A re-evaluation of the renal ablation model of progressive renal disease in rats

Kee Hyuck Kim[1], Youngki Kim[2], Hye Won Park[3], Hyeon Joo Jeong[4], Michael Mauer[2]

[1]Department of Pediatrics, NHIC Ilsan Hospital, Koyang - Korea
[2]Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota - USA
[3]Department of Pediatrics, Pochon CHA University, Sungnam - Korea
[4]Department of Pathology, Yonsei University College of Medicine, Seoul - Korea

ABSTRACT: ***Background:*** **The remnant kidney model, usually involving sudden removal or ablation of 1-½ to 1-⅚ of renal mass, results in compensatory hypertrophy followed by hypertension, proteinuria and declining glomerular filtration rate (GFR) associated with focal (FSG) and then global glomerulosclerosis (GS) and tubulointerstitial injury (TI). Since most renal diseases involve much more gradual injury, we asked whether slow ablation (SA) produced a different natural history than fast ablation (FA).**

Methods: **Male Münich-Wistar rats underwent heminephrectomy, 3 weeks later a second, and 3 weeks later a third heminephrectomy (SA). They were compared to littermates undergoing simultaneous removal of 1-½ kidneys (FA) and sham operated controls (C).**

Results: **Three weeks after the second heminephrectomy, the SA rats had no FSG and glomerular volume (GV) was similar to that of FA rat renal tissue removed at that time. Eight weeks following the final surgical procedure (FSP), the SA and FA groups had similar blood pressures (BP) but higher than C. Albumin excretion rates (AER) were higher in SA and FA vs. C at 1 month after the FSP and, throughout most of the subsequent 5 months, greater in the SA vs. FA groups. At 24 weeks, cortical interstitial fractional volume was double C values in both the SA and FA groups. Percentage of glomeruli with FSG and size (score) of FSG lesions was much higher in SA and FA than C. Moreover, the percentage of FSG in SA (61.2±16%) and FSG score (1.7±0.7) was greater than in FA animals (35.6±11.9% and 0.9±0.4, $p<0.01$ for each comparison). Mean GV, increased at 24 weeks in both groups over C ($1.4\pm0.2 \times 10^6$ µm³) was greater in SA ($3.4\pm0.7 \times 10^6$ µm³) than FA rats ($2.1\pm0.4 \times 10^6$ µm³; $p<0.005$).**

Conclusions: **The gradual uninephrectomy in the SA group, insufficient *per se* to produce significant renal damage, preconditioned the residual kidney, upon further removal of another ½ kidney, to more albuminuria and FSG lesions than occurred following sudden 1-½ nephrectomy, despite similarly elevated BP. Perhaps more time for glomerular enlargement in the SA group preconditioned the remnant kidney to accelerated injury.**

Key words: *Rats, Remnant kidney model*

INTRODUCTION

The rat remnant kidney model, usually involving the removal or ablation of 1-½ to 1-⅚ of renal mass, has been widely used to investigate mechanisms of renal injury and principles derived from this model have been applied to human renal research. The rat model initially results in compensatory hypertrophy of the residual normal renal tissue. This is followed by the development of hypertension, proteinuria, and gradually declining glomerular filtration rate (GFR) associated with focal and then global glomerular sclerosis and progressive tubular and interstitial injury, eventually culminating in the animal's death in advanced uremia (1-3). These processes are associated with increased glomerular capillary pressures and flows (1, 4), thought to be pathogenetically important since manipulation of these variables by reduction in protein intake (1, 5) or anti-hypertensive therapy (6) is associated with reduction in the rate of injury in this model. Compensatory glomerular hypertrophy may also be important, since, in a model manipulated to prevent this glomerular enlargement, glomerular capillary hyperfiltration and hypertension alone were insufficient to induce this renal injury process (3). A possible limitation in the remnant kidney model as a representation of human renal injury is that clinical renal disease in humans rarely results from the sudden loss of the large majority of renal mass. Rather, most human renal diseases are characterized by more gradual loss of functioning renal tissue. The current study tested the hypothesis that a more gradual reduc-

tion in functioning renal mass in rats could result in a different natural history in the rat remnant kidney model.

Materials and Methods

Male Münich-Wistar rats (Bioproducts Division, Harlan Sprague-Dawley, Madison, WI) weighing 250 grams at the start of the experiments were randomly allocated into 3 groups.

Slow ablation (SA) group. Gradual renal mass reduction: Rats had an initial heminephrectomy under general anesthesia. Through a left flank incision, the mass of the left kidney was reduced by approximately one half by removal of the upper and lower poles of the left kidney. In preliminary studies performed on 3 rats, we confirmed using the Cavalieri method (7) that, in fact, about half of the renal mass and cortex was removed using this method. Three weeks later, the remainder of this kidney was removed through a midline incision. Three weeks later, in a final surgical procedure (FSP), a contralateral right heminephrectomy was performed as described above through a right flank incision. Duration in the SA group was timed from the day of this final surgical procedure.

Fast ablation (FA) group. Sudden renal mass reduction: Rats had sham operations performed at the times of the first 2 procedures in the SA group. Sham operations were carried out by exposing the appropriate kidney and removing the renal capsule. At the initial sham operation, the left kidney was exposed and renal capsule was removed. At the second sham operation, the left kidney was again exposed and scar tissues removed from renal surface. Three weeks later these rats underwent a 1-1/2 nephrectomy on the day of the FSP in the SA group.

In order to evaluate renal structure at the time of the FSP, 6 additional Münich-Wistar rats (the SA group) underwent heminephrectomy. Three weeks later, the remainder of this kidney was removed and 3 weeks later the contralateral kidney tissue was obtained for morphologic study. Another 6 rats (the FA group) had sham operations performed at the times of the first 2 procedures in the SA group. Three weeks later, contralateral kidney tissue was obtained for morphologic study.

Control group. Control rats underwent sham operations at the times described above for the FA group. At the third sham operation, the right kidney was exposed and its capsule removed. After the surgeries, all rats were allowed free access to water and Purina lab chow diet.

Functional studies. After the FSP, blood pressure, serum creatinine, hematocrit and 24-hour urinary albumin excretion rates (AER) were measured every 3 weeks until 20 weeks after the final surgical procedure.

Systolic BP was measured in awake rats by tail-cuff method using a Gilson photoelectric rat tail pulse pick up transducer (model T-4021) connected with an adapter (model A-4023) to IC-MP channel #1 and pressure transducer (model P23XL, Spectramed, Oxnard, CA, USA) to IC-MP channel #2 (Gilson Biophysical Duograph, ICT-2H Duograph, two IC-MP channel, Gilson Medical Electronics, Middleton, WI, USA). An average of 3 - 4 measurements for each rat were obtained during the study and on the day of glomerular filtration rate (GFR) study (see below). The tail BP measured on the day of GFR study was highly correlated with femoral mean arterial blood pressure that was obtained during the GFR study (8).

Serum creatinine was measured by the Jaffé rate method using the Beckman Creatinine Analyzer 2 (Beckman Instruments, Inc., Fullerton, CA, USA).

All rats were placed individually in metabolic cages for 24-hour urine collections to measure AER. Urine albumin concentration was measured with a laser nephelometer (Hyland, Deerfield, IL, USA) using a monoclonal antibody against rat serum albumin (Cappel Laboratories, West Chester, PA, USA).

Twenty-four weeks after the FSP, GFR and arterial BP measurements were obtained. On the day of these studies, rats were anesthetized with an intraperitoneal injection of Inactin (80 -100mg/Kg) and placed on a temperature regulated table to maintain a rectal temperature of 37°C. A tracheostomy was performed by inserting PE-240 tubing via the same surgical field as for the isolation of the jugular vein. PE-50 catheters were placed in the left femoral artery for blood sampling and BP monitoring using a Spectramed physiological pressure transducer (model P23XL, Spectramed, Oxnard, CA, USA) connected to the Gilson Biophysical Duograph. Arterial blood samples (200µl) were obtained at the beginning of the experiment and at the mid-point of each clearance period for the measurement of hematocrit and plasma Iothalamate concentrations.

A double lumen catheter with PE-50 tubing was inserted into left external jugular vein for infusion of 5% B.S.A. at 0.5% of body weight (BW) in a period of 20 minutes during the surgery, followed by a constant infusion rate of 0.6ml/hr per rat. A bolus of 0.5cc of sodium Iothalamate 125 I in isotonic saline solution was infused over 10 minutes via the second lumen followed by a constant infusion rate of 0.8ml/hr for the remainder of the study. The range of radioactive iodine activity infused was predetermined in each group of rats in order to achieve a plasma level of approximately 1000 counts per min/ml, and 5 and 7mCi/ml of sodium Iothalamate 125 I were infused (9).

The bladder was cannulated (using PE-50 tubing) directly through a small suprapubic incision in order to

obtain a urine sample for each clearance period. After a 30-minute equilibration period, 2-3 clearance periods of 20 minutes each were obtained.
I-125 counts were determined using a Gamma 400 counting system counter (Beckman Scientific Instrument Division, Irvine, CA, USA). The GFR was calculated by the formula: GFR (ml/min) = (Urine CPM x Urine volume/20min)/Arterial CPM and expressed as ml/min/Kg where CPM=counts per minute (9).
After the GFR study was completed, a PE-50 polyethylene catheter pre-filled with Millonig's buffer was inserted into the aorta and advanced to the level of the aortic bifurcation. The perfusate was infused at a pressure equivalent to the individual rat's mean arterial pressure (MAP). The pressure of the perfusate was monitored with a Spectramed physiological pressure transducer (model P23XL). The kidneys were perfused until completely blanched with 1% glutaraldehyde in Millonig's buffer for 2 min. The renal tissue was then removed and left overnight in the same fixative and processed for embedding (10).

Morphologic Studies

To estimate kidney volume (KV) and cortical volume, each kidney was cut into 2mm slices. The Cavalieri method was used to estimate kidney volume, volume fraction (Vv) of kidney which is cortex (C) (Vv C/K) on these slices (7). Renal slices were embedded in paraffin, and serially sectioned at 4µm. Sections were stained with periodic acid-Schiff (PAS) and examined for the volume fraction of cortex which is glomerulus (Vv G/C) (11), volume fraction of cortex which is interstitium (I) (Vv I/C) (12), frequency (%) of glomeruli with focal segmental glomerulosclerosis (FSG) lesions and the size (score) of FSG (see below). Total glomerular volume in an animal was calculated from the kidney volume, Vv(C/K) and Vv(G/C) using the formula:

$$\text{Total glomerular volume per animal} = \text{Kidney volume} \times Vv(C/K) \times Vv(G/C) \quad (11)$$

Mean glomerular volume (GV) was measured at an approximate magnification of X110 using the point-counting method of Weibel and Gomez (13). Twenty-two to 41 (median 29) glomerular profiles per animal were measured.
All the glomeruli present on one slide from each experimental rat were examined to estimate the frequency (%) and score of FSG in the study groups. The number of glomeruli examined per rat was 170±53 ($\bar{X}$ ± SD) in SA group and 151±32 in the FA group. One hundred glomeruli were examined in the control group. FSG was recognized as an increase of mesangial matrix substance associated with capillary wall wrinkling and collapse. These sclerotic lesions were not always associated with adhesions to Bowman's capsule. Hyalinosis was defined by the presence of PAS-positive hyalin material included in or separated by sclerotic regions in the subendothelium or in the mesangium (15).
The severity of FSG in a given tissue specimen was assessed by assigning a score of 1+ to 4+ to each glomerulus according to the proportion of the tuft demonstrating FSG: normal glomerulus, 0; up to 25% involvement, 1+; 25% to 50% involvement, 2+; 50% to 75% involvement, 3+; and more than 75% involvement, 4+. The FSG score for each tissue specimen was the sum of individual glomerular scores multiplied by the percent of glomeruli with the same score:

$$\text{FSG Score} = \sum_{i=0}^{4} i(n_i/n)100$$

where n_i is the number of glomeruli in the tissue specimen with FSG score $_i$, and n is the total number of glomeruli in the sample (15).

Statistics

Data from multiple groups were compared using ANOVA followed by paired two-sided Student's t-tests. Repeated measures of ANOVA and regression analysis were used to compare the 24-hour UAE between the SA and FA groups from 2 weeks to 20 weeks after FSP and the slopes of the UAE regression lines were compared. Values of $p<0.05$ were considered significant.

Results

Functional studies

Blood pressure

The SA group initially consisted of 12 rats, with 13 rats in the FA group, and 12 rats in the control group. There were no significant group differences in systolic BP by the tail method at the time of the first three surgical procedures. However, from the 8th week after the FSP, systolic BP in the SA and FA groups were significantly higher than in the control group ($p<0.05$) for each comparison (Fig. 1). There were, however, no significant differences in BP between the SA and FA groups. The increasing BP in the SA and FA groups appeared to level off by the 11th week when they were 150±15 and 157±16 mmHg, respectively and at 20 weeks after FSP these BPs were about 17-24mmHg higher than controls (Fig. 1).

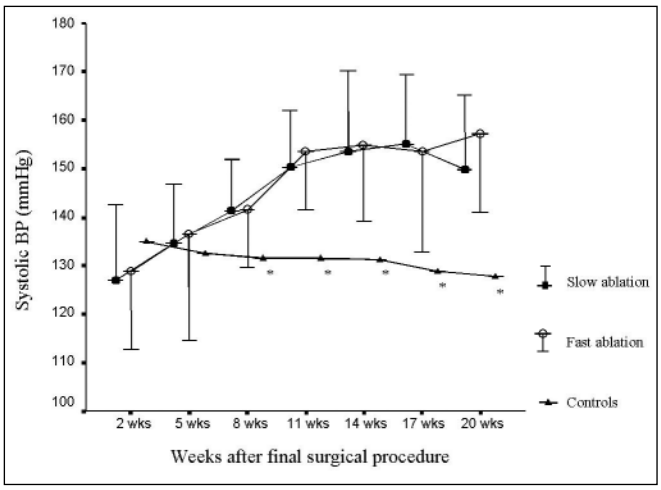

Fig. 1 - The course of systolic blood pressure after the final surgical procedure (FSP) in the three groups of rats. Blood pressure was measured by tail method. Data are $\bar{X}$ ± SD. *P=<0.05 vs. slow and fast ablation groups.

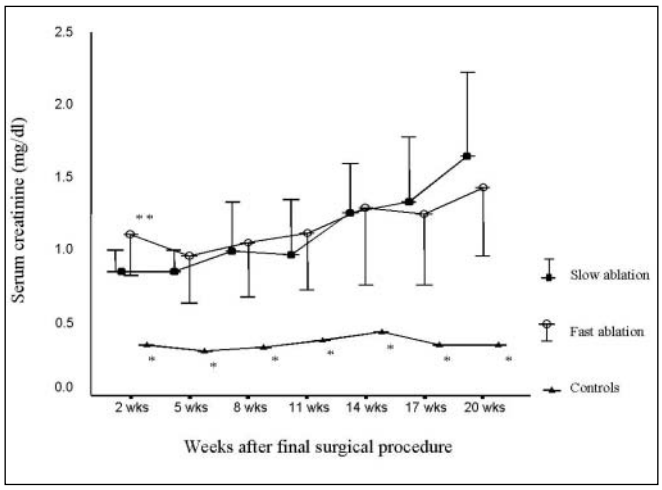

Fig. 2 - The course of serum creatinine after the final surgical procedure in the three groups of rats. *P=<0.001 vs. slow and fast ablation groups. **P=<0.01 vs. slow ablation group.

Serum creatinine

Serum creatinine levels in the SA and FA groups were higher than in the control group from the 2nd week onwards ($p<0.001$) for each comparison (Fig. 2). There were no differences between the SA and FA groups during the 20 week period after the FSP except for the 2nd week when the serum creatinine levels were higher in the FA group ($p<0.01$) (Fig. 2).

Albumin excretion rate

AER after the FSP was consistently higher in the SA and FA groups than in controls, ($p<0.0005$ for each comparison, Fig. 3). Repeated measures of ANOVA was used to compare the AER between the SA and FA groups from weeks 2 to 20 after the FSP. But for the 5th and 20th weeks, there was a significant difference between the two groups ($p<0.01$) indicating that the increase in AER in the SA group was greater, independent of the effects of time on AER. Also, the slopes of the regression lines of AER and time were different for the SA ($y=17.2x - 8.2$) vs. FA ($y=10.5x - 0.7$; $p<0.001$) groups.

Final kidney function studies

Eight of 12 SA group rats survived to 24 weeks after the FSP. However 2 of these animals were very sick on the day of final renal function studies. Thus 6 rats were included for the final GFR and morphologic studies. Ten of the initial 13 FA group rats survived and were included in these final studies. While 11 control rats survived, 7 were randomly selected for functional and morphological study, since this number was considered to be sufficient.

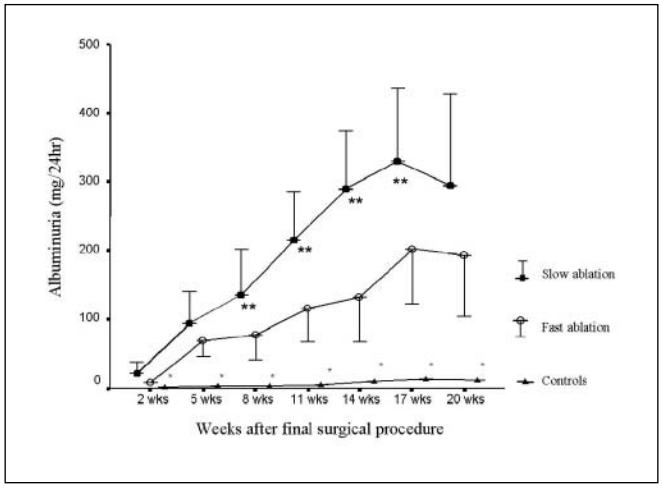

Fig. 3 - The course of 24-hour urinary albumin excretion rate (AER) after the final surgical procedure (FSP) in the three groups of rats. *P=<0.005 vs. slow and fast ablation groups. **P=0.01 vs. fast ablation group.

The GFR at 24 weeks after FSP was lower in the SA and FA groups than in the control group ($p<0.001$ both comparisons) (Tab. I). There was no difference in final GFR between the SA and FA groups.

The values for mean intra-arterial pressure (MAP) at 24 weeks paralleled values for systolic BP by the tail method in awake animals. MAP was 44-50 mmHg higher in the SA and FA groups vs. controls but was not different in the SA vs. FA groups (Tab. I).

Hematocrits at sacrifice were lower in the SA and FA groups (34.5±2.4% and 37±3.6%, respectively) than in the control group (47.6±1.6%; $p<0.001$, both comparisons). Hematocrits in the SA and FA groups did not differ.

Kidney structural studies

There were no FSG lesions in either the SA or FA groups at the time of the final FSP. Further, GV in the SA group ($0.65\pm0.6 \times 10^6 \mu m^3$) and FA group ($0.61\pm0.04 \times 10^6 \mu m^3$) were not significantly different at this time. The total kidney volume per animal at the end of the study as measured by the Cavalieri method was closely correlated with the kidney weight ($y=0.94x + 0.28$, $r=0.95$). There was no significant difference between the SA and FA groups in final kidney weight (Tab. II). Total kidney weight in the control group exceeded those in either the SA or FA groups (Tab. II). Kidney weight in the SA was higher than the weight of a single kidney in the control group ($p<0.05$), but there was no difference in this comparison between the FA and control groups.

There were no significant differences in Vv C/K between groups (Tab. II). The cortical interstitial volume fraction (Vv I/C) was much higher in both the SA and FA groups than in the control group. There was no significant difference, however, between the two ablated groups (Tab. II). The volume fraction of cortex which is glomerulus (Vv G/C) and the total GV per animal were decreased in both the ablated groups compared to the control group (Tab. II). There was no difference in total GV per animal between the SA and FA groups. However, at 24 weeks after the FSP the mean GV was greater in the SA group than in the FA group and was greater in both ablated groups compared to the control group (Tab. II).

The frequency (%) of FSG lesions at 24 weeks was higher in both the SA and FA groups than in the control group. The frequency (%) and the size (score) of FSG lesions were also higher in the SA than in the FA group (Tab. II).

DISCUSSION

The remnant kidney model in rats has been widely used to investigate mechanisms involved in the progression of renal disease. In this model, nephron number is suddenly reduced by surgical ablation or infarction of kidney tissue. Initially, normal remnant nephrons develop injury at rates which depend on the method of ablation (16), the amount of renal tissue removed, and the strain and sex of rats being used (17).

However, the sudden decrease in the functioning kidney tissue by removal and/or destruction of $1\text{-}^1/_2$ or more of the animal's kidney tissue is unlike most renal diseases in humans, which are characterized by the much more gradual loss of functioning renal tissue. This study compared the structural and functional

TABLE I - FINAL RENAL FUNCTION DATA

	GFR (ml/min/Kg)	AER (mg/24hr)	Mean arterial BP (mmHg)
SA group	1.1±0.8	322.8±164.2	186.0±22.0
FA group	1.0±0.4	196.9±97.4	179.8±17.6
Control group	6.6±1.3*	7.3±5.3*	136.3±10.9*

**p<0.001 vs. SA and FA groups*
Abbreviations: SA=slow ablation; FA=fast ablation; GFR=glomerular filtration rate; BP=blood pressure; AER=albumin excretion rate.

TABLE II - RENAL STRUCTURAL DATA AT 24 WEEKS AFTER FINAL SURGICAL PROCEDURE

	Total kidney weight per animal (gram)	Vv(Cortex/kidney)	Vv(Interstitium/cortex)	Vv(Glomerulus/cortex)	Total glomerular volume per animal (ml)	Mean glomerular volume ($\times 10^6 \mu m^3$)	Frequency (%) of FSG	Size (Score) of FSG
SA group	2.45±0.43	0.69±0.02	23.5±3.8	0.04±0.01	0.07±0.02	3.4±0.7**	61.2±16.0*	1.7±0.7**
FA group	2.21±0.47	0.68±0.03	22.0±3.7	0.04±0.01	0.05±0.01	2.1±0.4	35.6±11.9	0.9±0.4
Control group	4.04±0.40[a]	0.66±0.01	10.2±1.2[a]	0.05±0.003[b]	0.12±0.01[a]	1.4±0.2[b]	0.6±1.1[a]	0.01±0.02[a]

**p<0.01, **p<0.005 vs. FA group*
[a]p<0.001 vs. SA and FA groups
[b]p<0.005 vs. SA and FA groups.

manifestations of the remnant kidney model in rats subjected to gradual vs. sudden reduction in renal mass. Moreover, most studies of this model have not followed the animals long enough to characterize the ultimate progressive reduction in GFR and the associated structural changes.

An important consideration in the design of these studies is that the standard ablation model of unilateral nephrectomy and infarction of a large segment of the contralateral kidney (by occluding branches of the renal artery) results in a marginal infarct zones which produces increased local renal renin production and marked hypertension (18). Surgical subtotal nephrectomy was used in our study in order to more closely mimic the course of most human renal diseases which typically are unassociated with severe hypertension early in the course of injury. In fact, the BP in the FA and SA groups were normal during the first 5 weeks after the final surgical procedure, leveled off by 11 weeks and remained stable thereafter.

It is possible that the systemic hypertension in SA and FA animals promoted the development of albuminuria and FSG lesions, perhaps by contributing to glomerular capillary hypertension (1). However, because systemic BP, estimated by either the tail cuff method or by direct intrarterial measurement, was similar in the SA and FA groups, this variable cannot easily explain why SA animals had more albuminuria following the FSP and more FSG lesions at the end of the experiment. However, it is not possible to exclude greater glomerular capillary hypertension in the SA group as the cause of their greater AER and FSG lesions, since these measurements were not done.

Nonetheless, elevated glomerular capillary pressure and blood flow alone may not fully explain the albuminuria and FSG lesions which develop in rats with reduced functioning renal mass. In fact, rats subjected to $^{2}/_{3}$ infarction of one kidney with contralateral intraperitoneal ureteral drainage (effectively removing the clearance function of this second kidney) develop glomerular capillary hypertension, no glomerular hypertrophy and no FSG lesions (3). This was in contrast to rats subjected to uninephrectomy and $^{2}/_{3}$ infarction of the other kidney where glomerular hypertrophy together with equivalent levels of glomerular capillary hypertension was associated with severe FSG lesions (3).

Our studies eliminated the possibility that the increase in FSG lesions in the SA vs. the FA rats represented the addition of FSG lesions present at the time of the FSP to lesions developing subsequent to the FSP. It should be recalled that the SA animals were first subjected to a heminephrectomy and, 3 weeks later, to removal of the rest of that kidney, completing a uninephrectomy. Three weeks later, at the time of the FSP, FSG lesions were not detected in either the SA or FA groups and there was no significant difference in GV between these groups. The study by Hostetter et al (19), also did not detect an increase over controls in FSG lesions 4 months after uninephrectomy in Münich-Wistar rats.

It is possible that the greater glomerular volume seen in the SA vs. FA animals at sacrifice in our studies resulted from the longer time available for compensatory glomerular hypertrophy to occur in the SA rats. Alternatively, the worse FSG lesions in the SA animals could have stimulated greater compensatory glomerular hypertrophy in these rats, perhaps contributing to further glomerular injury. The mechanism whereby glomerular hypertrophy alone or in concert with glomerular hemodynamic perturbations could lead to albuminuria and FSG lesions is unknown, but there is support for the notion that the glomerular visceral epithelial cells may not proliferate in response to the increased surface they must cover with glomerular volume increase, and this may lead to their detachment and adhesion to parietal epithelial cells initiating the FSG lesion and proteinuria (20).

It is also possible that the increased albuminuria in the SA rats in the 24 weeks after the FSP contributed to the increase in FSG lesions in these rats. However, Nagase analbuminemic rats have similar severity of FSG lesions compared to Sprague-Dawley rats given Adriamycin, despite marked differences in proteinuria between the two groups (21).

Tubulointerstitial injury may contribute to the loss of remnant nephron function (22). Both the SA and FA groups had Vv(Interstitium/cortex) values more than twice the values for controls. Multiple studies suggest that proteinuria could lead to tubular and interstitial injury (23, 24), and the extent of tubular, interstitial and glomerular injury are correlated with protein excretion rates in rats with renal ablation (16). In this context, it is unclear why SA rats, with greater AER for several months and greater FSG lesions at sacrifice, had no greater increase in Vv(Interstitium/cortex) than FA rats.

It is reasonable to assume that the greater serum creatinine in FA vs. SA groups 2 weeks after the FSP, occurred because the SA group had time for compensatory adaptation, since at 5 weeks after FSP, serum creatinine in the FA group had decreased and, thereafter, there were no serum creatinine differences between the SA and FA groups. Moreover, the GFRs were not different between these groups at 24 weeks after the FSP.

In summary, these studies demonstrate that removal of renal mass in a quantity and for an insufficient time to, *per se*, produce detectable glomerular injury, preconditions the residual nephrons for accelerated injury upon further loss of renal mass. The study did not provide a clear explanation for the mechanism of this

acceleration. Nonetheless, if early losses in nephron mass can predispose to accelerated residual nephron injury with further nephron mass reduction, this would suggest that intervention strategies might be beneficial earlier in the course of many progressive renal diseases, perhaps even before any renal functional disturbances such as albuminuria, hypertension or decline in GFR are detectable.

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Address for correspondence:
Michael Mauer, M.D.
University of Minnesota
Department of Pediatrics
420 Delaware Street S.E.
Mayo Mail Code 491
Minneapolis, MN 55455, USA
mauer002@tc.umn.edu

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