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Cytokine and lymphocyte activation during experimental acute pyelonephritis

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Abstract We studied the cellular and humoral events which follow experimental acute pyelonephritis from P-fimbriated *Escherichia coli* to gain insight into the relationships among cells and specifically cytokines to determine how early events in untreated infection lead to renal damage. Cynomolgus (*Macaca fascicularis*) monkeys were studied after they were subjected to unilateral ureteral bacterial inoculation. We evaluated the blood for leukocytosis and studied lymphocyte subsets using flow cytometry and monoclonal antibodies to the subsets and serum, complement, cytokines and antibody titers. Interleukin-1, 2 and 6 and tumor necrosis factor (TNF) were assayed by enzyme-linked immunoadsorbent assay (ELISA), using monoclonal and polyclonal antibodies. Leukocytosis was marked and there were significant elevations in serum cytokines, interleukin-1α, 2 and 6 with only small changes in the level of TNF. Interleukin-2 levels were sustained and may have upregulated the homing receptor for virgin lymphocytes. The studies illustrated the unique relationship between cytokines and lymphocytes and the response to bacterial infection, showing that the inflammatory response is regulated not only by cytokine activity but also by lymphocyte activation.

Key words Pyelonephritis · Lymphocytes · Cytokines

Our previous studies in the monkey showed that the renal infection which occurs after experimental bacterial challenge is self-limited due to both a local and generalized immune response [18]. The cellular immune response is most marked in regional lymph nodes and the infection does lead to a humoral systemic response. Loss of renal function with attendant renal scarring results from nephron loss. This appears to be due to the active infection and the inflammatory response more than to the immune response [17]. Within minutes after intrarenal inoculation of P-fimbriated *Escherichia coli* in our monkey model, activation of the immune response leads to consumption of complement [21]. This chemotactic event leads to granulocytic aggregation, which causes capillary obstruction and renal ischemia which on reperfusion leads to release of toxic forms of oxygen with cell death from lipid peroxidation of cell membranes [20]. The ensuing inflammatory response also causes renal damage from the release of toxic forms of oxygen during the respiratory burst of phagocytosis [22].

In the present study cynomolgus monkeys (*Macaca fascicularis*) were challenged with a renal inoculation of P-fimbriated *E. coli*. In addition to serum anti-P-fimbriated antibody, and serum complement, hematologic data from lymphocyte subsets and serum cytokine levels were obtained during the course of the acute infection. Evaluation of the relationships among these cells and cytokines will give additional insight into the early events which in untreated infection lead to renal damage.

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Materials and methods

Four monkeys were challenged with a unilateral ureteral inoculation of P-fimbriated *E. coli*, leading to renal inoculation by means of pyelotubular backflow. The strain JR1 has both P and type 1 fimbriae, is hemolytic and shows resistance to bactericidal activity of serum. This method of inoculation has been used extensively in this laboratory, and details of the procedure and the data obtained from it have been published [19].

Bacteriology and immunology

Peripheral blood was obtained at 0, 0.8, 1, 2, 7, 14, 21 and 28 days after infection. Blood culture, white blood cell count and differential white count were done at these times. Lymphocyte subsets were evaluated by flow cytometry using fluorescein or phycoerythrin-con-

jugated monoclonal antibodies (mAbs). Serum was stored in aliquots at –70°C for future analyses of complement, various cytokines and antibody titers.

Lymphocyte subset evaluation with mAbs

The following mAbs were used to stain the following subset molecules on lymphocytes: CD20, fluorescein (FITC) conjugated B1 (Coulter, Hialeah, Fla., USA); CD2, phycoerythrin (PE) conjugated T11 (Coulter); CD4, FITC-OKT4 (Ortho, Raritan, NJ, USA); CD29, PE-4B4 (Coulter); CD45RA, PE-2H4 (Coulter); L-selectin PE-Leu8 (Becton/Dickinson, San Jose, Calif., USA); and CD8, FITC-Leu2α (Becton/Dickinson).

Antibodies were combined as follows to evaluate certain subsets: B1/T11–% $CD20^+$ B cells and $CD2^+$ T cells; OKT4/4B4–% $CD4^+$ $CD29^+$ Helper/inducer $CD4^+$ T cells; OKT4/2H4–% $CD4^+$ $CD45RA^+$ suppressor/inducer $CD4^+$ T cells; OKT4/Leu8–% $CD4^+$ $Leu8^-$ true helper $CD4^+$ T cells; Leu2/Leu8 -% $Leu2^+$ $Leu8^+$ L-selectin$^+$ $CD8^+$ cells. Samples of whole blood were incubated with these mAbs for 10 min. The samples were then treated with Coulter's Immunoprep Leukocyte Preparation System (Q-Prep). Red blood cells in the preparation are lysed with formic acid followed by stabilization of the leukocytes with a carbonate-chloride-sulfate solution. The leukocytes were then fixed in paraformaldehyde. The percentage of various subset populations were determined on the Coulter Epics 541 Flow Cytometer, counting 5000 cells.

Cytokines

The interleukins and TNFα were assayed by ELISA kits as follows:

Tumor necrosis factor (Genzyme)

The microtiter plate comes precoated with monoclonal anti-human TNFα. Serum samples and standards are applied and become immobilized on the bound antibody. The second antibody is biotinylated polyclonal anti-human TNFα.Horseradish peroxidase-streptavidin binds to the biotin and the color is generated by tetra-methylbenzidine (TMB) with hydrogen peroxide added. The reaction is stopped by 1 M sulfuric acid.

IL-6 (Biosource International)

The microtiter plates come precoated with polyclonal anti-human IL-6 antibody. Serum samples and standards are immobilized on the plate. The second antibody is a mouse monoclonal anti-IL6 labeled with biotin followed by peroxidase-streptavidin. Again color is produced by TMB and hydrogen peroxide and the reaction is stopped with sulfuric acid.

IL-1α and IL-2 (Assay Research)

These are competitive enzyme immunoassays. The polyclonal anti-human antibody is bound to the microtiter plate. Serum samples and standards are added and the biotinylated cytokine (IL-1α or IL-2) is added at the same time. Incubation is overnight as the cytokine in the sample or standard competes with the tagged cytokine for antibody sites. As the amount of cytokine in the sample increases, the amount of biotinylated cytokine bound decreases. Streptavidin-conjugated alkaline phosphatase binds to the biotin. The substrate is *p*-nitrophenol phosphate (*p*NPP) and the amount of color developed is inversely related to the amount of cytokine present in the sample or standard.

Complement

Total serum hemolytic complement (CH50) was determined using sensitized sheep erythrocytes [23].

Statistics

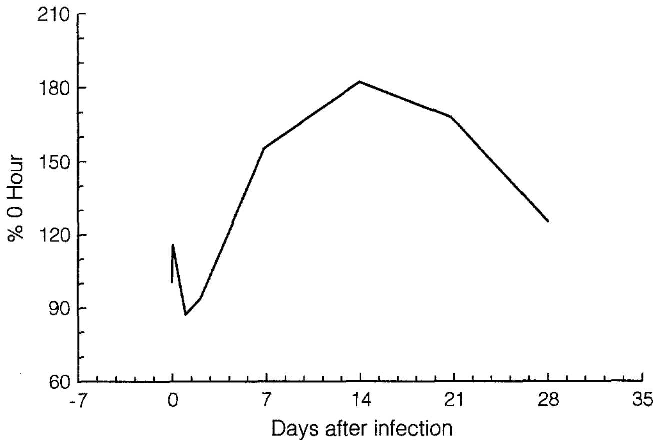
Data were analyzed by one-way analysis of variance with repeated measures and all data from the four animals are reported as the mean values of their percentages of the 0-day values except for P-fimbriae antibody, which is reported as the mean reciprocal of the titer.

Results

Bacteremia was not detected by blood cultures Serum complement dropped markedly within hours, then rose over the ensuing weeks (Fig. 1). Leukocytosis was marked early and continued for the ensuing weeks, while lymphocyte counts decreased 1–2 days postinfection, then increased toward the normal pre-infection numbers by day 7 (Fig. 2). The percentage of total T lymphocytes did not change markedly after infection. However, there was an early marked increase in the percentage of B cells over the first 2 days postinfection, followed by a rapid decrease toward pre-infection values (Fig. 3a). Following the peak of B cell production (Fig. 3a), serum antibodies rose slowly during the course of the infection (Fig. 3b), peaking at about the mean time of bacteriuria (24.84.3 days).

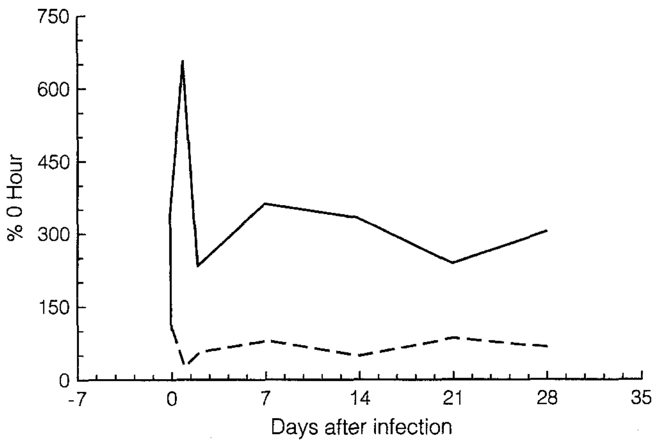
The percentage of $CD4^+$ cells was significantly increased in the 1st week after infection, then progressively decreased during the remainder of the experiment (Fig. 4a). Within the $CD4^+$ subset, the percentage of $CD4^+$ CD45RA (suppressor-inducer) cells decreased slightly for the first 2 days after infection, followed by a marked increase for 7 days (Fig. 4b). In contrast, there was a significant decrease in the percentage of $CD4^+$ $Leu8^-$ (true helper/L-selectin) cells, particularly 2–7 days postinfection. Similar changes in the percentage of CD4+CD29+ (helper-inducer/memory) cells occurred, with a trend toward a decrease 2–7 days postinfection. The percentage of $CD8^+$ cells decreased progressively over the first 48 h after infection, then increased markedly later in the infection (Fig. 4a). Within the $CD8^+$ subset, the percentage of L-selectin$^+$ cells ($CD8^+$ $Leu8^+$) tended to decrease over the first 1–2 days postinfection, then increased markedly (Fig. 4b).

Significant elevations of serum cytokines were observed over time among IL-1α, IL-2 and IL-6; with only small changes being observed in the level of TNF (Fig. 5). There was a marked transient increase in serum IL-6 on days 1–2 postinfection (Fig. 5), coincident with the early increase in the percentage of B lymphocytes (Fig. 3a). Progressive increases in serum IL-1 and IL-2 occurred over the first 7 days postinfection (Fig. 5), coincident with the early increase in the percentage of CD4+cells (Fig. 4a). Later, IL-1 levels declined toward pre-inoculation values, but the IL-2 increase was sustained for the duration of the experiment (Fig. 5), while the percentage of CD4+cells dropped and the CD8+cells (particularly the CD8+Leu8+subpopulation) continued to rise throughout the study (Fig. 4a).



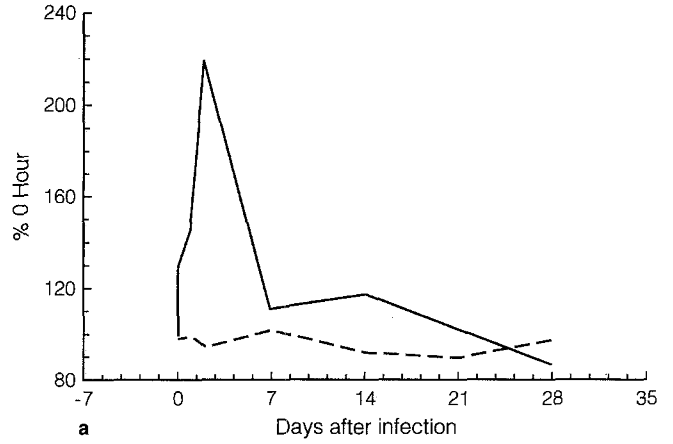
	Days after infection						
	0.08	1	2	7	14	21	28
Complement (% 0 h mean)	115.3	86.6	92.9	154.6	181.2	166.8	124.1
SE	11	9	8	16	31	35	15

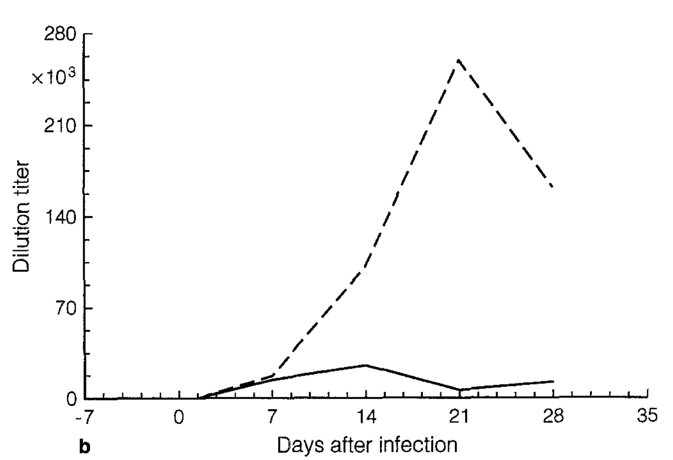
Fig. 1 Serum complement is seen to drop rapidly after infection in the first 24 h and then rise over time. Analysis of variance over time (ANOVA-t) shows that there are significant changes in serum complement levels with an initial fall and a later rise (P=0.003)



	Days after infection						
	0.08	1	2	7	14	21	28
PMN (mean)	334.1	651.4	232.2	358.2	328.1	235.8	301.1
SE	163	248	56	119	39	95	124
Lymph (mean)	107.8	24.9	57.2	79.6	48.7	83.5	65.9
SE	7	3	18	25	6	26	15

Fig. 2 Concomitant with the drop in serum complement is a marked leukocytosis which drops within 48 h to levels still markedly higher than those in the normal peripheral blood. ANOVA-t shows no significant change in polymorphonuclear cell levels, P=0.09, with a significant change in lymphocytes (– – –) over time, P=0.008, because the increase continues over time



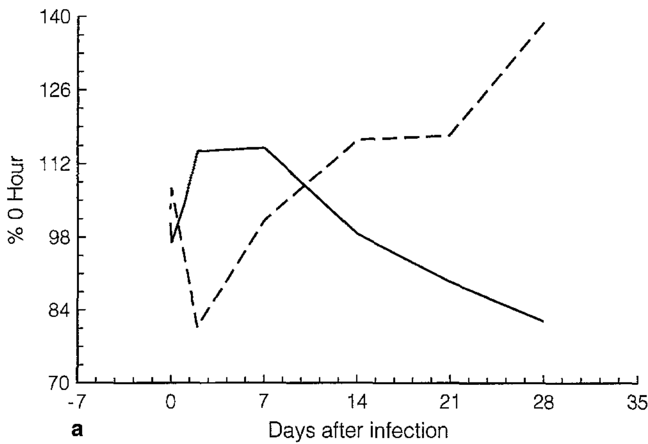


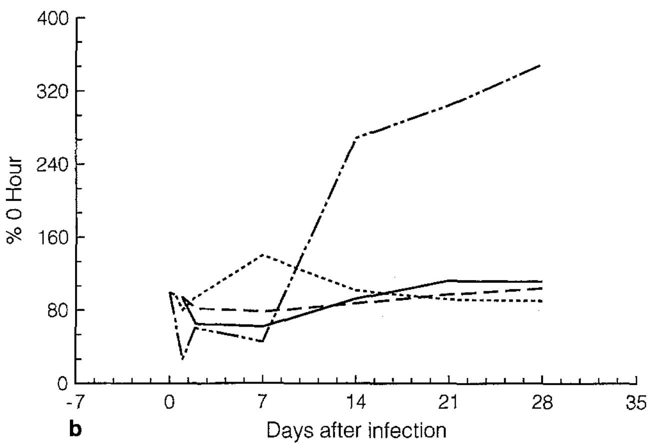
	Days after infection						
	0.08	1	2	7	14	21	28
a							
B (mean)	129.5	144.2	218.0	110.7	117.2	102.3	86.3
SE	20	19	57	20	18	18	15
T (mean)	98.3	98.9	94.1	101.6	91.7	89.3	86.7
SE	0.2	3	2	1	5	10	5
b							
IgG (mean)	325	575	325	16 125	97 000	257 000	162 000
SE	195	412	195	5 569	47 506	89 804	101 681
IgM (mean)	400	475	550	14 100	24 200	4 900	11 400
SE	87	22	144	5 858	6 755	1 552	4 180

Fig. 3a The marked increase in B cell levels (——) is shown over time (ANOVA-t, P=0.01), while no significant change in total number of T cells was noted. **b** Serum antibodies to P-fimbriae rise slowly beginning at 1 week after infection following the peak production of B cells at 48 h. The peak antibody response at 3 weeks correlates with the late rise in CD4 helpers. There was a marked increase in both IgG (– – –) and IgM (——) over time, the IgM rising earlier than IgG to its peak, then falling (ANOVA-t, IgG P=0.01, IgM P=0.009)

Discussion

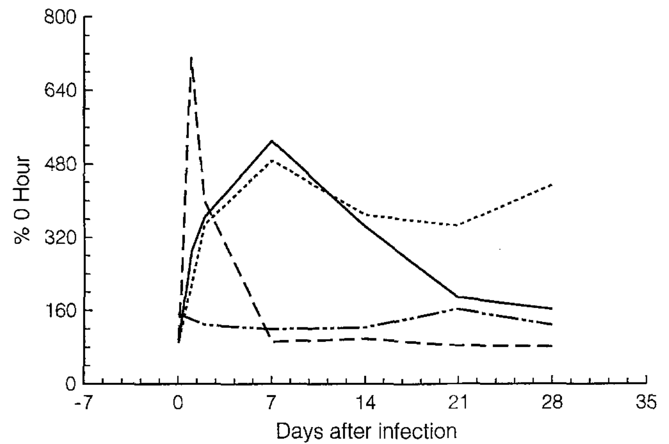
We have shown the relationship between lymphocyte subset alterations and cytokine activation in a model of bacterial renal infection due to *E. coli*. The results suggest that





	Days after infection						
	0.08	1	2	7	14	21	28
a							
CD4 (mean)	97.1	103.7	114.6	115.3	99.0	89.5	81.9
SE	5	2	6	4	5	9	8
CD8 (mean)	107.8	97.3	80.6	101.1	116.6	117.4	138.8
SE	24	17	17	25	28	24	26
b							
CD4CD29	104.5	96.5	82.6	77.8	87.8	97.5	104.2
CD4CD4RA5	95.2	79.4	95.3	140.8	102.7	91.7	89.9
		13	24	16	19	17	29
$CD4^+Leu8^-$	96.0	94.7	65.5	62.2	69.9	112.3	111.1
SE	2	10	10	6	6	13	12
$CD8Leu8^+$	129.1	164.3	347.4	253.9	332.3	342.0	332.6
SE	17	13	31	23	134	152	174

Fig. 4a There is a marked rise in CD4 (——) cells (ANOVA-t, P=0.002). At the same time, CD8 (– – –) cells dropped early showing a marked rise later as CD4 cells fell (ANOVA-t, P=0.04). **b** Lymphocyte subsets show a large increase in $CD8^+$ $Leu8^+$ cells acutely, falling by 1 week but then rising again. There is a marked significant change in $CD4^+$ $Leu8^-$ cells which is sustained (ANOVA-t, P=0.001). The same is true for $CD4^+$ $CD45RA^+$ (ANOVA-t, P=0.02). Both CD4 helper and helper inducer cells rise by 3 weeks. —— $CD4^+Leu8^-$; – – – $CD4^+CD29^+$ (p=0.021); ---- $CD4^+CD45RA^+$ (P=0.0002); – · · – $CD8^+Leu8^+$ (p=0.019)



	Days after infection						
	0.08	1	2	7	14	21	28
IL-1 (mean)	91.1	290.0	363.9	531.0	343.6	187.0	161.5
SE	14	119	115	135	133	51	46
IL-2 (mean)	118.9	204.5	348.6	490.9	367.4	343.7	430.6
SE	28	66	110	148	78	149	170
IL-6 (mean)	95.0	726.8	329.0	90.0	97.6	82.4	78.5
SE	12	296	81	25	17	11	8
TNF (mean)	118.2	139.1	127.5	118.6	122.4	162.3	127.7
SE	11	22	10	8	7	21	10

Fig. 5 The rapid rise and fall of IL-6 levels is a highly significant change (ANOVA-t, P=0.002). Significant rises of IL-1 and IL-2 levels occur somewhat later, both being shown to be significant changes by analysis of variance, while TNF does not show a significant change, although rising somewhat later. —— IL-1 (P=0.003); ······ IL-2 (P=0.011); – – – IL-6 (P=0.002); – · · – TNF (P=0.12)

dynamic alterations in lymphocyte subsets were associated, directly or indirectly, with changes in the levels of serum cytokines, acting alone or in concert.

The lymphocyte subsets examined in this work include those with defined functional capacities in humans. The CD4+CD45RA+subpopulation has been reported to contain suppressor-inducer activity [14] and showed a significant increase in our study. Previous studies in animals with kidney infection have also shown suppression of splenic lymphocyte response to mitogens [25, 12], and it was shown that human T-lymphocyte response to phytohemagglutinin could be suppressed by bacterial lipopolysaccharide [7]. Our studies would suggest that suppressor T cells would be responsible for this suppression. The CD4+Leu8- subpopulation has been demonstrated to contain helper-inducer activity [8, 13] and in our study there was a significant drop in these helper-induced cells which coincided with the increase in suppressor cells. The CD4+CD29+subpopulation has been shown to more clearly delineate helper-inducer cells, separating helper-inducer and suppressor inducer activities [14]. This set of cells did not show significant change The other subsets showed no significant change in our model. CD4+CD29+cells have been demonstrated to be previously activated cells containing mem-

ory activity and having a propensity to localize at sites of tissue inflammation [24, 6]. This subset rose only slightly weeks after infection but this was in peripheral blood. We did not study tissue localization. The Leu8 monoclonal antibody identifies cells that have the surface receptor (LAM-1, L-selectin) for high endothelial cells of the post-capillary venules of lymph nodes and are capable of migrating between blood and lymph nodes [4]. The CD8+Leu8+population may therefore have unique recirculatory properties.

We were limited in the ability to detect the complete repertoire of cytokines in monkeys when exposed to bacteria, but in order to learn how to reduce mortality and morbidity from renal infection in our model of bacterial renal infection we studied the cytokines most frequently associated with inflammation [3]. Lymphokine production is in general a consequence of antigen recognition, while cytokine synthesis by nonlymphoid cells can be triggered by many different activators. It has been shown in humans that *E. coli* stimulates urothelial cells to secrete IL-6 into the urine concomitantly with elevation of serum levels [9]. In vitro studies of urothelial cells in tissue culture showed that IL-1α, IL-6, and IL-8 but not TNF were produced when stimulated by *E. coli* [1]. In our study, serum IL-6 was markedly elevated within hours, then rapidly fell as expected for this cytokine, which initiates the acute phase response. IL-6 has also been shown to stimulate B-cell differentiation as it did in our study [26]. Lipopolysaccharide predominantly induces IL-1 and TNF production in monocytes, while $CD4^+$ T cells also produce TNF, which also induces IL-1 production [16].IL-1α induction was marked in the infected animals. The ability of IL-1 to activate immunocompetent cells seems unique among the group of cytokines which affect cellular growth and proliferation: however, it is not known whether IL-1 production is an absolute requirement for a primary immune response. While cytokines primarily are thought to have autocrine and paracrine activity, we felt that blood levels would parallel cellular production of cytokines. The monocyte with its receptor for bacterial endotoxin (CD14) initiates the cytokine cascade to involve endothelial cells, neutrophils, lymphocytes and fibroblasts [5]. However, the macrophage requires priming by interferon-gamma (IFN-); thus a combination of inflammatory cells and the lymphocytes which produce IFN- as well as TNF, are important in the inflammatory response [23]. This appears to place lymphocyte activation in a prime position and thus we attempted to correlate CD4 T cells, T-helper cells and the production of IL-1α, IL-2, IL-6 and TNF. IL-2 is produced by T-helper lymphocytes upon stimulation with antigen and is the major T-cell growth hormone. It is responsible for amplification of antigen-specific T lymphocytes and may upregulate the function of B cells, monocytes and other cells that participate in the immune response [10]. We found that infection produced a slight elevation in serum TNF with a marked elevation in both IL-1α and IL-2 which positively correlated with the increase in CD4 cells. However, the elevated IL-2 levels were sustained and may have upregulated the homing receptor for $Leu8^+$ virgin lymphocytes in the infected animals as the increase in IL-2 in peripheral blood correlated with the trend to a late increase in $CD8^+$ $Leu8^+$ cells. This has been shown to occur in cutaneous inflammation where $Leu8^+$ (L-selectin) naive cells selectively traffic from blood to lymph nodes [4].Such recirculation through lymph nodes is an effective route for naive lymphocytes, to recognize a new antigen. On the other hand, in most instances a primary immune response, as occurred in this experiment, is usually initiated in a regional lymph node draining the infected tissue as we have previously shown [18]. Subsequent to stimulation of lymphocytes in the node, $CD29^+$ $Leu8^-$ memory cells then migrate via efferent lymph vessels, to the circulating blood and ultimately to the tissue [11].

T lymphocytes, as well as polymorphonuclear cells, secrete enzymes that degrade components of extracellular matrix [15]. The increase in CD4 cells in our acute infection, therefore, may have assisted in capillary transmigration of inflammatory cells to the site of antigen expression by the bacteria. While pro-inflammatory cytokines such as IL-1α and TNFα are unable to modulate endothelial permeability, they may contribute indirectly by increasing endothelial expression of adhesion molecules for polymorphonuclear leukocytes such as ICAMs, leading to adhesion and migration of inflammatory cells to the antigenic site, where capillary obstruction may occur and phagocytosis begins, both leading to release of toxic forms of oxygen which may damage renal tubules, leading to their death [2]. Our studies illustrate the unique relationships between cytokines and lymphocytes in the response to bacterial infection as the inflammatory response is regulated not only by cytokine activity but also by lymphocyte activation. Attempts to modulate the inflammatory response and decrease renal damage, while not affecting the ability of the host to eradicate the bacterial parasite, will probably include treatment with mAbs to IL1, TNF or IFN-, or modulation of their effects by treatment with soluble receptors for those cytokines.

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