

Animal Model of Human Disease

Accelerated (Proliferative) Lupus Nephritis

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Biologic Features

Systemic lupus erythematosus (SLE), a prototype chronic immune complex (IC) disease, often affects the kidneys and results in considerable morbidity and mortality.¹ Whereas a number of animal models of SLE exists,^{2,3} each has varied resemblance to human SLE, except the New Zealand black/white (NZB/W) hybrid, which more closely mimics the human condition.² Thus various investigations have been performed in NZB/W mice and they have contributed significantly to the understanding of genetic, hormonal, immunologic, and environmental factors in the pathogenesis of SLE. One of the disadvantages of this hybrid mouse, however, is that it does not develop significant renal disease until late in life, by 5 to 6 months of age, and proliferative glomerulonephritis does not evolve until 6 to 8 months of age. An accelerated form of nephritis would appear to be interesting because various studies could be performed at an earlier age with considerable savings in breeding and maintenance costs. In addition, if acceleration of nephritis could be induced by an agent commonly present in the environment, then an insight into the influence of environmental factors also could be gained.

It is known that bacterial lipopolysaccharide (LPS) causes intense polyclonal B-cell activation (PBA),⁴ that chronic administration of this agent modulates lupus nephritis,^{5,6} and that it induces nephritis in immunologically normal mice.⁷⁻⁹ We sought to determine whether short-term administration of LPS might produce an accelerated model of proliferative lupus nephritis in NZB/W mice.

We report herein that LPS from gram-negative bacteria induces proliferative lupus nephritis in 3- to 3.5-month-old

NZB/W and that the mechanism of induction involves, at least in part, PBA and results in renal insufficiency and massive proteinuria.

Model Description

Hybrid NZB/W mice at 8 weeks of age are exposed to 50 μ g of LPS from *Salmonella minnesota* Re595 twice a week for 5 weeks. The LPS is dissolved in 0.2 ml of sterile saline and is administered *via* an intraperitoneal route.⁷

With completion of the injection period, NZB/W mice treated with LPS (NZB/W LPS) consistently developed serologic features that are characteristic of PBA with hypergammaglobulinemia, enhanced concentration of antibodies to single-stranded DNA (ssDNA) and C1q-reactive materials in the circulation, raised creatinine concentration, and abundant proteinuria (Table 1).

Glomeruli from NZB/W LPS mice were enlarged and showed proliferation of intrinsic cells, infiltration with leukocytes, and occasional necrosis of loops and crescent formation (Figure 1A). There were deposits of IgG, IgM, IgA, and C3 in mesangia and capillary loops (Figure 1B), which were confirmed by electron microscopy. By contrast, matched NZB/W control mice had minimal increase in mesangial matrix and cells, no infiltration with leukocytes (Figure 2A), and small amounts of the referenced reactants in a mesangial location (Figure 2B).

Publication sponsored by the Registry of Comparative Pathology, Armed Forces Institute of Pathology and supported by Grant RR-00301 from the Division of Research Resources, NIH, under the auspices of Universities Associated for Research and Education in Pathology, Inc., and by Hazelton Laboratories America, Inc.

Supported in part by Grants DK-38644 from the National Institute of Diabetes and Digestive and Kidney Diseases, from Rhode Island Foundation Grant 87215, and from the Institutional Endowment Funds for Research from Rhode Island Hospital.

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Table 1. Summary of Assays in LPS-treated and Control NZB/W Mice *

Groups	IgG (mg/ml)	ssDNA†	C1qBA‡	Creatinine (mg/dl)	Proteinuria (mg/24 h)
NZB/W LPS	27.0 ± 0.3	80.3 ± 0.4	7.5 ± 1.0	0.18 ± 0.01	17.6 ± 1.1
NZB/W control	9.5 ± 0.8	27.8 ± 2.9	0.6 ± 0.1	0.10 ± 0.00	2.8 ± 0.1

* Values are means ± standard error of the mean.
 † Percentage DNA binding by 10.0 μL of plasma.
 ‡ mg equivalent of aggregated human IgG/ml.
 || $P \leq 0.003$.
 IgG concentrations in plasma determined by solid-phase immunoassay.³
 Antibodies to ssDNA in plasma determined according to Izui et al.¹⁰
 C1q binding assay (C1q-BA) in plasma determined according to Zubler et al.¹¹
 Creatinine concentration in plasma determined by automated color reaction (Ektachem 700).
 Urinary protein excretion determined by a modified Lowry's assay.¹²

Comparison with Human Disease

The LPS-induced accelerated proliferative glomerulonephritis in NZB/W mice mimics proliferative lupus nephritis in humans from the viewpoint of clinical and serologic aspects, immunopathologic findings, and organ dysfunction.^{1,2}

Potential Usefulness of the Model

The similarities in serologic and immunopathologic changes in this accelerated model of lupus nephritis

makes it a valuable resource for studies into the pathogenesis of lupus, and in particular, that of proliferative lupus nephritis. In addition, because of the accelerated nature of the model, valuable information regarding therapeutic approaches or immunologic manipulations can be obtained within a much shortened time. Also, because LPS from *Salmonella* is an agent commonly present in the environment,¹³ and because other bacterial LPS also appear to cause nephritis,¹⁴ the role of PBA may be more sharply focused, overall, to advance the knowledge of modulators of nephritis.

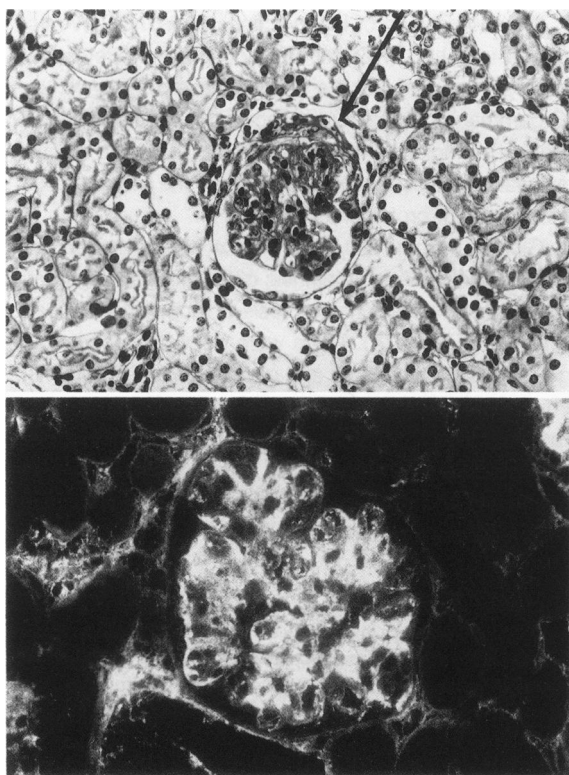


Figure 1. Glomeruli from a NZB/W LPS mouse. **A:** There is enlargement of the tuft with increased number of cells and leukocytic infiltration of capillary loops; a crescent formation (arrow) is evident. Periodic acid Schiff stain, ×270. **B:** Deposits of immunoreactants, increased compared to Figure 2B, are located in mesangia and capillary loops. Fluoresceinated antibody to mouse IgG, ×360.

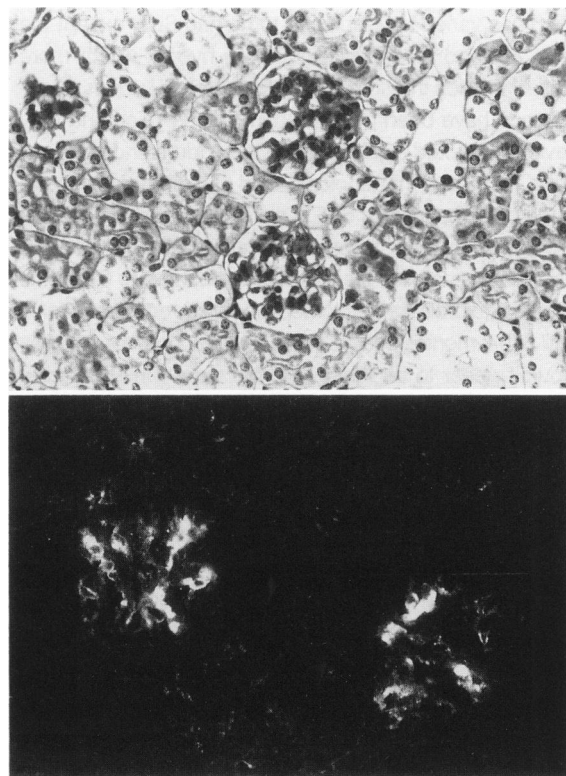


Figure 2. Glomeruli from a BW mouse. **A:** There is increase in mesangial matrix and cells; capillary loops are patent. Periodic acid Schiff stain, ×270. **B:** Deposits of immunoreactants are shown in mesangia. Fluoresceinated antibody to mouse IgM, ×360.

Availability

NZB and NZW mice are available from the Jackson Laboratories (Bar Harbor, ME). Bacterial LPS is available from commercial sources (Calbiochem-Behring, La Jolla, CA). Lipopolysaccharide derived from the rough mutant Re595 is preferable because it is rich in lipid A, which is mitogenic and minimally antigenic, and it can induce long-lasting production of IgG and IgM autoantibodies.^{4,15,16}

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Acknowledgments

Rodney Nunley, Joseph Langevin, and Kerry Graves assisted with the experimental protocols. Annette Ragosta and Colette Charland performed the serologic assays. Laura Gantt provided expert secretarial support.