blood monocytes accumulate in glomerular capillary lumens, differentiate and infiltrate into the mesangium and, where there are ruptured capillaries, migrate into Bowman's space. The mechanisms involved are less well understood than those for neutrophils, but as for neutrophils, require margination and attachment to endothelium and movement along chemotactic gradients [2]. The sequential expression of different adhesion molecules and chemotactic agents are important factors in determining the predominant leukocyte type present at different phases of the inflammatory response.

Adhesion molecules

Adhesion molecules have an important role in leukocyte infiltration. Their expression and regulation in the kidney have recently been reviewed [3, 4]. Macrophages express beta 2 leukocyte integrins (LFA-1, CR3 and p150/95), the beta 1 integrin VLA-4, and L-selectin which interact with ligands on endothelium. The endothelial ligands which appear important in macrophage trafficking are VCAM1 and ICAM-1 [5] and other as yet unidentified ligands for beta 2 integrins. While many of these interactions also affect neutrophil infiltration, interaction between VLA-4 and VCAM appears to be selective for macrophages [3]. The change from a predominant neutrophil infiltrate to a macrophage infiltrate, which starts approximately six hours after injury, is associated with cytokine-induced changes in adhesion molecule expression [5], and extravasation of monocytes may be associated with further changes in integrin expression [6].

The role of these molecules in glomerulonephritis is currently a major focus of research, and will be clarified further by the recent availability of new antibodies and molecular biological reagents.

The localization of adhesion molecules in rodent glomeruli relevant to experimental models of glomerulonephritis has recently been reviewed [3], and is different from that found in humans (see below). ICAM-1 and VCAM expression is found in the mesangium in the murine glomerulus, and ICAM in glomerular endothelium, podocytes and Bowman's capsular cells in the rat. There are several recent studies on the vital role of these molecules in the induction of glomerular injury. In heterologous nephrotoxic nephritis, neutrophil infiltration and proteinuria was dependent on leukocyte B1 and B2 integrins and glomerular expression of ICAM-1 and probably VCAM1 [7]. Renal arterial perfusion with TNF, or TNF antibodies showed that this enhanced expression of ICAM1 and VCAM1 was induced by TNF (IL-1 had no effects in the model). The authors speculated that the enhanced expression of ICAM-1 and VCAM-1, if persisting into the autologous phase, might be mechanisms for macrophage recruitment. There are now published data on adhesion molecule expression in macrophage-dependent GN. Kawasaki et al [8] and Nishikawa et al [9] have reported up-regulation of ICAM-1 in the glomeruli of WKY rats during nephrotoxic nephritis, associated with a substantial increase in monocytes expressing LFA-1. Treatment with monoclonal antibodies against rat ICAM-1 or LFA-1 prevented development of proteinuria, monocyte influx and subsequent crescent formation, demonstrating the crucial role of these adhesion molecules in monocyte accumulation, and again confirming the role of macrophages in glomerular injury. LFA-1 and CR3 expression are also present in infiltrating macrophages in anti-Thy1 nephritis (E. de Heer, personal communication). The role of both ICAM-1 and VCAM is supported by the finding of enhanced expression in murine lupus nephritis [3, 10]. In addition, *in vitro* inhibition of monocyte binding to cytokine-stimulated mesangial cells by anti-ICAM-1 antibodies [11] has been demonstrated. *In vitro* monocyte binding to glomerular endothelial cells was inhibited by antibodies against L-selection [12].

In humans ICAM-1 expression is present on normal glomerular endothelium [13–15], and induction is reported on parietal epithelium and mesangium in diverse types of GN [15]. Conversely, VCAM1 is present on normal parietal epithelium [15–17]. In the study of Bruijn and Dinklo [15] this molecule was reported on capillary walls and mesangium in types of human GN known to be associated with macrophage infiltration such as cryoglobulinemia, lupus nephritis, and Wegeners, but not in membranous nephropathy. These recent studies begin to show how cytokine-induced changes in specific adhesion molecules affect macrophage recruitment, an area of glomerular research where rapid progress can be expected.

Although *in vitro* cytokines are the most potent inducers of adhesion through activation of leukocytes and endothelium, *in*

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vivo changes in capillary flow by vasoactive mediators such as histamine, platelet activating factor (PAF), eicosanoids, endothelin, and possibly nitric oxide may also favor the arrest and margination of leukocytes. Chemotactic agents and T cell-mediated reactions are also essential components in the accumulation of macrophages in glomeruli.

Chemotaxis

Macrophage chemoattractant protein 1 (MCP-1) is a recently described specific macrophage chemotactic agent, expressed by a variety of cell types, and stimulated by cytokines [18]. This protein also regulates adhesion molecule expression in monocytes [19]. A potent *in vivo* role is suggested by production of macrophage infiltrates on intradermal injection [20] and the effects of specific antibodies on immune complex-induced lung injury [21]. MCP-1 is produced by cytokine-stimulated human [22, 23] and rat [24] mesangial cells, and has been detected in nephritic glomeruli in accelerated nephrotoxic nephritis (A. Rees, personal communication). *In vitro*, mesangial cell MCP-1 is increased by Fc receptor binding to preformed IgG immune complexes [25], suggesting a mechanism for the previously reported Fc dependence of macrophage infiltration in autologous nephrotoxic nephritis [26]. T cells are also a potential source of MCP-1 (see *Cell mediated immunity*). Of other possible chemoattractants, complement does not appear to be involved in glomerular macrophage infiltration [26], and defibrination while abrogating crescent formation, does not prevent intraglomerular macrophage accumulation. A lipid chemoattractant released by nephritic glomeruli has been reported [27] but is as yet uncharacterized. The role of chemotactic cytokines has yet to be defined, as does the contribution of eicosanoids, platelet-derived growth factor (PDGF), thrombin, granulocyte-macrophage colony stimulating factor (GMCSF) and PAF.

Kinetics

In acute macrophage-dependent GN macrophage influx begins approximately six hours after injury, which is similar to macrophage infiltration at other inflammatory sites [1]; the infiltrate peaks at three and four days and slowly declines, persisting for several weeks in some models. As in granulomas induced by immunological stimuli the infiltrate is maintained by the longevity of the macrophages and possibly some ingress of new monocytes, but with little proliferation, as the proliferative rate of inflammatory macrophages is very low [1], and most local proliferation in nephritic glomeruli occurs in intrinsic glomerular cells [28, 29]. Little is known of the fate of these macrophages, that is, whether they die *in situ*, or emigrate. There is evidence suggesting migration of activated macrophages into the periglomerular interstitium [30]. The macrophage kinetics in human GN are unknown and cannot be accurately assessed. Biopsy findings in diffuse endocapillary GN of post-streptococcal type suggest a possible life span of around three months [31].

Two other situations where macrophages are found in glomeruli are firstly as a transient influx (lasting approximately 24 hours) following systemic macrophage mobilization [32, 33] and secondly in the normal glomerulus. This small population of resident macrophages was first described in the rat glomerulus [34], but is most probably also present in humans [35, 36]. The turnover time for this population is about four days [37, 38]. Its role is unknown.

Cell mediated immunity

T cells have a key role in autoimmune diseases [39]. Despite evidence for this in immune interstitial nephritis [40], until recently there have been few studies on T cell involvement in GN [41–43]. Small numbers of T cells are now confirmed in both experimental [44] and human GN [45–48]. In experimental antiglomerular basement membrane (GBM) GN the timing of T cell infiltration and the production of lymphokine have suggested a role for T cells in induction of macrophage infiltration [44–50]. In this respect, it should be noted that T cells are also a source of MCP-1. CD 8 cell depletion by monoclonal antibodies in this model in the WKY rat, a highly susceptible strain which develops a severe crescentic GN, resulted in complete amelioration of proteinuria and reduction in histological lesions [51]. The most interesting aspect of this study was that depletion did not affect the early phase of macrophage infiltration, but only from three days onwards, which suggests different mechanisms operating at different stages of macrophage infiltration. The authors were unable to determine whether the CD 8 positive cells targeted were T cells or NK cells. An essential cell-mediated component has also been demonstrated in the autoimmune nephritis in MRL-lpr mice [52]. These recent results, which are strongly suggestive of an important role for cell-mediated immunity in some types of GN, should provide a further impetus to studies in this area.

Macrophage phenotype

Macrophage activation occurs through a complex multistep process, regulated by a large number of extracellular signals [53]. In infiltrating macrophages this produces a mixed population of responsive, primed and activated macrophages whose heterogeneity is compounded by the diversity and transience of activation. There are objective markers for these differing phenotypes; assessment of some of these in GN shows a high proportion of primed or activated macrophages. They express Class II MHC antigens [54, 55], have an enhanced respiratory burst [55, 56], secrete cytokines [57, 58], plasminogen activator [59] and characteristic eicosanoids [55], and generate nitric oxide [60], a recently identified product of activated macrophages. The macrophages in crescentic GN are also of activated type as demonstrated by their high Class II expression and reaction with monoclonal antibody ED3 [61], and Ram II expression in the rabbit [62]. In human disease, a significant proportion of cells expresses IL-2R [48]. The regulation of macrophage activation in glomerular inflammation may be explained by generation of extracellular signals such as cytokines, CSFs, MCP-1, PAF and prostaglandins, all of which have been identified in nephritic glomeruli or cultured glomerular cells, although which of these factors are involved *in vivo* is uncertain. In murine lupus nephritis a role for CSF-1 is suggested by the detection of enhanced CSF-1 mRNA expression by glomeruli in the early phase of the nephritis, when macrophage influx is a prominent feature [63]. Of particular interest in this study was evidence for a change in glomerular macrophage phenotype with progression of disease, with macrophages isolated from the early preproteinuric phase showing CSF-1 dependent proliferation and differentiation. Perhaps the

most important macrophage activator, γIFN, has not been demonstrated in GN, although its presence is suggested by the ameliorative effects of anti-γIFN antibodies in experimental lupus nephritis [64], and the recognition of T cell infiltration in the early phases of GN. In normal glomeruli a considerable proportion of the resident macrophages is also of activated phenotype expressing MHC Class II antigens and capable of antigen presentation [65]. Increased Class II expression can be induced *in vivo* in this population by administration of γIFN [66].

Role of macrophages in glomerulonephritis

In this section of the review experiments which have identified macrophages as mediators of glomerular injury will be described, followed by discussion of the effector mechanisms that have been investigated in macrophage-dependent GN, and the possible role of macrophages in resolution of glomerular inflammation.

Macrophages mediate glomerular injury

This was first demonstrated in a model of accelerated (autologous phase) nephrotoxic nephritis in the rat [67], where macrophage depletion by irradiation markedly reduced proteinuria. Depletion by antimacrophage sera demonstrated similar macrophage-dependent injury in acute serum sickness [68, 69] and passive autologous nephrotoxic nephritis [68] in rabbits; in macrophage-depleted animals injury was partly restored by macrophage repletion [70]. The injury in these models appears to be entirely macrophage dependent, and they are therefore extremely useful systems for defining the effects of macrophages in GN. However, two important points must be recognized: firstly, in other models, and almost certainly in most human GN, the mediators of injury are multiple with evidence for a macrophage component in combination with other mediators, including complement and neutrophils [71, 72]; secondly, the index of injury is usually proteinuria. Although this is the most quantitative measure of injury available, its structural basis [73] is still uncertain, and it is only one component of glomerular injury. There is as yet little information on the effects of macrophages on other aspects of the inflammatory response and its sequelae.

Effector mechanisms

Apart from their established role in phagocytosis [74], which is almost certainly an important function of macrophages in GN, macrophages are effector cells through their secreted products of which more than a hundred are so far known. Only a small proportion of these have been studied in macrophage-dependent GN, and as many are also produced by other cell types, determining the source of these products is a complex task. Enzymes, oxygen radicals, PAF, coagulation products, eicosanoids, and most recently, nitric oxide have been studied to varying extents. They can somewhat arbitrarily be divided into factors which might (1) induce tissue injury; (2) participate in crescent formation; (3) stimulate reactive proliferative or paracrine responses in glomerular cells; and (4) mediate hemodynamic changes. Clearly, some factors may have several roles.

Factors inducing tissue injury. In vitro, monocyte neutral proteinase is a highly effective degrader of GBM, severalfold more potent than the neutrophil enzyme [75]. There are, however, scant *in vivo* data. In one study, *in vivo* administration of a protease inhibitor in accelerated nephrotoxic nephritis clearly reduced proteinuria, although the authors emphasized that this was not necessarily through direct interference with enzymes digesting GBM [76]. A possible role has been suggested in the removal of glomerular immune complexes, and this has been achieved by *in vivo* administration of a number of proteolytic enzymes [77].

The evidence that macrophage-derived reactive oxygen species effect glomerular injury is indirect, in contrast to strong evidence for this mechanism in neutrophil-mediated glomerular damage. Two pieces of evidence suggest a role: one is the demonstration of macrophage-dependent oxygen radical damage in immune complex lung injury [78] and the second is the high level of superoxide production in macrophages isolated from nephritic glomeruli in rat acute *in situ* immune complex GN [55] and rabbit accelerated nephrotoxic nephritis [56]. Nitric oxide (NO) is a potent effector molecule produced by activated macrophages [79, 80]. In these cells it is synthesized from L-arginine through the action of an inducible nitric oxide synthase (NOS), recently characterized as a cytochrome P450 type hemoprotein [81]. NOS induction, which requires activation of macrophages by cytokines [82, 83] or bacterial products [84], causes prolonged release of NO. The high reactivity of this transient molecule with complexing to iron-containing groups in target cells [85, 86] accounts for much of the cytostatic effects of activated macrophages. In addition, studies in neutrophils suggest that in leukocytes the combination of NO with simultaneously formed reactive oxygen species, forms further toxic radicals such as peroxynitrite anion [87, 88]. Synthesis of NO by glomeruli has been demonstrated in several experimental models of GN in the rat [89–92] (Table 1), and its role in glomerular pathology recently reviewed [93]. All these models have a glomerular macrophage infiltrate. At least in Heymann nephritis, depletion studies show macrophages are the major source of NO [91]. Elevated urinary excretion of nitrite and nitrate is also found in nephritic animals, but this reflects systemic activation by foreign antigen, most probably through induction of NOS in antigen processing macrophages, and not renal synthesis [94]. Normal rat glomeruli do not produce basal NO, as measured by *ex vivo* nitrite generation, but can be induced to produce small amounts by high dose LPS—this effect being due to stimulation of the resident macrophage population [92]. NO may be an important effector of macrophage-dependent GN. It has already been implicated in experimental immune complex injury in the lung [95], and there is preliminary evidence for effects on the ultrafiltration coefficient in acute nephrotoxic nephritis [96]. Further studies may reveal that this pathway is one of the thus far elusive mechanisms by which macrophages mediate glomerular injury. Certainly the NO levels in severe models of GN where a substantial macrophage infiltrate is present are of the order of those inducing cytostatic and cytotoxic changes *in vitro*, and we now have evidence from immunocytochemistry that the inducible form of NOS found in macrophages is present in glomeruli in acute *in situ* GN induced by cationized IgG (**Note added in proof**). Other properties of NO suggest a possible role in leukocyte infiltration [97], thrombosis [98], hemodynamic changes [99, 100] and proliferation [101] in GN.

Table 1. Glomerular NO synthesis in rat models of experimental glomerulonephritis

Model	Max. basal NO_2^- levels *nmol/2000 gloms/48 hr*	Macrophage infiltration *cells/glomerulus*	Effect of irradiation	Reference
Accelerated nephrotoxic nephritis	158 ± 8	94 ± 18	ND	[89]
In situ GN, induced by cationized HuIgG	48.8 ± 22.8	381 ± 64	ND	[90]
Active Heymann nephritis	7.1 ± 1.4	32 ± 6	Inhibited	[91]
Anti-Thy 1.1 GN				
mesangiolytic phase	8.4 ± 1.8	60 ± 15	ND	[92]
mesangial proliferative phase	1.6 ± 0.4	13 ± 1		
Normal glomeruli	<1.5	12	None	[92]
	6.2 ± 0.3 (LPS 100 μg/ml)		Inhibited	

ND is not done.

Crescent formation. The composition of crescents has fascinated renal morphologists and clinicians alike, and some controversy still surrounds this subject, for the mixture of mononucleated cells accumulating in Bowman's space cannot be characterized by morphology alone. Summarizing the results from *in vitro* culture of crescentic glomeruli, enzyme histochemistry, kinetic studies with bone marrow and proliferating cell labeling, and monoclonal antibodies, it is certain that crescents are a mixture of glomerular epithelial cells and macrophages. Which cells predominate, whether this varies with the age of the crescent, and whether the macrophage infiltrate comes entirely from within the glomerular capillaries are still points for discussion, as are possible differences in the composition of crescents in different diseases, and whether the epithelial cells are of parietal or visceral origin. Most of these concerns await answers. However, there is good evidence that parietal epithelial cells are the most likely source of the epithelial component for firstly, cytokeratin expressed in parietal but not visceral epithelium is expressed in crescentic cells [102], and secondly only parietal epithelial cells show a significant proliferative capacity, as shown by tritated thymidine incorporation in explanted glomeruli [103] and *in vivo* in experimental nephrotoxic nephritis [104]. The stimuli to epithelial cell proliferation have not been extensively studied. Macrophage conditioned medium, epidermal growth factor [105] and thrombin [106] stimulate proliferation in cultured glomerular epithelium, but platelet-derived growth factor does not [105]. It is surprising that fibrin and its products have not been investigated *in vitro*.

The essential role of fibrin deposition in crescent formation and the anticoagulant and defibrinating experiments which have lead to this conclusion have been recently reviewed by McClusky and Andres [107]. In macrophage-dependent GN, fibrin deposition appears to depend on the presence of the macrophage infiltrate, through enhanced expression of macrophage procoagulant activity [59, reviewed in 108]. It is still unclear whether fibrin formation within Bowman's space is the essential trigger, or whether intraglomerular fibrin also can stimulate crescent formation. Capillary rupture is another essential factor. How these breaks occur are unknown, but weakening through the direct action of antibody, activity of macrophages, and increases in intracapillary pressure can all be invoked. The importance of pressure effects is suggested by the way in which hypertension can transform a mild form of nephrotoxic nephritis into severe disease with glomerular thrombosis and crescent formation [109]. The experimental evidence provides a basis for the following view of crescent formation: activation of monocytes in glomerular capillaries by cytokines and T cells causes injury and generation of macrophage and possibly endothelial procoagulants; breaks in the capillary wall, reflecting the severity of the inflammatory reaction allow egress of fibrin and macrophages into Bowman's space. Once this occurs, there is further fibrin deposition and macrophage recruitment through similar mechanisms, and a reactive proliferation of parietal epithelium. Later, a collagenous scar replaces the acute inflammatory tissue.

Factors stimulating responses in intrinsic glomerular cells. There are *in vivo* experiments which suggest that macrophage infiltration stimulates mesangial proliferation. In an elegant study of proliferation in acute serum sickness, Hunsicker et al [110] found that increased thymidine-labeling in glomeruli occurred subsequent to the macrophage influx, and enhanced outgrowth of mesangial cells has been observed in glomeruli explanted from nephritic rat kidneys at the height of macrophage infiltration [111], prevented by prior *in vivo* macrophage depletion [112]. Macrophages synthesize several mitogens known to affect mesangial cell proliferation *in vitro*. *In vivo*, expression of platelet-derived growth factor [113, 114] and fibroblast growth factor [115] have been reported in mesangial proliferation, but the source of these mitogens has not been determined.

Cytokines are implicated in the role of macrophages in GN through their ability to alter a multitude of cellular functions, including the macrophage functions referred to in this review, and functions of intrinsic glomerular cells. They can therefore have effects on leukocyte infiltration, proteinuria, mesangial proliferation and matrix production. Although increased expression of many cytokines has been demonstrated in GN, the source and *in vivo* role of most has not been determined, and this review will focus on *in vivo* studies which suggest macrophages as a source of cytokines in GN. TNF [reviewed in 116] has the strongest association with macrophage infiltration. Macrophages isolated from the glomeruli of MRL/*lpr* mice express TNF mRNA, and synthesize TNF [117]. In accelerated nephrotoxic nephritis not only can the isolated glomerular

macrophages account for TNF production in nephritic glomeruli [58], but anti-TNF antibodies reduce proteinuria in a dose-dependent manner, and reduce glomerular necrosis [76]. Macrophages are also a source of IL-1 in the same models [57, 118, 119], and treatment of accelerated anti-GBM GN in the rat with IL-1 receptor antagonist has recently been reported [120]. Although the effects on interstitial inflammation and renal function were dramatic, the effect on proteinuria and acute glomerular lesions was less marked. TGF beta has recently been shown to have a significant role in the pathogenesis of anti-Thy 1.1 [121]; the pattern of TGF beta immunostaining in glomeruli suggests that macrophages are possibly the predominant source. TGF beta mRNA has been extracted from macrophages isolated from glomeruli in accelerated nephrotoxic nephritis, with results suggesting these cells as the predominant source in this model [122].

Glomerular hemodynamics. Acute glomerular injury is associated with acute, reversible falls in glomerular filtration rate and renal plasma flow. Enhanced glomerular eicosanoid synthesis, which has been demonstrated in various forms of GN, has a major role in these hemodynamic changes [reviewed in 123]. The most frequent profile is that of acute initial production of lipoxygenase products, with after some hours a more sustained elevation of cyclooxygenase products. Depletion experiments suggest that infiltrating leukocytes are a major source of some of these products, particularly LTB4 [124–126]. The changing pattern of eicosanoid generation may not only reflect differing cellular sources, but also different activation states in infiltrating leukocytes [55]. The effects of manipulating glomerular eicosanoids are still somewhat controversial, particularly with regard to possible non-hemodynamic roles in glomerular injury such as immunoregulation. Some E-series prostaglandins are anti-inflammatory, and ameliorate both proteinuria and leukocyte infiltration [127], as does manipulation of dietary fatty acids [128, 129]. Study on nitric oxide in glomerular pathophysiology is still in its infancy. It is almost certain that this molecule has an important role in glomerular hemodynamics in both the normal glomerulus, and in GN. PAF, another macrophage product also produced by a wide range of other cell types, has been implicated in immune complex reactions [reviewed in 130], particularly its intravascular generation by sensitized basophils, and platelets in experimental serum sickness. Although systemic infusion produces renal hemodynamic changes, and intra renal perfusion produces glomerular lesions with platelet thrombi and leukocyte accumulation, its role in GN is uncertain. One of its major effects on the glomerulus when exogenously administered is neutralization of fixed anionic sites on capillary walls, leading to permeability changes [131]. Thus, the effects of these important mediators may not be confined to hemodynamics, but may also involve leukocyte recruitment and structural glomerular changes.

Macrophages promote resolution of glomerular inflammation

In many well-recognized forms of acute inflammation, macrophages, through their ability to lyse fibrin and phagocytose cellular debris are instrumental in resolution. Acute lobar pneumonia is an example of this process, and it is notable that in post-streptococcal GN where there is a substantial macrophage infiltrate, the majority of cases undergo complete resolution. Striker, Mannik and Tung [74], based on their earlier studies on the glomerular deposition of preformed immune complexes [132], clearly demonstrated macrophage phagocytosis of mesangial immune deposits, using the specific giant lysosomal marker present in the Chediak-Higashi mouse strain. Although there is no definite evidence that in immune complex glomerulonephritis a failure of this mechanism could lead to progression of disease, one of the central tenants of the pathogenesis of inflammation is the role of ineffective macrophage phagocytosis in chronic inflammation. This suggests that in glomerulonephritis there are instances where macrophage activity has a protective effect, and prevents irreversible sequelae which would result from persistence of inflammatory debris. Somewhat paradoxically, at least in non-immune models of glomerular scarring, there is also evidence for a contributory role for macrophages in progression of disease [133]. This aspect of macrophage involvement in the inflammatory process has parallels in other organs, such as the lung and joints. Further discussion on this extremely important aspect of glomerular disease is beyond the scope of this review.

Conclusion

These recent advances in our understanding of how macrophages are involved in acute glomerular inflammation clearly show stages in the pathogenesis of some types of GN which depend on macrophage accumulation. They show that macrophage infiltration is a consequence of interactions between cytokine-stimulated adhesion molecules on monocytes and intrinsic glomerular cells, chemoattractant proteins, hemodynamic changes, and cell-mediated reactions. The resulting macrophage infiltrate which has a substantial activated component is maintained by macrophage longevity and further monocyte recruitment. Our understanding of specific macrophage products responsible for injury, the mechanisms controlling macrophage-dependent inflammation, and the possible role of macrophages in progression to chronic GN is still incomplete, but will finally provide the scientific basis for therapeutic intervention in human GN.

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Note added in proof

The *in vivo* induction of iNOS in nephritic glomeruli has now been confirmed by immunohistochemistry (see Jansen et al, **Rapid Communication**, this issue). The results also confirm that there is no expression of iNOS in normal glomeruli. In addition, there is now preliminary evidence for a role for NO in GN (KETTELER et al, (abstract) *J Am Soc Nephrol* 4:610, 1993).

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