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Gastric Dilatation Syndrome Associated with Chronic Nephropathy, Hypergastrinemia, and Gastritis in Mice Exposed to High Levels of Environmental Antigens

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Gastric dilatation (GD) has been observed in Tac:(SW)fBR surveillance mice, with mean age of 10 months, that are exposed to high levels of environmental antigens during routine exposure to dirty bedding. The aim of the study reported here was to determine whether GD was associated with other systemic conditions affecting mice. Three groups of nine animals including—surveillance mice not exposed to dirty bedding (control), surveillance mice without GD (NGD), and surveillance mice with GD (group GD)—had mean stomach weight with ingesta of 0.5 ± 0.02 g, 1.09 ± 0.07 g (*P* < 0.0001), and 2.54 ± 0.4 g (*P* < 0.0001), respectively. Mean serum creatinine concentration was significantly higher in GD (1.6 ± 0.25 mg/dl), compared with NGD (0.17 ± 0.22 mg/dl, *P* < 0.0001) and control (0.2 ± 0.16 mg/dl, *P* < 0.0001) mice. In addition, lesions consistent with severe chronic nephropathy and mild gastritis were common in GD, compared with NGD and control mice. Finally, serum amidated gastrin concentration was significantly high in GD (179.37 ± 53.86 p*M*, *P* < 0.03) and NGD (264.89 ± 115.89 p*M*, *P* < 0.009), compared with control (60.77 ± 8.39 p*M*) mice. Gastric dilatation syndrome is associated with chronic nephropathy, hypergastrinemia, and gastritis in surveillance mice exposed to high levels of environmental antigens.

Chronic gastric dilatation (GD) often occurs as a secondary manifestation of metabolic, neurologic, or muscular disorders (1). In humans with chronic renal failure with uremia, gastrointestinal manifestations are common (2). Gastric motility becomes impaired, leading to delayed gastric emptying and gastroparesis (3-6). Those individuals may have dyspepsia, gastroesophageal reflux, and/or symptoms of stasis, including anorexia, nausea, vomiting, early satiety, abdominal pain, and bloating (7). Many conditions have been associated with this syndrome and include electrolyte disturbances, high levels of uremic toxins, high plasma concentrations of gastrointestinal hormones, and dysfunction of the autonomic nervous system (8).

Chronic nephropathy in rodents has been described extensively. In rats, the pathogenesis is not clear, but genetic background, sex, and environmental factors influence onset and progression of the renal lesions (9). Similarly, environmental factors and sex influence spontaneous development of immune complex-type glomerular lesions in outbred mice. Such lesions may be triggered by various microbial agents (10). Interestingly, gastric emptying in rats with renal insufficiency is more sensitive to the action of bacterial lipopolysaccharide (LPS) (11).

Health surveillance in colonies consisting of large numbers of mice is often accomplished by exposing sentinel animals to contact bedding used by the colony members (12). Prior to 1999, the MIT Murine Health Monitoring Program consisted of four sentinel mice per cage that were removed for diagnostics and necropsy at six-month intervals. Two mice remained in the cage for six months, and the other two were kept in the cage for one year. Consequently, with introduction of a new program, there was a doubling of mice with mean age of 10 months during the second half of 1999. The observation of GD coincided with an increase in morbidity by the end of the year. The purposes of the study reported here were to investigate the conditions associated with GD and elucidate the pathogenesis of this syndrome.

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Materials and Methods

Surveillance program. The MIT Murine Health Monitoring Program consists of approximately 330 Swiss Webster mice. The program was re-designed in 1999 on the basis of a rotating schedule in which, every six months, two sentinel mice are removed for diagnostic (including serologic) testing and necropsy and are replaced by two new mice. With this system, there are always four mice in one cage. Animals remain in the program for one year; however, if they die or become clinically ill, they are replaced and diagnostic tests are performed.

Surveillance mice are placed in cages at two months of age and are exposed to dirty bedding to determine whether colony mice are infected with murine pathogens. Procedurally, one 40-cm^3 plastic scoop of dirty bedding from each of 30 colony cages is transferred to each surveillance cage weekly to achieve a ratio of one part clean to two parts dirty bedding in each cage. Clinical monitoring is performed daily, and mice that die are submitted for necropsy.

Animals. Three groups of nine Tac:(SW)fBR female mice (Taconic Farms, Germantown, N.Y.), with mean age of 10 months, were studied, and consisted of: surveillance mice not exposed to dirty bedding (control), surveillance mice exposed to dirty bedding without GD (NGD), and surveillance mice with GD (group GD) exposed to dirty bedding. Surveillance mice were assigned to the GD group at necropsy on the basis of gross observation of GD. The NGD and control groups of mice were harvested at 10 months of age and findings were compared with those

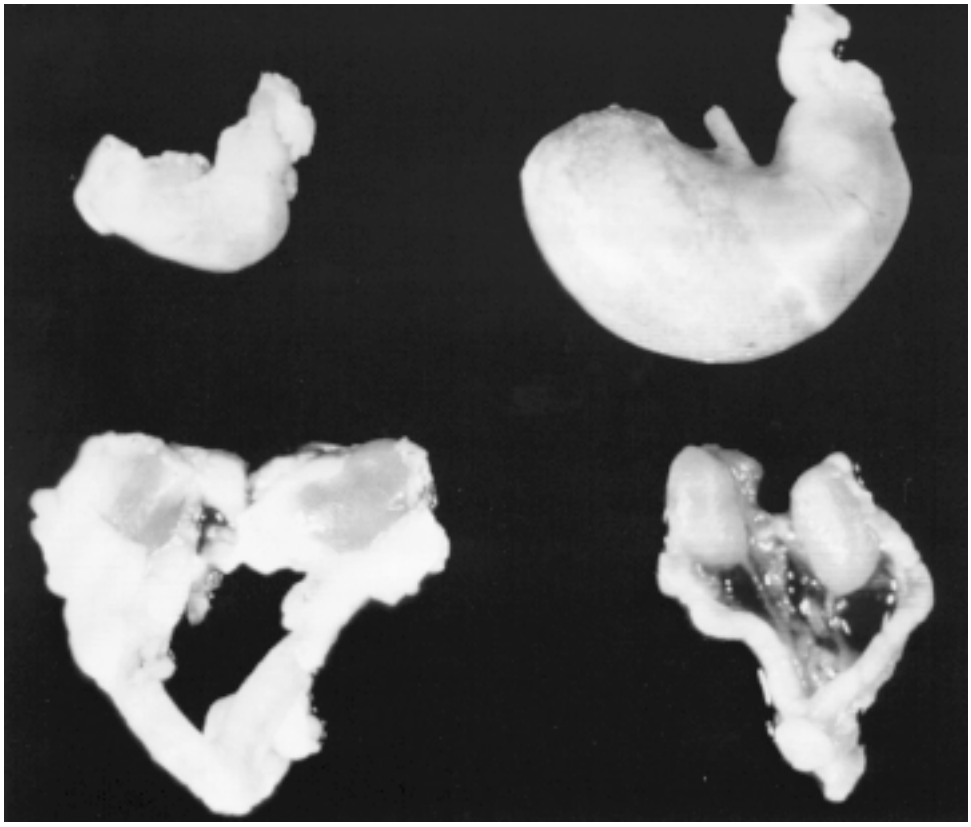

Figure 1. Comparison of the stomach and kidneys of control mice (left) and mice with gastric dilatation (GD; right). The GD mice had dilated stomach full of ingesta, pale discoloration of the kidneys, and lack of perirenal adipose tissue. Control (left) and surveillance mice without GD (NGD) did not have gross pathologic changes.

of the GD group. Animal use was approved by the MIT Committee on Animal Care.

Health status. As determined by commercial vendors supplying colony mice and our monitoring of surveillance mice, resident mice were free of ecto- and endoparasites and were antibody free to all known viral and bacterial mouse pathogens, with the exception of several *Helicobacter* spp., including *H. hepaticus*, *H. bilis*, and *H. rodentium* (13). Importantly, some mice of the GD group were housed in specific-pathogen-free (*Helicobacter*- and *Pasteurella*-free) facilities (13).

Housing. All mice were housed in facilities approved by the Association for the Assessment and Accreditation of Laboratory Animal Care. The light cycle was 12 h light and 12 h darkness; humidity was kept between 40 and 70%, and room temperature was 22°C. Heat-treated hardwood was used for bedding (Sanichips, PJ Murphy Inc., Montville, N.J.). Pelleted diet (RMH 3000, Purina Mills Inc.,Richmond, Ind.) and water were provided ad libitum.

Gross necropsy. Animals were euthanized by CO_2 inhalation and weighed, then blood was collected via intracardiac puncture. Complete necropsy was performed. The stomach was excised (2 mm proximal to the distal esophageal sphincter and 2 mm distal to the pyloric sphincter) and weighed with the gastric contents included, using a described method (14). Stomach weight measurements in all three groups were performed between 10 a.m. and 2 p.m.

Clinical pathologic examination. Serum biochemical analysis for creatinine and glucose was performed (747 Hitachi spectrophotometer, San Jose, Calif.). Total amidated gastrin concentration was measured by use of a radioimmunoassay as described (15).

Culturing. Aerobic and anaerobic culturing was performed on the gastric contents of two animals with GD. Aerobic culturing was performed at 37°C, using MacConkey, blood (trypticase soy agar with 5% sheep blood), and chocolate agars, and trypticase soy broth (Remel, Lenexa, Kans.). Anaerobic culturing was also performed at 37°C, using blood agar. Aerobic and anaerobic culture plates were incubated for two and five days, respectively, before determining that there was no bacterial growth. Blood culturing for aerobes and anaerobes also was performed in three other mice with GD, using a pediatric blood culture system (BBL, Septi-Chek, Becton Dickinson and Company, Cockeysville, Md.). The blood cultures were incubated for seven days and examined for growth on days three, five, and seven.

Histologic examination. Tissues were fixed in neutral-buffered 10% formalin, embedded in paraffin wax, sectioned at 5- to 6-µm thickness, and stained with hematoxylin and eosin (H&E). Kidney specimens also were stained with Masson's trichrome for collagen and Congo red for amyloid. Histologic analyses of the kidneys, stomach, small and large intestines, liver, spleen, pancreas, heart, lungs, reproductive tract, salivary glands, thymus, lymph nodes, and brain from mice of the GD group were performed. Age-matched control and NGD groups were analyzed for renal and gastric lesions, and results were compared with those of mice of the GD group. The kidneys and stomach were evaluated in blind manner, and the histologic changes were scored. The interstitium, tubules, glomeruli, and vasculature were scored separately, using a scale of 0 to 4 (normal, minimal, mild, and marked). The interstitium was scored for inflammation and fibrosis; the tubules were scored for luminal dilatation and epithelial alterations, including degeneration, necrosis, atrophy, regeneration, and hypertrophy. The glomeruli were evaluated on the basis of size, degree and character of cellularity, amount of matrix, and fibrosis; the vasculature was evaluated based on expansion of the vessel wall with inflammatory cells. The fundus and pylorus of the stomach were evaluated separately for inflammation and hyperplasia, using a scale of 0 to 4 (normal, minimal, mild, and marked).

Statistical analysis. Results were expressed as mean ± SEM. Comparison of the mean values was carried out by use of the Student's *t* and Wilcoxon rank sum tests. Differences were considered significant if $P < 0.05$.

Results

Prevalence of GD in the surveillance program. During the second half of 1999, there were approximately 15, compared

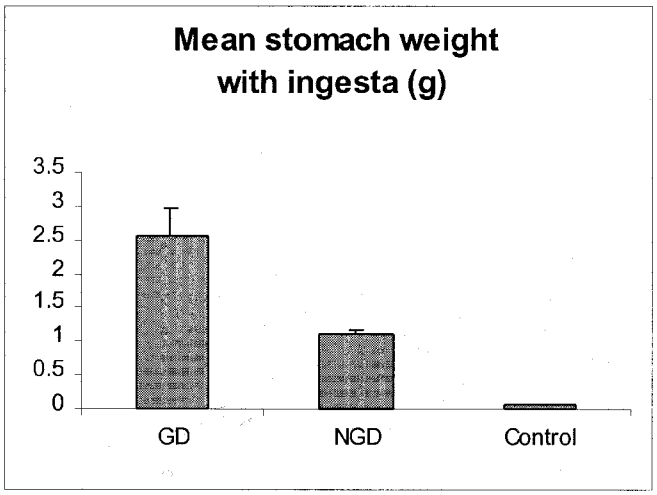

Figure 2. Mean stomach weight with ingesta in GD, NGD, and control groups of mice. Animals with gross GD had mean stomach weight with ingesta significantly higher than that of NGD ($P < 0.001$) and control ($P < 0.0001$) groups. Mean stomach weight for the NGD group was significantly higher ($P < 0.0001$) also than that of the control group.

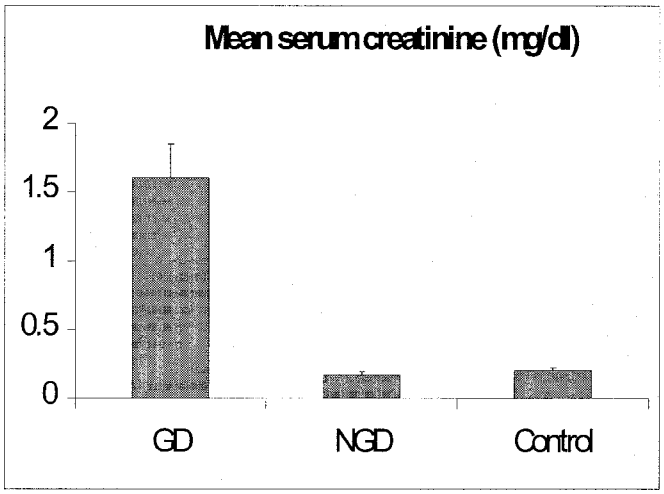

Figure 3. Mean serum creatinine concentration in GD, NGD, and control groups. The GD mice had mean serum creatinine values that were significantly higher than those of NGD ($P < 0.0001$) and control ($P < 0.0001$) mice.

with 5 deaths during the first half. Gross GD was observed in 5 animals (31%) that died during the second half of 1999; however, no cases were detected during the first half of the year.

Clinical assessment. Mice of the NGD and control groups remained clinically normal, and gross inspection of all major abdominal organs at necropsy failed to detect lesions. Mice of the GD group had mean age of 10 months and clinical signs of disease, including lethargy, dehydration, poor body condition, hunched posture, and abdominal distention. Gross findings at necropsy included loss of adipose tissue, dilated stomach full of ingesta, and pale discoloration of the kidneys (Fig. 1). Mean stomach weight with ingesta was significantly higher in mice with gross GD (2.54 ± 0.41 g) than in NGD (1.09 ± 0.07 g, $P < 0.001$) and control (0.5 ± 0.02 g, $P < 0.0001$) mice (Fig. 2).

Clinical pathologic findings. Animals of the GD group were uremic; mean serum creatinine concentration was significantly higher in GD (1.6 ± 0.25 mg/dl) than that in NGD (0.17 ± 0.22 mg/dl, $P < 0.0001$) and control (0.2 ± 0.16 mg/dl, $P < 0.0001$) mice (Fig. 3). There was no significant difference in mean serum glucose values, which were normal in control (217 ± 7.39 mg/dl), NGD (217 ± 12.17 mg/dl), and GD (201 ± 76.27 mg/dl) mice. In addition, mean serum amidated gastrin concentration was significantly high in GD (179.37 ± 53.86 p*M*, $P < 0.03$) and NGD (264.89 ± 115.89 p*M*, $P < 0.0009$), compared with control (60.77 ± 8.39 p*M*) mice. However, there was no significant difference in serum amidated gastrin concentration between NGD and GD mice (Fig. 4).

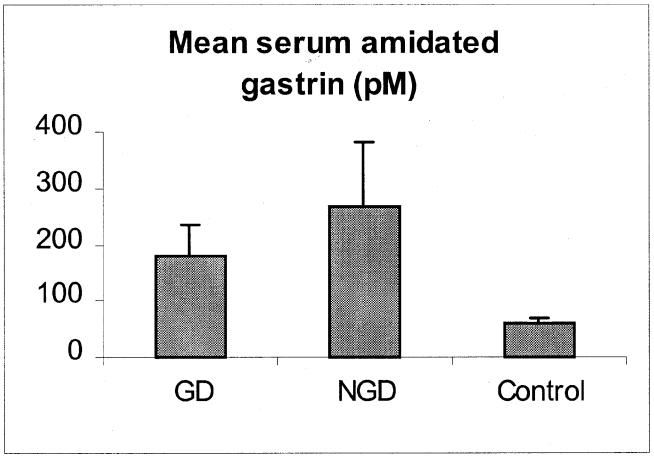

Figure 4. Mean serum amidated gastrin concentration in GD (179.37 ± 53.86 pM), NGD (264.89 ± 115.89 pM), and control (60.77 ± 8.39 pM) groups. The GD ($P < 0.03$) and NGD ($P < 0.0009$) mice had mean serum amidated gastrin values that were significantly higher than control values. There was no significant ($P < 0.53$) difference in serum gastrin concentration between NGD and GD groups.

Culture results. Pathogenic organisms were not isolated from the gastric contents and blood of mice with GD.

Histopathologic findings. The kidneys of GD mice contained extensive lesions with a significantly ($P < 0.001$) greater degree of change, compared with those of NGD and control mice (Table 1). Interstitial inflammation was predominantly lymphoplasmacytic in a perivascular orientation associated with the large arcuate vessels and glomeruli. Interstitial fibrosis was localized to the immediately periglomerular areas surrounding affected glomeruli. Tubular epithelial changes were characterized by degeneration and hyperplasia, with notable absence of atrophy or necrosis (Fig. 5). Dilated tubular lumens contained eosinophilic proteinic material. Affected glomeruli had loss of capillary detail with thickened, eosinophilic, variably fibrotic mesangium, thickened basement membranes, and multifocal adherence to Bowman's capsule, frequently resulting in ablation of Bowman's space (Fig. 6). Vascular changes were most prominent in the walls of the arcuate vessels, which were variably expanded by homogenous eosinophilic material containing small amounts of cellular debris, and were frequently surrounded by a prominent lymphoplasmacytic cuff. Renal amyloid was not detected on the basis of Congo red staining.

Changes within the gastric tissues examined were minimal and consisted of a minimal to mild infiltrate of lymphocytes and plasma cells within the deep lamina propria with no extension into glandular lumens or the submucosa. However, the degree of gastritis in the fundus was significantly greater in GD (mean score = 1.12), compared with NGD (mean score = 0.2, $P < 0.004$) and control (mean score = 0.4, $P < 0.02$) mice. Other morphologic changes were not detectable in the fundus and pylorus of the stomach.

Table 1. Mean scores for renal lesions in mice with and without gastric dilatation (n = 9/group)

Group	Vascular changes	Interstitial inflammation	Interstitial fibrosis	Tubular dilation	Tubular epithelial changes	Glomerular morphology	Glomerular fibrosis
GD	1.25+0.53	2.18+0.16	2.0+0.32	3.31+0.18	3.35+0.18	3.25+0.28	0
NGD	0	0.4+0.13	0	0	0.27+0.14	0.22+0.15	0
Control	0	0.38+0.14	0	0	0.05+0.05	0.22+0.22	0.11+0.1

The most prominent lesions were observed in the tubules and glomeruli of GD mice. All renal changes in GD mice were significant ($P < 0.001$), compared with those in NGD and control mice.

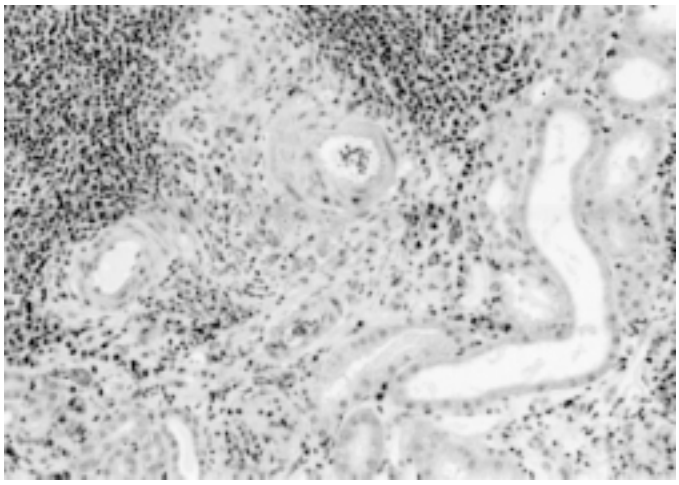

Figure 5. Photomicrograph of a section of kidney from a mouse of the GD group with chronic nephropathy. Tubules have dilated lumens, with degenerative to hypertrophied epithelium. Interstitial perivascular dense mononuclear aggregates are adjacent to vessels with expanded walls. H&E stain; magnification = 100x.

Discussion

The study reported here documents a syndrome of GD in surveillance Tac:(SW)fBR mice, with mean age of 10 months, exposed to high levels of environmental antigens. A strong association existed between this clinical syndrome and the pathologic diagnoses of chronic nephropathy, hypergastrinemia, and gastritis in surveillance mice. Although pathogenic microorganims were not isolated from the gastric contents and blood of affected mice, the chronic nephropathy we observed could have been the result of high concentrations of bacterial antigens in the dirty bedding (10). Experimentally, C57BL/6, BALB/c, DBA/2, and OF1 female mice infected with *Escherichia coli* developed immune complex glomerulonephritis (16, 17). In addition, oral and intraperitoneal administration of other gram-negative bacteria as well as LPS causes IgA nephropathy in C3H/HeN mice (18). In this study, the most prominent renal lesions affected the tubules and glomerular tufts of mice of the GD group. The mean score for degeneration and hypertrophy of renal tubular epithelium was higher in NGD than control mice. Interestingly, tubular epithelial lesions can be induced by LPS injection in rats (19). In addition, gastric emptying in rats suffering from moderate renal insufficiency is more susceptible to the effects of LPS (11). Since gram-negative bacteria are commonly isolated from feces of colony and surveillance mice in our facility, it is possible that these bacteria and their LPS may have played a role in the pathogenesis of chronic nephropathy in affected mice.

Gastrointestinal disease is common in patients with chronic renal failure. Gastric mucosal abnormalities ranging from edema to ulceration develop in two thirds of humans dying of uremia (2). Chronic nephropathy is also associated with hypergastrinemia and delayed gastric emptying, and the term "uremic gastroparesis" has been used to describe this syndrome in humans (6, 20-23). Although motility measurements were not performed in the mice of this study, GD suggested gastric stasis. In addition, hypergastrinemia was observed in both groups of surveillance mice (NGD and GD) exposed to dirty bedding and was not dependent on the presence of chronic nephropathy and uremia. However, bacterial antigens in combination with proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) can stimulate gastrin release from cultured G cells (24, 25). A similar mechanism in combination with chronic renal failure may be important in the pathogenesis of GD in surveillance mice (26).

The GD mice had significant hypergastrinemia and gastritis. In contrast, the NGD mice also were hypergastrinemic, but had only a minimal degree of gastritis. This suggests that the greater amount of gastric inflammation observed in the GD mice was secondary to gastric stasis (27). The high gastrin concentration may have predisposed or contributed to the development of GD through a mechanism of delayed gastric emptying (6).

Although paresis of peristalsis and ileus of the small intestine have been recognized in lactating mice, GD in surveillance mice appears to have a different pathogenesis (28). Importantly, conditions that induce neuromuscular dysfunction of the gastrointestinal tract have the potential to cause gastric stasis and result in GD. Two possible causes affecting surveillance mice include autoimmune and metabolic neuropathies. Although dysautonomia secondary to demyelinating polyneuropathy may have caused GD, the two main causes of metabolic neuropathies are diabetes mellitus and chronic renal insufficiency (6, 29). The pathogenesis of gastric stasis involved in diabetes mellitus is associated with hyperglycemia and vagal autonomic neuropathy. However, serum glucose values were normal in all three groups of mice studied. Autonomic neuropathy secondary to chronic renal failure cannot be excluded since it is a recognized complication (21). In humans with uremia, high serum TNF-α values are associated with neuropathy, altered production of neuromuscular neurotransmitters, and gastric hypomotility (30, 31). Recently, gastroparesis has also been associated with remodeling of the networks of the interstitial cells of Cajal which generate electrical pacemaking in the stomach (32). In addition, gastric stasis was observed in neuronal nitric oxide (NO) synthase-deficient knockout mice (33). In the stomach, excess and deficient NO production have been reported to induce gastric stasis. Interestingly, induction of large amounts of NO release by injection of LPS has been documented to delay gastric emptying (34-36).

In conclusion, this study has documented that gastric dilatation syndrome is associated with chronic nephropathy, hypergastrinemia, and gastritis in surveillance mice exposed to high levels of environmental antigens. Endotoxins (LPS) and bacterial products in dirty bedding may have initiated or contributed to the pathologic changes observed in clinically affected mice. Preliminary immunohistochemical examination of renal tissues from mice with GD suggests deposition of IgA and complement in

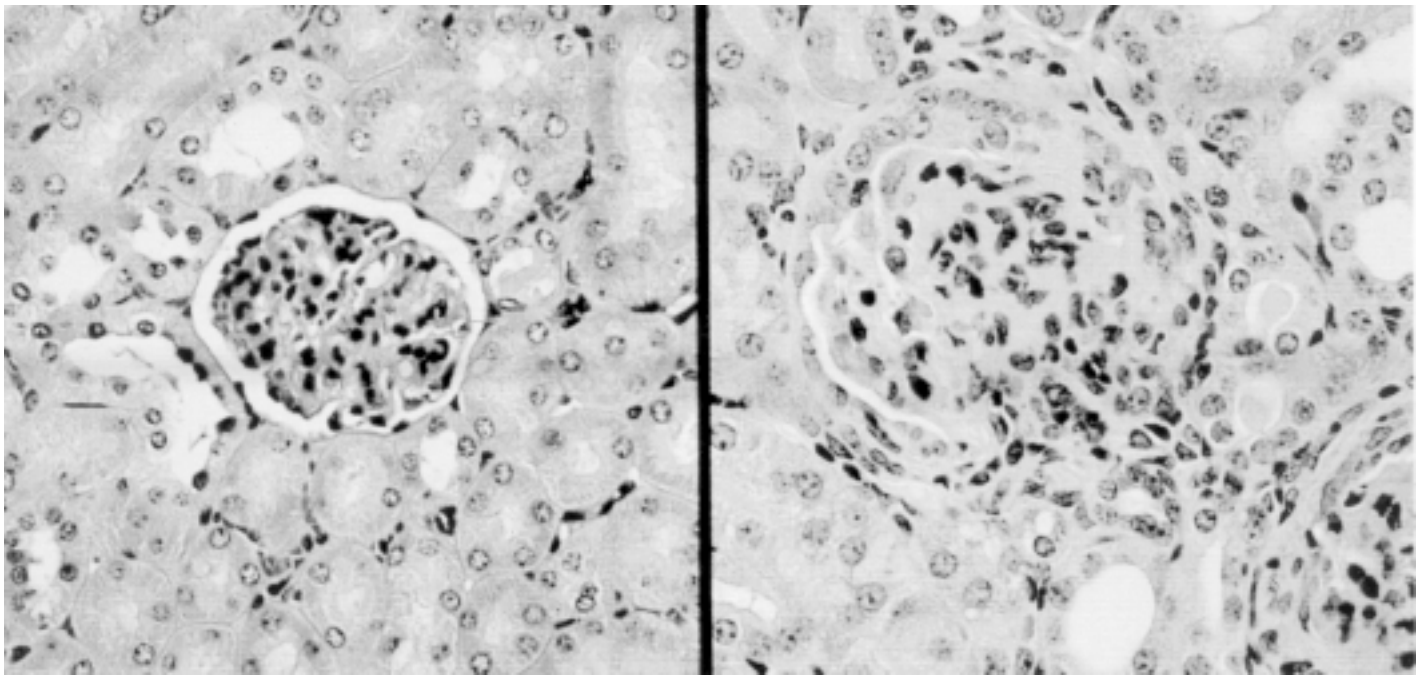

Figure 6. Photomicrographs of sections of glomeruli from control or NGD (left) and GD mice (right). Expanded, hypercellular GD glomerular tuft lacks capillary detail and is multifocally adherent to Bowman's capsule, with obliteration of Bowman's space and squamous crescent hypertrophy of the parietal epithelium. Features of control or NGD glomeruli are unremarkable. H&E stain; magnification = 400x.

the glomerular tufts. This finding may support an immune-mediated cause. Future studies are in progress to explore the detailed pathogenesis of this syndrome.

Acknowledgments

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