Histol Histopathol (1997) 12: 241-250

Histology and Histopathology

Invited Review

T cell subsets in immunologically-mediated glomerulonephritis

I.E. van Alderwegen, J.A. Bruijn and E. de Heer
Leiden University, Department of Pathology, The Netherlands

Summary. Until recently, research on the pathogenesis of glomerulonephritis has been mainly focused on the characterization of humoral immune responses in the initiation of glomerular injury. However, there is a growing recognition that both cellular and humoral immune responses, in varying proportions, are involved in the pathogenesis of immunologically-mediated glomerulonephritis.

T lymphocytes are essential cellular elements of cell-mediated immunity. Both in experimental models of immune-mediated renal disease and in histopathological analyses of human nephropathies, the involvement of T cells has been demonstrated in the immunoregulation of nephritogenic immune responses and in the immune injury in the kidney. T cell activation resulting in either delayed-type hypersensitivity, cytolytic reactions, abnormal expression of major histocompatibility complex (MHC) molecules, or B cell activation can result in glomerulonephritis. These different types of responses are exerted by distinct T cell subsets defined by cell surface markers and cytokine profiles. $CD4^+$ T cells *in vivo* are functionally heterogeneous with respect to cytokine production and the CD45 isoforms that are found on their surface. Like $CD4^+$ T cells, $CD8^+$ T cells may also be heterogeneous at the level of cytokine production. The roles of $CD4^+$ and $CD8^+$ cells and their cytokine profiles in glomerulonephritis have not been extensively investigated yet, but such studies might improve the understanding of the pathogenesis and possibly lead to new therapeutic approaches of human glomerulonephritis. In this review the role of distinct T lymphocyte subsets in experimental and human glomerulonephritis will be discussed.

Key words: T cells, T cell subsets, Glomerulonephritis

Offprint requests to: Dr. Isolde E. van Alderwegen, Dept. of Pathology, Leiden University Hospital, P.O. Box 9600, Building 1, L1-Q, 2300 RC Leiden,The Netherlands

Introduction

Until recently, most research on the pathogenesis of glomerulonephritis has been devoted to the characterization of humoral immune responses in the initiation of glomerular injury (Holdsworth and Tipping, 1991). However, the participation of antibody, immune complexes, complement, and neutrophils alone cannot completely explain many events occurring in experimental and human glomerulonephritis (Rovin and Schreiner, 1991). It is now recognized that both cellular and humoral immune responses, in varying proportions, are involved in the pathogenesis of immunologically-mediated glomerulonephritis (Holdsworth and Tipping, 1991; Rovin and Schreiner, 1991). Cell-mediated immunity can also be the main cause of renal damage in certain forms of glomerulonephritis (Bolton, 1984; Holdsworth and Tipping, 1991; Brouwer et al., 1993; Neilson, 1993; Rennke et al., 1994). T lymphocytes are essential cellular elements of cell-mediated immunity. T cell activation resulting in either delayed-type hypersensitivity, cytolytic reactions, abnormal expression of major histocompatibility complex (MHC) molecules, or B cell activation might result in glomerulonephritis (Florquin and Goldman, 1994). These different types of responses are exerted by distinct T cell subsets defined by cell surface markers and cytokine profiles (Florquin and Goldman, 1994). The topic of this review is the role of distinct T lymphocyte subsets in experimental and human glomerulonephritis.

Heterogeneity of $CD4^+$ T cell subsets based on cytokine production

Mosmann and Coffman were able to define two subsets among fully differentiated $CD4^+$ T cell clones in the mouse, on the basis of a restricted cytokine profile *in vitro*, designated Th1 and Th2 clones (Mosmann and Coffman, 1989). Upon activation, Th1 clones produce interleukin-2 (IL-2), interferon-γ (IFN-γ) and tumor necrosis factor-ß (TNF-ß), but not IL-4, IL-5, IL-6, or

IL-10, whereas Th2 clones produce IL-4, IL-5, IL-6, IL-10 and IL-13, but not IL-2 or IFN-γ. Both types of clones are able to produce IL-3, granulocyte-macrophage colony-stimulating factor (GM-CSF) and tumor necrosis factor alpha (TNF-α). Apart from this distinction, Th clones which secrete a mixture of Th1 and Th2 cytokines have also been characterized. These Th clones are designated Th0 clones (Mosmann and Coffman, 1989). A clearcut dichotomy, as found in mice, does not seem to exist in humans (Maggi et al., 1988). However, in different disease states human $CD4^+$ T cell clones are found which exhibit Th1 or Th2 profiles (Romagnani, 1991), and both Th1 and Th2 cells are shown to be involved in the pathogenesis of immunological disorders (Trembleau et al., 1995). Although the Th1/Th2 model is a valuable model to investigate and explain many immune reactions, it is likely that the T-cell responses *in vivo* are more diverse and sophisticated (Kelso, 1995). However, up till now there is still evidence that $CD4^+$ T cells *in vivo* are functionally heterogeneous in that responses are essentially either Th1-like or Th2-like (Fowell et al., 1991).

Functional heterogeneity of $CD4^+$ T cell subsets based on the expression of CD45

Besides the heterogeneity of $CD4^+$ T cells based on cytokine production, $CD4^+$ T cells are also heterogeneous with respect to the CD45 isoforms that are found on their surface (Fowell et al., 1991; Kampinga et al., 1992; Mason, 1992). The leukocyte-common antigen, CD45, has been shown to exist in man, mouse and rat in a number of different isoforms, generated by differential usage of three exons (A, B, and C) of a single gene (Thomas, 1989). Isoform usage varies with T cell maturation, activation and differentiation (Mason, 1992).

To some extent there is an association between the CD45 phenotype of $CD4^+$ memory T cells and the potential to secrete particular cytokines upon activation, which can be linked to the Th1 and Th2 phenotypes discussed before (O'Garra and Murphy, 1993). It is supposed that there are two memory phenotypes $CD4^+CD45RA^{low}B^{low}C^{low}O^{high}$ and $CD4^+CD45RA^{low}B^{high}C^{high}O^{high}$ (Mason and Powrie, 1990). They release predominantly IL-4 (memory cells for humoral response) respectively IFN-γ and IL-2 (memory cells for cell-mediated responses) following stimulation (Bottomly et al., 1989; Mason and Powrie, 1990; Fowell et al., 1991; Mason, 1992). However, the association between lymphokine synthesis and CD45R isoform expression is quantitative rather than absolute, and therefore these subsets should not be interpreted as bona fide Th2 and Th1 cells respectively, but more as a Th2-"like" and Th1-"like" cells (Fowell et al., 1991).

Functional heterogeneity of $CD8^+$ T cells

The two major functions of $CD8^+$ cells are cytolysis and immunosuppression. Like $CD4^+$ T cells, $CD8^+$ T cells may also be heterogeneous at the level of cytokine production, and this determines whether they exhibit inflammatory- or suppressor-type properties (O'Garra and Murphy, 1993). $CD8^+$ cells can secrete Th1 cytokines such as IFN-γ and IL-2, and Th2 cytokines such as IL-10 (de Jong et al., 1991; Inoue et al., 1993). They can also produce TGF-ß, which mediates at least part of their suppressive function (Miller et al., 1992).

Inoue et al. showed that mouse $CD8^+$ T cell clones could be subdivided into cytotoxic (Tc) and suppressor (Ts) subgroups by the pattern of cytokine production and CD45 expression (Inoue et al., 1993). These mouse $CD8^+$ subsets correspond strongly with the human *Mycobacterium leprae*-specific Type 1 and Type 2 $CD8^+$ T cell subsets derived from patients with leprosy, as described by Salgame and Bloom et al. (Salgame et al., 1991; Bloom et al., 1992). There is no direct correlation between $CD8^+$ subsets and $CD4^+$ Th1 and Th2 subsets, since most alloreactive and antigen-specific $CD8^+$ T cell clones produce large amounts of IFN-γ (Kemeny et al., 1994).

The nephritogenic immune response and the role of T cells in glomerulonephritis

The nephritogenic immune response consists of several interacting elements represented by the components of the immune system, the renal parenchymal cells and a genetic or environmental disturbance that sets it all off (Karp et al., 1991). There is a growing recognition of the importance of T cells in mediating renal injury (Meyers, 1995). The effector cells of the nephritogenic autoimmune response are autoreactive Th cells, capable of activating both B cells and cytotoxic T lymphocytes and recruiting additional leukocytes, such as macrophages (Karp et al., 1991; Rovin and Schreiner, 1991). Suppressor T cells in renal autoimmunity have recently been the focus of interest, especially in experimental anti-tubular basement membrane disease (Kelly et al., 1985) and mercuric chloride-induced anti-glomerular basement membrane disease (Pelletier et al., 1987). Immune injury can induce MHC class II expression on mesangial cells, predominantly through the production of IFN-γ by T lymphocytes (Madrenas et al., 1991). This may enhance the ability of mesangial cells to interact with infiltrating leukocytes and serve as antigen-presenting cells (Rovin and Schreiner, 1991), thus playing a role in the development or maintenance of a nephritogenic T cell response (Karp et al., 1991). Alternatively, renal tubular epithelial cells may promote anergy in autoreactive T cells, thus down-regulating the autoimmune responses within the kidney (Singer et al., 1993).

The essential components of cell-mediated immunity are present in both human and experimental glomerulonephritis (Rovin and Schreiner, 1991). Experimental renal pathology demonstrates a correlation between the presence of mononuclear cell infiltrates and glomerular

dysfunction, particularly with respect to proteinuria, diminished glomerular blood flow, and ultimate effacement of glomerular structure (Rovin and Schreiner, 1991). Characterization of renal inflammatory cells could give further insight into the pathogenesis of distinct forms of glomerulonephritis (Markovic-Lipovski et al., 1990).

T cell subsets in experimental glomerulonephritis

Murine models of lupus nephritis

Systemic lupus erythematosus is a disease characterized by B cell hyperactivity, autoantibody production and immune complex deposition in vital organs (Theofilopoulos and Dixon, 1981). Murine models of spontaneous lupus (MRL-*lpr/lpr*, (NZBx NZW)F1 and BXSB mice) and models of induced lupus, such as the parent-into-F1 model of graft-versus-host disease, have been useful in elucidating the importance of cytokines and cell-cell interactions in the pathogenesis of lupus nephritis (Handwerger et al., 1994).

MRL-*lpr/lpr* mice spontaneously develop an autoimmune disease characterized by vasculitis, massive lymphadenopathy, glomerulonephritis, and autoantibody formation (Jabs et al., 1992). The autoimmune disease was recently identified as a defect in the Fas antigen which results in resistance to apoptosis (Watanabe-Fukunaga et al., 1992). According to Díaz Gallo et al. (1992), the predominant renal interstitial infiltrate in MRL-*lpr/lpr* is composed of unique lymphoid cells regulated by the *lpr* gene (Kelley et al., 1993). These MRL-*lpr/lpr* kidney infiltrating 'double negative' T cell clones ($CD3^+$, TCR α/β^+, $B220^+$, $CD4^-$, $CD8^-$) are autoreactive, kidney-specific, exclusively proliferating to renal tubular epithelial and mesangial cells, and they secrete IFN-γ (Díaz Gallo et al., 1992; Kelley et al., 1993). Several observations suggest that these *lpr*-regulated T cells cause renal disease in MRL-*lpr/lpr* mice: their accumulation in lymph node, spleen and kidney prior to renal injury; increasing numbers of these cells in the kidney correlate with disease severity; prevention of renal injury can be obtained by therapeutic elimination of these T cells; and they express transcripts of cytokines associated with inflammatory responses (IFN-γ, TNF-α, TNF-ß) (Díaz Gallo et al., 1992; Kelley et al., 1993). Although these kidney-infiltrating cells do not express CD4 or CD8, their proliferation is MHC-restricted. Their supernatants induce class II and ICAM-1 on the surface of cultured renal tubular epithelial cell (Díaz Gallo et al., 1992). The cytokine profiles of the clones are heterogeneous, suggesting that there is an oligoclonal population of T cells within the renal interstitium (Díaz Gallo et al., 1992). All clones transcribe mRNA for at least one cytokine capable of inducing MHC Class II and ICAM-1 (IL-4, TNF-α, IFN-γ), suggesting that these T cell clones might cause the up-regulation of MHC Class II and ICAM-1 on tubular epithelial cells (Kelley et al., 1993). The authors speculated that autoreactive kidney-specific T cells recognize a kidney-specific antigen on the surface of tubular epithelial cells (Kelley et al., 1993).

In contrast, Jabs et al. (1992) suggest that $CD4^+$ T cells play a central role in the development of the autoimmune disease in MRL-*lpr/lpr* mice. They described that the target organ lesions in MRL-*lpr/lpr* mice, including the kidney, are largely composed of $CD4^+$ cells (Jabs et al., 1992), while only the massively enlarged lymph nodes are composed primarily of 'double negative' T cells. Anti-$CD4^+$ monoclonal antibody therapy demonstrated marked suppression of the autoimmune disease as determined by reversal of the immunopathological lesions, improvement in autoantibody production, and decrease of IgG levels in the group treated with anti-$CD4^+$ monoclonal antibody (Jabs et al., 1992). Glomerulonephritis, interstitial nephritis and proteinuria were either reduced or completely eliminated (Jabs et al., 1992). The authors suggested that the $CD4^+$ cell plays an essential role in the autoimmune process and that the massive accumulation of double-negative T cells is not a primary factor in the development of the autoimmune disease. Recent studies using MRL/lpr mice lacking $CD4^+$ T cells also show a diminished autoimmune disease despite an accumulation of $CD4^-CD8^-$ 'double negative' cells in spleen and lymph nodes (Koh et al., 1995).

In the graft-versus-host disease model of systemic autoimmune disease, depending on the parent and F1 strain combinations used, mice develop either an acute illness, with T cell activation patterns similar to those reported in allograft rejection, or a chronic, lupus-like graft-versus-host disease, with anti-DNA antibody production and deposition of immune complexes in skin and glomeruli (Via et al., 1987). In chronic graft-versus-host disease only donor $CD4^+$ allogenic MHC Class II-reactive T cells appear to be activated, resulting in the delivery of help to host allogeneic MHC Class II-bearing B cells, including autoreactive B cells (Handwerger et al., 1994). Chronic graft-versus-host disease is characterized by a selective deficiency in cells secreting IL-2 and IFN-γ and a hyperactivation of Th2 cells (de Wit et al., 1993; Charlton and Lafferty, 1995). Mice suffering from this disease spontaneously produce lymphokines of Th2 origin, such as IL-4, IL-10, and possibly IL-6 (Goldman et al., 1991; de Wit et al., 1993; Handwerger et al., 1994; Rus et al., 1995). The disease can be prevented by administration of either IFN-γ or IL-12 at the time of cell transfer (Donckier et al., 1994; Via et al., 1994). IL-4 was shown to be responsible for the increased expression of class II antigen on B cells (de Wit et al., 1993).

Mercury-induced anti-glomerular basement membrane disease

In the mercuric chloride ($HgCl_2$)-induced autoimmune model of anti-glomerular basement membrane nephritis in Brown Norway rats, polyclonal B-cell

activation occurs as a result of activation of autoreactive T cells directed against MHC class II molecules (Pelletier et al., 1986; Karp et al., 1991). The self-reactive T cells are shown to be $CD4^+$, since $CD8^+$-depleted Brown Norway rats develop an anti-glomerular basement membrane nephritis after passive transfer of $HgCl_2$-sensitized Brown Norway $CD4^+$ T cells (Pelletier et al., 1988b). The disease is self-limiting (showing an induction and a regulation phase (Druet et al., 1995)) and characterized by the presence of anti-glomerular basement membrane antibodies that bind to the glomerular capillary wall (Karp et al., 1991). Total serum Ig levels increase, mainly due to an increase in IgE, IgG1 and IgG2b isotypes (Pelletier et al., 1988a), suggesting involvement of Th2-like T cells in the pathogenesis of mercury-induced glomerulonephritis (Goldman et al., 1991; Charlton and Lafferty, 1995). Up-regulation of the Th2-type cytokine IL-4, has been shown in response to $HgCl_2$ in the mouse and in the rat, both in vivo and in vitro (Goldman et al., 1991; Ochel et al., 1991; Gillespie et al., 1995; Prigent et al., 1995). In susceptible mouse strains, treatment with an anti-IL-4 monoclonal antibody abrogates the increase in total serum IgE levels and the production of autoantibodies with the IgG1 isotype (Ochel et al., 1991). Treatment of susceptible rats with an antibody to CD45RB (Th1-like subset) before administration of $HgCl_2$ leads to exacerbation of aspects of the autoimmune syndrome (Mathieson et al., 1993) and antibodies to IFN-γ also exacerbate disease (Van der Meide et al., 1995a, 1995b).

Since non-susceptible strains can mount a delayed-type hypersensitivity response to mercuric chloride, which is a Th1 function, it was postulated that susceptibility for mercury-induced glomerulonephritis may be determined by the selective emergence of the Th2 subset (Ochel et al., 1991). During the regulation phase of the disease in susceptible mouse strains the Th1-like cytokine IFN-γ is produced, which may contribute to the remission by down-regulating the nephritogenic Th2 cells (Druet, 1991; Castedo et al., 1994).

Suppressor T cells may also play a role in $HgCl_2$-induced glomerulonephritis (Bigazzi, 1992). When autoreactive T cells from $HgCl_2$-infected rats are transferred into normal recipients, they initiate the appearance of $CD8^+$ suppressor T cells which prevent the expansion of the autoreactive $CD4^+$ T cells (Pelletier et al., 1988b). Since such suppressor cells do not appear in $HgCl_2$-injected rats, this indicates that such cells are inhibited by mercury (Pelletier et al., 1988b).

Another type of suppressor T cell appears to be involved in mercury-induced glomerulonephritis, as was shown in experiments in which the $CD8^+$ suppressor T-cell population was depleted with a monoclonal antibody in both susceptible Brown Norway rats, in which suppressor cells emerge as the disease subsides, and non-susceptible Lewis rats, in which non-specific suppressor cells emerge at the onset (Pelletier et al., 1990). Despite marked depletion of $CD8^+$ T cells and *in vitro* evidence of loss of suppression, anti $CD8^+$ therapy neither prolonged the disease in Brown Norway rats, nor induced it in Lewis rats (Pelletier et al., 1990). A possible suppressor function of the $RT6.2^+$ T cell subset was reported by Kosuda et al. (1991), who examined this subset in mercury-induced glomerulo-nephritis in the rat. $RT6.2^+$ T cells constitute 45% of the $CD4^+$ T cell population and 80% of the $CD8^+$ cell population, and can passively transfer protection from mercury-induced glomerulonephritis in rats lacking $RT6.2^+$ T cells (Angeullo et al., 1988). They found that there was a decrease in the $RT6.2^+$ cell population over the course of the disease in Brown Norway rats that correlated with the peak in anti-glomerular basement membrane antibody titer (Kosuda et al., 1991). If $RT6.2^+$ T cells (which include both $CD4^+$ and $CD8^+$ cells) are the true suppressor population in this model they may not have been depleted adequately by a $CD8^+$ therapy (Karp et al., 1991). The factors that cause the differential effects of $HgCl_2$ on the immune dysregulation in susceptible versus non-susceptible rats are largely unknown, but differences in both MHC and non-MHC-linked genes are implicated in the control of susceptibility (Druet et al., 1977; Sapin et al., 1984; Bigazzi, 1992).

Heymann's nephritis

Active Heymann's nephritis is induced by immunization of susceptible rat strains with crude preparations of renal tubular epithelium in complete Freund's adjuvant (CFA) (Heymann et al., 1959). The pathology of Heymann's nephritis in the rat closely resembles idiopathic membranous nephropathy in man (Alousi et al., 1969). The disease is caused by a $CD4^+$ helper T cell-dependent (Cheng et al., 1988) humoral autoimmune response which results in the *in situ* deposition of auto-antibodies in glomeruli (Couser and Salant, 1980) and complement activation (De Heer et al., 1985a). The autoimmune response in Heymann's nephritis is under regulatory influence by T lymphocyte subsets (De Heer et al., 1985b). Insights into the role of $CD4^+$ and $CD8^+$ T cell subsets in Heymann's nephritis are obtained from T cell depletion (Cheng et al., 1988; Quiza et al., 1991, 1992) and transfer (De Heer et al., 1985b, 1986; Cheng et al., 1988) experiments.

The role of T cells in the mediation of Heymann's nephritis was investigated by treatment with monoclonal antibody specific for T cell subsets for 6 weeks after immunization (Quiza et al., 1992). Anti-CD4 monoclonal antibody therapy totally prevented proteinuria. Moreover, it reduced antibody and complement deposition in the glomerulus and auto-antibody titers in serum. Anti-$CD8^+$ monoclonal antibody therapy markedly reduced proteinuria, but had no effect on auto-antibody titers or on the deposition of antibody and complement in the glomerulus (Quiza et al., 1992). This suggest that both cytotoxic $CD8^+$ and $CD4^+$ effector T cells may have a direct role in the mediation of glomerular dysfunction in Heymann's nephritis (Quiza et

al., 1992).

In rats with active Heymann's nephritis the number of auto-antibody-producing B cells decreases after 8-10 weeks (De Heer et al., 1985b). This spontaneous down-regulation of the autoimmune response is due to suppressor $CD8^+$ T cells (De Heer et al., 1986). These cells were able to suppress the autoimmune response when transferred to native recipients that were subsequently challenged (De Heer et al., 1986).

Tolerance to Heymann's nephritis can be induced by immunization with renal tubular antigen in incomplete Freund's adjuvant (IFA) (Harmon et al., 1980; De Heer et al., 1985b, 1986; Cheng et al., 1988). When tolerant rats are rechallenged with renal tubular antigen in CFA, the onset of Heymann's nephritis is either completely prevented or only minor proteinuria will develop (Harmon et al., 1980). This unresponsiveness is mediated by antigen-specific thymus-derived $CD8^+$ suppressor T cells (De Heer et al., 1985b). Transfer experiments with splenic $CD8^+$ T cells from tolerant rats resulted in a significant suppression of the autoimmune response in subsequently challenged recipients, while transfer of splenic $CD8^-$ T helper cells enhanced the autoimmune response (De Heer et al., 1985b).

Quiza et al. (1991) investigated the effects of therapy with monoclonal antibody to T cell subsets on induction of tolerance of Heymann's nephritis following preimmunization with renal tubular antigen in IFA (Quiza et al., 1991). Anti-CD4 monoclonal antibodies given for 2 weeks after the preimmunization abolished the capacity of renal tubular antigen in IFA pretreatment to induce unresponsiveness to Heymann's nephritis. $CD4^+$ cells are thus critical for the induction of tolerance to Heymann's nephritis (Quiza et al., 1991). Furthermore, in non-tolerant animals, anti-CD4 therapy administered prior to immunization did not prevent the induction of Heymann's nephritis, but even enhanced the severity of the disease (Quiza et al., 1991). The authors suggested that the monoclonal antibody used for the depletion of $CD4^+$ cells (MRC OX35) might mainly remove suppressor $CD4^+$ cells or that after the therapy new thymus-derived $CD4^+$ cells provide better help to the B cells. Anti-CD8 monoclonal antibodies did not prevent induction of tolerance and had no effect on the severity of the disease in responsive animals (Quiza et al., 1991). This suggests that there is no requirement for $CD8^+$ cells in the induction phase immediately after pre-immunization with renal tubular antigen in IFA (Quiza et al., 1991). However, $CD8^+$ T cells may participate in the maintenance of long-term unresponsiveness, as was shown by the transfer experiments with splenic $CD8^+$ T cells discussed earlier (De Heer et al., 1985b).

All together it is clearly shown that T lymphocyte subsets play an important role in the regulation of Heymann's nephritis. It appears that $CD4^+$ T cells play a critical role both in the induction of Heymann's nephritis (Cheng et al., 1988) and in induction of un-responsiveness to the disease (Quiza et al., 1991). $CD8^+$ T cells are involved in the mediation of glomerular barrier dysfunction (Quiza et al., 1992), in the spontaneous down-regulation of the active disease (De Heer et al., 1986) and in maintenance of suppression after induction of tolerance (De Heer et al., 1985b). Further investigation is required on the cytokine profiles and regulation of the different T cell subsets in order to obtain more insights in the mechanisms by which the cells exercise their suppressive or effector functions. In addition, the role of T cells in human membranous glomerulonephritis has to be assessed.

Chronic serum sickness

Chronic serum sickness in rats, induced by sub-cutaneous injections of BSA in Freund's incomplete adjuvant as described by Van Liew, Brentjens and Noble (Van Liew et al., 1983), is a model of proliferative immune complex glomerulonephritis, which progresses to death from kidney failure in three distinct stages: a mild, moderate and a final, severe stage (Van Liew et al., 1983). In the mild stage of the disease, histology and kidney function are normal. In the moderate stage, immune complex deposits accumulate in the peripheral capillary wall and the glomeruli become enlarged and hypercellular, finally resulting in segmental glomerular necrosis in the severe stage (Van Liew et al., 1983). T lymphocyte accumulation in glomeruli is a consistent and significant feature of chronic serum sickness nephritis, although T cells are present only in low numbers, only for a brief period and only in the moderate stage, before the development of severe kidney insufficiency (Noble et al., 1990). As long as T cells are present in glomeruli, inflammation has relatively benign functional consequences. This suggests that T cells might have an immunosuppressive function, preventing severe glomerular dysfunction by blocking the differentiation of macrophages along abnormal pathways (Noble et al., 1990) Therefore, this model promises to be an excellent tool with which to evaluate the possible immunoregulatory role of glomerular T cells in proliferative immune complex glomerulonephritis (Noble et al., 1990).

Tubulo-interstitial glomerulonephritis

Murine anti-tubular basement membrane disease, induced in susceptible mouse strains, is an autoimmune kidney disease mediated by tubular antigen-specific $CD8^+$ nephritogenic effector T cells which are delayed-type hypersensitivity-reactive and cytotoxic to renal epithelial cells (Meyers and Kelly, 1994). Recently, the 3M-1 target antigen, secreted and expressed by proximal tubular cells, of murine anti-tubular basement membrane disease has been sequenced and a major nephritogenic domain has been identified (Neilson et al., 1991).

Both $CD4^+$ Th-cell clones and $CD8^+$ effector T cell clones have been evaluated in this model (Meyers and Kelly, 1991, 1994; Heeger et al., 1994). The Th cell response in this model is predominantly a Th1

phenotype, with IL-2 and IFN-γ expression in the absence of IL-4 excretion (Heeger et al., 1994). These Th cells also secrete an antigen-binding T helper factor, ThF, that induces the $CD8^+$ nephritogenic effector T cell response (Hines et al., 1990). Meyers and Kelly (1991) have derived a $CD8^+$, 3M-1- specific, class I-restricted nephritogenic effector T cell line from susceptible mice immunized with renal tubular antigen. The cells display cytotoxicity against tubular cells *in vitro* and can mediate both interstitial nephritis and delayed-type hypersensitivity to the 3M-1 target antigen (Meyers and Kelly, 1991). Some subclones of this cell line show differential activity: one clone is cytotoxic but not delayed-type hypersensitivity-reactive, and several are delayed-type hypersensitivity-reactive with less cytotoxic activity (Meyers and Kelly, 1994). Adoptive transfer experiments demonstrated qualitative differences in the tubulo-interstitial lesions induced by the distinct clones (Meyers and Kelly, 1994). The delayed-type hypersensitivity-reactive clones induced inflammatory cellular lesions, whereas the cytotoxic clone elicited a more diffuse pattern of injury characterized by tubular dilatation and atrophy (Meyers and Kelly, 1994). The two phenotypes also expressed different cytokine profiles (Meyers and Kelly, 1991). The delayed-type hypersensitivity-reactive clones expressed IL-2, IL-4, IL-6, IFN-γ, TNFα, and TGF-ß; the cytotoxic subset expressed a similar profile, except for IL-2 and TGF-ß (Meyers and Kelly, 1994).

Non-susceptible strains of mice also develop 3M-1-specific T cells, but these are $CD4^+$ and do not infiltrate and mediate inflammatory interstitial lesions (Neilson et al., 1985a). The development of $CD4^+$ and the suppression of $CD8^+$ effector T cells appears to be mediated by $CD8^+$ suppressor T cells (Kelly et al., 1988). In susceptible mice these suppressor cells are also present, but they are counteracted by *Vicia Villosa* lectin-adherent contrasuppressor cells, thus allowing for preferential maturation of nephritogenic $CD8^+$ effector T cells (Kelly et al., 1988).

Suppressor T cells can be experimentally induced in anti-tubular basement membrane disease (Neilson et al., 1985b). Intravenous injection of tubular antigen-coupled splenocytes into anti-tubular basement membrane disease-susceptible mice prevents development of the disease. Moreover it improves the histological lesions in animals with established disease by induction of two phenotypically and functionally distinct populations of suppressor T cells (Neilson et al., 1985b). The $CD4^+$ suppressor T cells (Ts1) inhibit an early stage in the differentiation of the nephritogenic $CD8^+$ effector T cells, and also induce a population of $CD8^+$ suppressor T cells. These $CD8^+$ suppressor T cells (Ts2) or soluble proteins secreted by these cells (TsF_2) directly inhibit the function of the nephritogenic $CD8^+$ effector cells through a non-cytotoxic mechanism (Neilson et al., 1985b).

TsF_2 was shown to functionally inhibit both 3M-1 specific cytotoxic and delayed-type hypersensitivity-reactive clones (Meyers and Kelly, 1994). The loss of function of the clones was an active cellular process, since it was dependent upon new mRNA and protein synthesis. In the cytotoxic clone, exposure to TsF_2 induced expression of TGF-ß1 mRNA (Meyers and Kelly, 1994). Neutralizing antisera to TGF-ß1 completely abrogated the suppression of the cytotoxicity, demonstrating that TGF-ß1 is required for TsF_2-induced suppression of cytotoxicity and nephritogenicity (Meyers and Kelly, 1994). However, delayed-type hypersensitivity-reactive clones, expressing TGF-ß1 themselves following activation, are not inactivated by exogenous TGF-ß1. Therefore, TsF_2 may inactivate such clones by other mechanisms (Meyers and Kelly, 1994).

T cell subsets in human glomerulonephritis

There is accumulating, although still limited, evidence that cellular immunity is active in human glomerular disease, particularly of a chronic or sclerosing nature (Rovin and Schreiner, 1991). Many forms of human glomerulonephritis are characterized by hypercellularity, of which infiltrating leukocytes constitute a significant proportion (Rovin and Schreiner, 1991). Analysis of leukocyte subsets in glomerulonephritis (Nolasco et al., 1987; Tuazon et al., 1987) has documented the presence of T lymphocytes in rapidly progressive glomerulonephritis with crescent formation, lupus nephritis, Henoch-Schönlein purpura, and transplant glomerulopathy. T lymphocytes of both the suppressor/cytotoxic and helper subsets are represented in glomerular lesions (Rovin and Schreiner, 1991). Glomerular leukocyte infiltrates typically do not correlate with the presence or absence of glomerular deposits of immune complexes (Nolasco et al., 1987; Rovin and Schreiner, 1991). A good example is immune-complex-negative rapidly progressive glomerulonephritis which can exhibit large numbers of glomerular mononuclear leukocytes (Nolasco et al., 1987; Holdsworth and Tipping, 1991). It has been emphasized that many glomerular lesions classified as primary glomerulonephritides are frequently accompanied by highly significant interstitial infiltrates, consisting principally of T lymphocytes and lesser numbers of macrophages (Hooke et al., 1987; Tuazon et al., 1987). Glomerular dysfunction often correlates even better with the intensity of the T cell interstitial infiltrate than the degree of glomerular hypercellularity (Hooke et al., 1987). Immunophenotyping of mononuclear leukocytes in kidney tissue revealed significant increases of $CD4^+$ and $CD8^+$ T cells in glomeruli of rapidly progressive glomerulonephritis, membranoproliferative glomerulonephritis and focal glomerulosclerosis (Markovic-Lipovski et al., 1990, 1991). Interstitial cells were mostly T lymphocytes in all forms of glomerulopathies investigated (minimal change, membranous nephropathy, membranoproliferative glomerulonephritis type I, mesangiocapillary glomerulonephritis, rapidly progressive glomerulonephritis, focal glomerulo-

sclerosis, IgA nephritis) (Markovic-Lipovski et al., 1990, 1991; Yoshioka and Maki, 1995). A high expression of HLA class II antigens was observed on interstitial mononuclear leukocytes, as a sign of their activation (Markovic-Lipovski et al., 1990). In all forms of glomerulonephritis with interstitial infiltrates the cells surrounded glomeruli like a corona, irrespective of their presence within the glomeruli (Markovic-Lipovski et al., 1990). In membranous nephropathy and mesangiocapillary glomerulonephritis, there was no evident increase of glomerular mononuclear leukocytes despite observed interstitial infiltrates in some patients (Markovic-Lipovski et al., 1990). The variable presence of interstitial cell infiltrates in these patients might reflect a different timing of biopsy or heterogeneity of the diseases (Markovic-Lipovski et al., 1990). In rapidly progressive glomerulonephritis, T cells were mainly detected within the glomerular tuft with a slight predominance of the $CD4^+$ subset (Markovic-Lipovski et al., 1990). The mean number of positive $CD4^+$ and $CD8^+$ T cells within the glomeruli decreased with the time of onset, suggesting a correlation between the presence of these cells and the duration of the disease (Markovic-Lipovski et al., 1990). In focal glomerulosclerosis, $CD8^+$ T cells were predominant and usually peripherally distributed within the glomerular tuft or at capillary adhesions and the glomerular T lymphocyte counts were not related to disease duration (Markovic-Lipovski et al., 1990). In IgA nephropathy the $CD4^+/CD8^+$ ratio varied and the presence of T cells correlated with renal function and the activity of glomerular crescents (Yoshioka and Maki, 1995). The number of interstitial inflammatory cells in focal segmental glomerulosclerosis was shown to correlate with the degree of impaired renal function (plasma creatinine level) at the time of biopsy (Markovic-Lipovski et al., 1991).

Increasing evidence indicates a crucial role for T cells, particularly $CD4^+$ cells, in driving B cell hyperactivity in systemic lupus erythematosus (Handwerger et al., 1994). T cell abnormalities are multiple and prominent in patients with systemic lupus erythematosus, and are crucial in the pathogenesis of the disease (Tsokos, 1992). These abnormalities include, among others, T lymphopenia, decreased suppressor cell activity, decreased cytotoxic responses and increased $CD4^+DR^+$ and 'double negative' T helper cell activity (Tsokos, 1992). Moreover, T lymphocytes show enhanced proliferative responses when stimulated via the CD3 pathway, which can contribute to the autoimmune activity in human systemic lupus erythematosus (Stekman et al., 1991). IL-2 production by stimulated peripheral blood T cells is decreased and the response of lymphocytes to IL-2 also seems to be decreased, possibly through decreased IL-2 receptor expression (Linker-Israeli, 1992; Tsokos, 1992; Horwitz and Jacob, 1994).

Although chronic murine graft-versus-host disease is obviously Th2 cell-mediated, the Th1/Th2 cytokine paradigm only partially explains the dichotomy between humoral and cellular immunity in human systemic lupus erythematosus (Horwitz and Jacob, 1994). In human systemic lupus erythematosus IgE is not increased and there is no convincing evidence that the production of IL-4 is increased (Horwitz and Jacob, 1994). However, there is preliminary evidence for elevated serum IL-10 levels (Horwitz and Jacob, 1994).

Further investigations on the role of T cells and cytokines in lupus nephritis will provide a framework for the development of more specific immunotherapeutic approaches to the treatment of this disease (Handwerger et al., 1994).

Summary and Conclusion

Both in experimental models of immune-mediated renal disease and in histopathological analyses of human nephropathies, the involvement of T cells has been demonstrated in the immunoregulation of nephritogenic immune responses and in the immune injury in the kidney. The roles of $CD4^+$ and $CD8^+$ cells and their cytokine profiles have not been extensively investigated, but such studies might improve the understanding of the pathogenesis and possibly lead to new therapeutic approaches of human glomerulonephritis (Florquin and Goldman, 1994).

Several approaches to the development of immunosuppressive modalities targeting injurious cellular immune responses have been taken in both autoimmune disease models and experimental transplant rejection (Meyers and Kelly, 1994). An ideal immunosuppressive modality, however, would be antigen or clone specific, targeting only those T cells involved in the autoimmune, or alloreactive, response (Meyers and Kelly, 1994). This type of immunosuppression could theoretically be achieved through preferential expansion of specific suppressor T cells in the host (Meyers and Kelly, 1994).

Further work in the area of cell-mediated immunity in renal disease will be required to develop specific therapies designed to interrupt immunologically sustained glomerular damage (Rovin and Schreiner, 1991).

References

Alousi M.A., Post R.S. and Heymann W. (1969). Experimental autoimmune nephrosis in rats. Am. J. Pathol. 54, 47-71.

Angeullo M., Greiner D.L., Mordes J.P., Handler E.S., Nakamura N., McKeever U. and Rossini A. (1988). Absence of $RT6^+$ T cells in diabetes-prone biobreeding/Worcester rats is due to genetic an cell developmental defects. J. Immunol. 141, 4146-4151.

Bigazzi P.E. (1992). Lessons from animal models: the scope of mercury-induced autoimmunity. Clin. Immunol. Immunop. 65, 81-84.

Bloom B.R., Modlin R.L. and Salgame P. (1992). Stigma variations: observations on suppressor T cells and leprosy. Annu. Rev. Immunol. 10, 453-453.

Bolton W.K. (1984). The role of cell mediated immunity in the pathogenesis of glomerulonephritis. Plasma Ther. Transfus. Tech. 5,

415-430.

Bottomly K., Luqman M., Greenbaum L., Carding S., West J., Pasqualini T. and Murphy D.B. (1989). A monoclonal antibody to murine CD45R distinguishes CD4 T cell populations that produce different cytokines. Eur. J. Immunol. 19, 617-623.

Brouwer E., Weening J.J., Klok P.A., Huitema M.G., Tervaert J.W. and Kallenberg C.G. (1993). Induction of an humoral and cellular (auto) immune response to human and rat myeloperoxidase (MPO) in Brown-Norway (BN), Lewis and Wistar Kyoto (WKY) rat strains. Adv. Exp. Med. Biol. 336, 139-142.

Castedo M., Pelletier L., Pasquier R. and Druet P. (1994). Improvement of TH1 functions during the regulation phase of mercury disease in Brown Norway rats. Scand. J. Immunol. 39, 144-150.

Charlton B. and Lafferty K.J. (1995). The Th1/Th2 balance in autoimmunity. Curr. Opin. Immunol. 7, 793-798.

Cheng I.K.P., Dorsch S. and Hall B.M. (1988). The regulation of autoantibody production in Heymann's nephritis by T lymphocyte subsets. Lab. Invest. 59, 780-788.

Couser W.G. and Salant D.J. (1980). In situ immune complex formation and glomerular injury. Kidney Int. 17, 1-13.

De Heer E., Daha M.R., Bhakdi S., Bazin H. and Van Es L.A. (1985a). Possible involvement of terminal complement complex in active Heymann nephritis. Kidney Int. 27, 388-393.

De Heer E., Daha M.R. and Van Es L.A. (1985b). The autoimmune response in active Heymann's nephritis in Lewis rats is regulated by T-lymphocyte subsets. Cell. Immunol. 92, 254-264.

De Heer E., Daha M.R., Burgers J. and Van Es L.A. (1986). Reestablishment of self tolerance by suppressor cells after Heymann's nephritis. Cell. Immunol. 98, 28-33.

de Jong R., Brouwer M., Miedema F. and van Lier R.A.W. (1991). Human CD8+ T lymphocytes can be divided into CD45RA+ and CD45RO+ cells with different requirements for activation and differentiation. J. Immunol. 146, 2088-2094.

de Wit D., van Mechelen M., Zanin C., Doutrelepont J.-M., Velu T., Gerard C., Abramowicz D., Scheerlinck J.-P., De Baetselier P., Urbain J., Leo O., Goldman M. and Moser M. (1993). Preferential activation of Th2 cells in chronic graft-versus-host reaction. J. Immunol. 150, 361-366.

Díaz Gallo C., Jevnikar A.M., Brennan D.C., Florquin S., Pacheco-Silva A. and Kelley V.R. (1992). Autoreactive kidney-infiltrating T-cell clones in murine lupus nephritis. Kidney Int. 42, 851-859.

Donckier V., Abramowicz D., Bruyns C., Florquin S., Vanderhaeghen M.L., Amraoui Z., Dubois C., Vandenabeele P. and Goldman M. (1994). IFN-gamma prevents Th2 cell-mediated pathology after neonatal infection of semiallogenic spleen cells in mice. J Immunol. 153, 2361-2368.

Druet E., Sapin C., Gunther E., Feingold N. and Druet P. (1977). Mercuric chloride induced anti-glomerular basement membrane antibodies in the rat. Genetic control. Eur. J. Immunol. 7, 348-351.

Druet P. (1991). Induction and regulation of autoimmune experimental glomerulonephritis. In: immunology of renal diseases. Pusey C.D. (ed). Kluwer Academic Publishers. Dordrecht, Boston, London. pp 29-43.

Druet P., Druet E., Potdevin F. and Sapin C. (1995). Immune type glomerulonephritis induced by $HgCl_2$ in the Brown- Norway rat. Ann. Immunol. 129C, 777-792.

Florquin S. and Goldman M. (1994). T cell subsets in glomerular diseases. Springer Semin. Immunopathol. 16, 71-80.

Fowell D., McKnight A.J., Powrie F., Dyke R. and Mason D. (1991). Subsets of CD4+ cells and their roles in the induction and prevention of autoimmunity. Immunol. Rev. 123, 37-64.

Gillespie K.M., Qasim F.J., Tibbatts L.M., Thiru S., Oliveira D.B. and Mathieson P.W. (1995). Interleukin-4 gene expression in mercury-induced autoimmunity. Scand. J. Immunol. 41, 268-272.

Goldman M., Druet P. and Gleichmann E. (1991). Th2 cells in systemic autoimmunity: insights from allogeneic diseases and chemically-induced autoimmunity. Immunol. Today 12, 223-227.

Handwerger B.S., Rus V., Da Silva L. and Via C.S. (1994). The role of cytokines in the immunopathogenesis of lupus. Springer Semin. Immunopathol. 16, 153-180.

Harmon W.E., Grupe W.E. and Parkman R. (1980). Control of autologous immune complex nephritis. I. Suppression of the disease in the presence of T cell sensitization. J. Immunol. 124, 1034-1038.

Heeger P.S., Smoyer W.E., Saad T., Albert S., Kelly C.J. and Neilson E.G. (1994). Molecular analysis of the helper T cell response in murine interstitial nephritis. T cells recognizing an immunodominant epitope use multiple T cell receptor Vß genes with similarities across CDR3. J. Clin. Invest. 94, 2084-2092.

Heymann W., Hackel B., Harwood S., Wilson S.G.F. and Hunter J.L.P. (1959). Production of nephrotic syndrome in rats by Freund's adjuvants and rat kidney suspensions. Proc. Soc. Exp. Biol. Med. 100, 660-664.

Hines W.H., Mann R.A., Kelly C.J. and Neilson E.G. (1990). Murine interstitial nephritis IX. Induction of the nephritogenic effector T cell repertoire with an antigen-specific T cell cytokine. J. Immunol. 144, 75-83.

Holdsworth S.R and Tipping P.G. (1991). Cell-mediated immunity in glomerulonephritis. In: Immunology of renal diseases. Pusey C.D. (ed). Kluwer Academic Publishers. Dordrecht, Boston, London. pp 97-122.

Hooke D.H., Gee D.C. and Atkins R.C. (1987). Leukocyte analysis using monoclonal antibodies in human glomerulonephritis. Kidney Int. 31, 961-972.

Horwitz D.A. and Jacob C.O. (1994). The cytokine network in the pathogenesis of systemic lupus erythematosus and possible therapeutic implications. Springer Semin. Immunopathol. 16, 181-200.

Inoue T., Asano Y., Matsuoka S., Furutani-Seiki M., Aizawa S., Nishimura H., Shirai T. and Tada T. (1993). Distinction of mouse CD8+ suppressor effector T cell clones from cytotoxic T cell clones by cytokine production and CD45 isoforms. J. Immunol. 150, 2121-2128.

Jabs D.A., Burek C.L., Hu Q., Kuppers R.C., Lee B. and Prendergast R.A. (1992). Anti-CD4 monoclonal antibody therapy suppresses autoimmune disease in MRL/Mp-lpr/lpr Mice. Cell. Immunol. 141, 496-507.

Kampinga J., Groen H., Klatter F., Meedendorp B., Aspinall R., Roser R. and Niewenhuis P. (1992). Post-thymic T cell development in rats: an update. Biochem. Soc. Transact. 20, 191-197.

Karp S.L., Albert S.E. and Neilson E.G. (1991). The nephritogenic immune response. Curr. Opin. Immunol. 3, 906-911.

Kelley V.R., Diaz-Gallo C., Jevnikar A.M. and Singer G.G. (1993). Renal tubular epithelial and T cell interactions in autoimmune renal disease. Kidney Int. 43 (Suppl. 39), S108-S115.

Kelly C.J., Silvers W.K. and Neilson E.G. (1985). Tolerance to parenchymal self: regulatory role of Major Histocompatibility Complex-restricted, OX8+ suppressor T cells specific for autologous renal tubular antigen in experimental interstitial nephritis. J. Exp.

Med. 162, 1892-1903.

Kelly C.J., Mok H. and Neilson E.G. (1988). The selection of effector T cell phenotype by contrasuppression modulates susceptibility to autoimmune injury. J. Immunol. 141, 3022-3028.

Kelso A. (1995). Th1 and Th2 subsets: paradigms lost? Immunol. Today 16, 374-379.

Kemeny D.M., Noble A., Holmes B.J. and Diaz-Sanchez D. (1994). Immune regulation: a new role for the CD8+ T cell. Immunol. Today 15, 107-110.

Koh D.R., Ho A., Rahemtulla A., Fung-Leung W.P., Griesser H. and Mak T.W. (1995). Murine lupus in MRL/*lpr* mice lacking CD4 or CD8 T cells. Eur. J. Immunol. 25, 2558-2562.

Kosuda L.L., Wayne A., Nahounou M., Greiner D.L. and Bigazzi P.E. (1991). Reduction of the RT6+ subset of T lymphocytes in Brown Norway rats with mercury-induced renal autoimmunity. Cell. Immunol. 135, 154-167.

Linker-Israeli M. (1992). Cytokine abnormalities in human lupus. Clin. Immunol. Immunopathol. 63, 10-12.

Madrenas J., Parfrey N.A. and Halloran P.F. (1991). Interferon gamma-mediated renal MHC expression in mercuric chloride-induced glomerulonephritis. Kidney Int. 39, 273-281.

Maggi E., Del Prete G., Macchia D., Parronchi P., Tiri A., Chr'tien I., Ricci M. and Romagnani S. (1988). Profiles of lymphokine activities and helper function for IgE in human T cell clones. Eur. J. Immunol. 18, 1045-1050.

Markovic-Lipovski J., Muller C.A., Risler T., Bohle A. and Muller G.A. (1990). Association of glomerular and interstitial mononuclear leukocytes with different forms of glomerulonephritis. Nephrol. Dial. Transpl. 5, 10-17.

Markovic-Lipovski J., Muller C., Risler T., Bohle A. and Muller G.A. (1991). Mononuclear leukocytes, expression of HLA class II antigens and intercellular adhesion molecule 1 in focal segmental glomerulosclerosis. Nephron 59, 286-293.

Mason D. (1992). Subsets of CD4+ T cells defined by their expression of different isoforms of the leucocyte-common antigen, CD45. Biochem. Soc. Transact. 20, 188-190.

Mason D. and Powrie F. (1990). Memory CD4+ T cells in man form two distinct subpopulations, defined by their expression of isoforms of the leucocyte common antigen, CD45. Immunology 70, 427-433.

Mathieson P.W., Thiru S. and Oliveira D.B.G. (1993). Regulatory role of OX22+ T cells in mercury-induced autoimmunity in the Brown Norway rat. J. Exp. Med. 177, 1309-1316.

Meyers C.M. (1995). T-cell regulation of renal immune responses. Curr. Opin. Nephrol. Hypertens. 4, 270-276.

Meyers C.M. and Kelly C.J. (1991). Effector mechanisms in organ-specific autoimmunity. I. Characterization of a CD8+ T cell line that mediates murine interstitial nephritis. J. Clin. Invest. 88, 408-416.

Meyers C.M. and Kelly C.J. (1994). Inhibition of murine nephritogenic effector T cells by a clone-specific suppressor factor. J. Clin. Invest. 94, 2093-2104.

Miller A., Lider O., Roberts A.B., Sporn M.B. and Weiner H.L. (1992). Suppressor T cells generated by oral tolerization to myelin basic protein suppress both *in vitro* and *in vivo* immune responses by the release of transforming growth factor ß after antigen-specific triggering. Proc. Natl. Acad. Sci. USA 89, 421-425.

Mosmann T.R. and Coffman R.L. (1989). TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. Annu. Rev. Immunol. 7, 145-173.

Neilson E.G., McCafferty E., Mann R., Michaud L. and Clayman M. (1985a). Murine interstitial nephritis. III. The selection of phenotypic (Lyt and L3T4) and idiotypic (RE-Id) T cell preferences by genes in Igh-1 and H-2K characterize the cell-mediated potential for disease expression: susceptible mice provide a unique effector T cell repertoire in response to tubular antigen. J. Immunol. 134, 2375-2382.

Neilson E.G., McCafferty E., Mann R., Michaud L. and Clayman M.D. (1985b).Tubular antigen-derivatized cells induce a disease-protective, antigen-specific and idiotype-specific suppressor T cell network restrited by I-J and Igh-V in mice with experimental interstitial nephritis. J. Exp. Med. 162, 215-230.

Neilson E.G., Sun M.J., Kelly C.J., Hines W.H., Haverty T.P., Clayman M.D. and Cooke N.E. (1991). Molecular characterization of a major nephritogenic domain in the autoantigen of anti-tubular basement membrane disease. Proc. Natl. Acad. Sci. USA 88, 2006-2010.

Neilson E.G. (1993). The nephritogenic T lymphocyte response in interstitial nephritis. [Review]. Semin. Nephro.l 13, 496-502.

Noble B., Ren K., Taverne J., Dipirro J., van Liew J., Dijkstra C., Janossy G. and Poulter L.W. (1990). Mononuclear cells in glomeruli and cytokines in urine reflect the severity of experimental proliferative immune complex glomerulonephritis. Clin. Exp. Immunol. 80, 281-287.

Nolasco F.E.B., Cameron J.S., Hartley B., coelho A., Hildreth G. and Reuben R. (1987). Intraglomerular T cells and monocytes in nephritis: study with monoclonal antibodies. Kidney Int. 31, 1160-1166.

O'Garra A. and Murphy K. (1993). T-cell subsets in autoimmunity. Curr. Opin. Immunol. 5, 880-886.

Ochel M., Vohr H., Pfeiffer C. and Gleichmann E. (1991). IL-4 is required for the IgE and IgG1 increase and IgG1 autoantibody formation in mice treated with mercurcic chloride. J. Immunol. 146, 3006-3011.

Pelletier L., Pasquier R., Hirsch F., Sapin C. and Druet P. (1986). Autoreactive T cells in mercury-induced autoimmune disease: In vitro demonstration. J. Immunol. 137, 2548-2553.

Pelletier L., Pasquier R., Rossert J. and Druet P. (1987). $HgCl_2$ induces nonspecific immunosuppression in Lewis rats. Eur. J. Immunol. 17, 49-54.

Pelletier L., Pasquier R., Guettier C., Vial M.C., Mandet C., Nochy D., Bazin H. and Druet P. (1988a). $HgCl_2$ induces T and B cell to proliferate and differentiatie in BN rats. Clin. Exp. Immunol. 71, 336-342.

Pelletier L., Pasquier R., Rossert J., Vial M., Mandet C. and Druet P. (1988b). Autoreactive T cells in mercury-induced autoimmunity. Ability to induce the autoimmune disease. J. Immunol. 140, 750-754.

Pelletier L., Rossert J., Pasquier R., Vial M.C. and Druet P. (1990). Role of CD8+ T cells in mercury-induced autoimmunity or immuno-suppression in the Rat. Scand. J. Immunol. 31, 65-74.

Prigent P., Saoudi A., Pannetier C., Graber P., Bonnefoy J.Y., Druet P. and Hirsch F. (1995). Mercuric chloride, a chemical responsible for T helper cell 2 mediated autoimmunity in Brown Norway rats directly triggers T cells to produce interleukin-4. J. Clin. Invest. 96, 1484-1489.

Quiza C.G., Leenaerts P.L. and Hall B.M. (1991). Induction of unresponsiveness to Heymann's nephritis: inhibited by monoclonal antibody to CD4 but not to CD8. Cell. Immunol. 133, 456-446.

Quiza C.G., Leenaerts P.L. and Hall B.M (1992). The role of T cells in the mediation of glomerular injury in Heymann's nephritis in the rat.

Int. Immunol. 4, 423-432.

Rennke H.G., Klein P.S., Sandstrom D.J. and Mendrick D.L. (1994). Cell-mediated immune injury in the kidney: acute nephritis induced in the rat by azobenzenearsonate. Kidney Int. 45, 1044-1056.

Romagnani S. (1991). Human Th1 and Th2 subsets: doubt no more. Immunol. Today 12, 256-257.

Rovin B.H. and Schreiner G.F. (1991). Cell-mediated immunity in glomerular disease. Annu. Rev. Med. 42, 25-33.

Rus V., Svetic A., Nguyen P., Gause W.C. and Via C.S. (1995). Kinetics of Th1 and Th2 cytokine production during the early course of acute and chronic murine graft-versus-host disease: Regulatory role of donor $CD8^+$ T cells. J. Immunol. 155, 2396-2406.

Salgame P., Abrams J.S., Clayberger C., Goldstein H., Convit J., Modlin R.L. and Bloom B.R. (1991). Differing lymphokine profiles of functional subsets of human CD4 and CD8 T cell clones. Science 254, 279-282.

Sapin C., Hirsch F., Delaporte J.P., Bazin H. and Druet P. (1984). Polyclonal IgE increase after $HgCl_2$ injections in BN and LEW rats. A genetic analysis. Immunogenetics 20, 227-236.

Singer G.G., Yokoyama H., Bloom R.D., Jevnikar A.M., Nabavi N. and Kelly V.R. (1993). Stimulated renal tubular epithelial cells induce anergy in $CD4^+$ T cells. Kidney Int. 44, 1030-1035.

Stekman L., Blasini A., Leon-Ponte M., Baroja M., Abadi I. and Rodriguez M. (1991). Enhanced CD3-mediated T lymphocyte proliferation in patients with systemic lupus erythematosus. Arthr. Rheumat. 34, 459-467.

Theofilopoulos A.N. and Dixon F.J. (1981). Etiopathogenesis of murine SLE. Immunol. Rev. 55, 179-216.

Thomas M.L. (1989). The leukocyte common antigen family. Annu. Rev. Immunol. 7, 339-369.

Trembleau S., Germann T., Gately M.K. and Adorini L. (1995). The role of IL-12 in the induction of organ-specific autoimmune diseases. Immunol. Today 16, 383-386.

Tsokos G.C. (1992). Lymphocyte abnormalities in human lupus. Clin. Immunol. Immunopathol. 63, 7-9.

Tuazon T.V., Schneeberger E.E., Bhan A.K., McCluskey R.T., Cosimi A.B., Schooley R.T., Rubin R.H. and Colvin, R.B. (1987). Mononuclear cells in acute allograft glomerulopathy. Am. J. Pathol. 129, 119-132.

Van der Meide P.H., De Labie M.C.D.C., Botman C.A.D., Aten J. and Weening J.J. (1995a). Nitric oxide suppresses IFN-gamma production in the spleen of mercuric chloride-exposed Brown Norway rats. Cell. Immunol. 161, 195-206.

Van der Meide P.H., Groenestein R.J., De Labie M.C.D.C., Aten J. and Weening J.J. (1995b). Susceptibility to mercuric chloride-induced glomerulonephritis is age-dependent: study of the role of IFN-gamma. Cell. Immunol. 162, 131-137.

Van Liew J.B., Brentjens J.R. and Noble B. (1983). Relationship of kidney function to immunopathology in chronic serum sickness of rats. Kidney Int. 24, 160-169.

Via C.S., Sharrow S.O. and Shearer G.M. (1987). Role of cytotoxic T lymphocytes in the prevention of lupus like disease occurring in a murine model of graft-vs-host disease. J. Immunol. 139, 1840-1849.

Via C.S., Rus V., Gately M.K. and Finkelman F.D. (1994). IL-12 stimulates the development of acute graft-versus-host disease in mice that normally would develop chronic, autoimmune graft-versus-host disease. J. Immunol. 153, 4040-4047.

Watanabe-Fukunaga R., Brannan C.I., Copeland N.G., Jenkins N.A. and Nagata S. (1992). Lymphoproliferative disorder in mice explained by defects in Fas antigen that mediates apoptosis. Nature 356, 314-317.

Yoshioka K. and Maki S. (1995). Human IgA nephritis: immunocytochemical evidence of a chronic inflammatory proliferative disorder. Histol. Histopathol. 10, 203-212.