REVIEW

The Aging Kidney: Insights from Experimental Studies

CHRIS BAYLIS* and BRUNO CORMAN†

*Department of Physiology, West Virginia University, Morgantown, West Virginia; and †Département de
Biologie Cellulaire et Moléculaire, CEA, Centre d'Etudes de Saclay, Gif-sur-Yvette, France.

From middle age onward, declines in GFR occur in many individuals and damage appears in various parts of the kidney. Usually, these age-dependent changes proceed slowly and function remains adequate for survival, but if other diseases are present, such as hypertension or diabetes, the aging kidney becomes vulnerable to failure. In addition, the aging kidney is susceptible to drug toxicity due to alterations in renal handling of drugs and their metabolites, and to alterations in the balance between vasoconstrictor and vasodilator influences. This bleak outlook, however, has been challenged by the results of the Baltimore Longitudinal Study, which show that an age-dependent fall in GFR is not inevitable. Thus, age-related changes in the kidney may be separated into normal aging and a variable occurrence of specific diseases. These aspects have been reviewed in a number of recent articles that concentrate on clinical aspects of the aging kidney (1–4). The present article focuses on animal studies, specifically of the rat, and addresses the mechanisms by which aging processes affect kidney structure and function, and contribute to increased susceptibility to diseases.

Structural Changes in the Aging Kidney
Kidney Size and Nephron Number

Summarizing the published data, hypertrophy, atrophy, and unchanged renal size have all been reported in senescent rats, based on wet kidney weights. This variability in kidney size with age may be due in part to the variable relationship between kidney and body size in different strains of rats. As a rule, during young adulthood, the kidney and body weight increase in parallel (5,6). Later, after the kidney has reached its optimal size (at approximately 8 mo of age), the ratio of kidney to body weight varies widely, depending on fat accumulation and, in some strains, renal hypertrophy. This age-related renal hypertrophy, regardless of the changes in body weight, occurs in male rats of many, but not all, strains and in some female rats (5–13). Age-dependent enlargement of glomeruli is usually in proportion to the increase in renal mass (9–11,14–17). Morphometric measurements indicate a proportional increase in glomerular tuft and Bowman's space. Within the glomerular tuft, mesangial matrix is markedly expanded and basement membrane thickness is increased throughout life. Despite hypertrophy of the whole glomerulus, the available capillary surface area, the width of the epithelial slit diaphragms, the length of foot processes, and the size of the endothelial fenestrae are not altered in female rats up to 42 mo of age (9). In males, glomerular hypertrophy is moderate and a decrease occurs in capillary surface area from 12 to 30 mo, due to a reduction in the number of glomerular capillaries or their tortuosities, resulting in a lower available filtering area (8,14).

The impact of aging on nephron number in rats differs according to strains. The number of functional glomeruli in female and male Sprague Dawley rats falls significantly with aging, accompanied by the appearance of glomerulosclerosis (18,19). In contrast, female Fischer 344 rats and female and male WAG/Rij rats, who are free of age-dependent renal injury, exhibit a constant number of glomeruli up to 30 mo of age (Figure 1) (5,8,11,18). Furthermore, glomerular number is unchanged in ddY/SLC female mice between 30 and 90 wk, which corresponds to the mean survival of the colony (20). Thus, it seems likely that the number of nephrons does not inevitably decrease with age in rodents, but is related to degenerative nephropathy.

Renal Lesions in Aging Rats

Renal lesions were reported in aging rats as soon as albino animals were used in research (15). Kidney disease, along with respiratory disease, is a major cause of early death in most colonies. The age-related renal lesions are complex and have been described as chronic nephritis, nephrosis, glomerulonephrosis, glomerulosclerosis, and most often as chronic progressive nephrosis, the term proposed by Gray (15). This is characterized by proteinuria associated with glomerular alterations, including enlargement of the whole glomerulus, thickening of the basement membrane, expansion of the mesangial domain, accumulation of extracellular matrix, fusion of the capillary tuft with Bowman's capsule, occlusion of glomerular capillaries, and ultimately destruction of the whole glomerulus. These lesions are frequently described as focal and segmental sclerosis. In addition, epithelial cell proliferation, atrophy, and retraction of foot processes have been reported, as well as proteinaceous casts in the tubule, protein droplets in glomeruli and tubular cells, tubulointerstitial fibrosis, cellular infiltration, calcium deposits in the renal parenchyma, and hydronephrosis (16,17,21–29). Medullary injury is present in some strains (e.g., Sabra, Fisher 344, and Sprague Dawley rats) with tubulointerstitial fibrosis and atrophy of the medullary thick ascending limb of the loop of Henle; when observed, these medullary changes precede damage to the glomerulus (30,31).
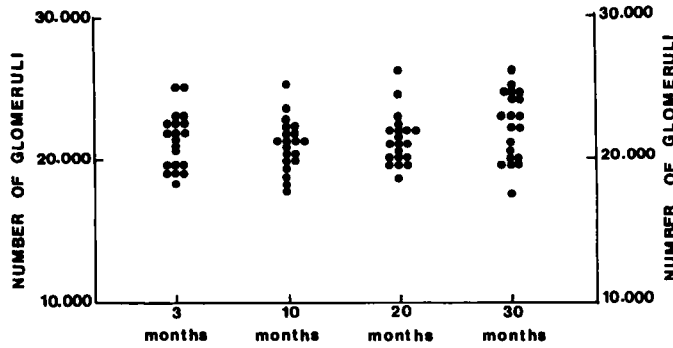
Figure 1. Number of glomeruli in aging female WAG/Rij rats that show no chronic progressive nephrosis with age. Each point corresponds to the total number of glomeruli in one kidney. Data are taken from reference 5.

Figure 2. Glomerular blood pressure (P_{GC}) measured by direct puncture of superficial glomeruli (□) and by the indirect stop flow method (▨), which samples deeper cortical glomeruli, in Munich Wistar rats at 8,12, and 19 mo of age. There is no age-dependent rise in P_{GC} in intact male or female rats (upper panels) or in castrated rats (lower panels). Figure reproduced with permission from reference 10.

Vascular disease, other than to the glomerulus, is not common in aging rats. This pattern of chronic progressive nephrosis is very similar from one study to another; however, the onset and severity of these lesions depend on a number of factors, such as strain, gender, food intake, or environment.

Severe proteinuria occurs in aging rats that display substantial chronic progressive nephrosis, but some increases in protein excretion also occur in rats that are protected from kidney damage (32–35). Composition of the urinary proteins varies with age and gender; young male rats excrete a high proportion of low molecular weight proteins, but with aging the percentage of albumin and globulin increases (34,36,37). The percentage of glycated plasma albumin increases with age, and the preferential excretion of glycated albumin observed in the normal kidney is lost with aging, suggesting altered tubular handling (38). Proteinuria precedes the increased urinary excretion of enzymes that reflect tubular damage (39) and, as in man, microalbuminuria in the rat is an early predictor of chronic renal disease (32,40). Old Sprague Dawley male rats become heavily proteinuric due to increases in glomerular pore size/number, as well as loss of glomerular anionic barrier function (35), and disordered distribution of anionic sites has been observed in the thickened glomerular basement membrane of middle-aged rats (41).

Mechanisms of the Age-Dependent Glomerular Injury

Many factors have been examined to determine their role, if any, in the pathogenesis of age-dependent glomerulopathy. Glomerular capillary hypertension is a primary risk factor for development of progressive glomerulopathies and has been implicated in age-dependent glomerular damage (42). However, glomerular blood pressure does not invariably increase with aging (Figure 2), and structural injury may *precede* increased glomerular blood pressure, as evidenced in intact male Munich Wistar rats (10). Similarly, male rats of the MWF/ZTM strain exhibit accelerated kidney disease, yet glomerular blood pressure remains normal (43). Compared with Munich Wistar rats, glomerular injury develops much more rapidly in the Sprague Dawley rat, and in this strain increases in glomerular blood pressure have been reported at 13 to 18 mo of age
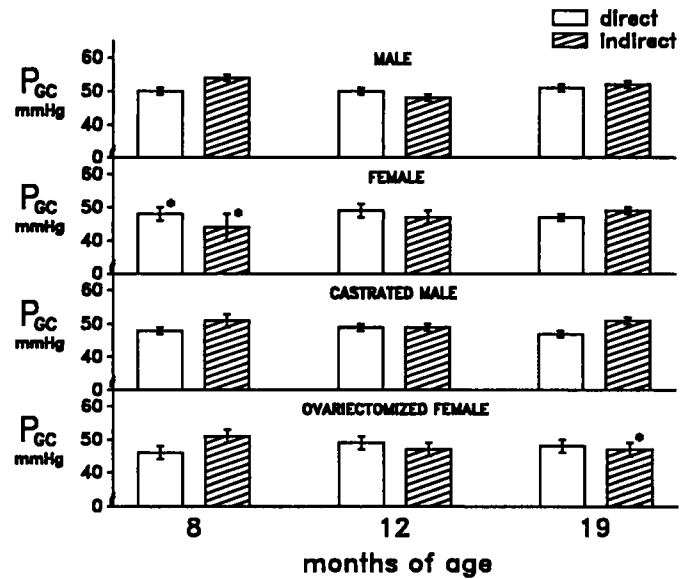
(44,45), although not at 20 to 22 mo (19). In view of the extensive evidence that systemic hypertension worsens glomerular injury (4,33,42), it is likely that when glomerular blood pressure does increase it will exacerbate the underlying development of age-dependent glomerular damage (42,46).

Glomerular tuft hypertrophy is another risk factor for development of glomerular injury, via increased intramural tension leading to physical disruption of glomerular integrity (47–49). Glomerular volume does increase with aging, but injury and glomerular hypertrophy can be dissociated by castration of the male (10,50,51). Thus, whereas both glomerular hypertension and glomerular hypertrophy will cause glomerular injury, age-dependent glomerulopathy can develop in the absence of these hemodynamic risk factors, as is the case with the slowly evolving glomerular damage in the Munich Wistar rat (10).

Gender is an important determinant of the rate at which chronic progressive nephrosis appears. In many strains of rats, renal disease occurs earlier in life and to a more severe extent in males than in females. Ovarian hormones are widely recognized to be protective of the cardiovascular system but, surprisingly, ovariectomized females remain protected from age-dependent glomerular damage (10). In view of this finding, and because castration of the male is protective, it seems that the presence of the androgens, rather than the absence of ovarian hormones, promotes age-dependent glomerular damage, at least in rats (10). This greater susceptibility of the male to develop glomerular injury is not limited to aging, but includes other progressive glomerulopathies and also extends to other species, including man (52–57).

The causes of age-dependent glomerular damage have not yet been determined. Mesangial cell expansion and extracellu-

lar matrix accumulation play a primary pathogenic role in some forms of glomerular injury (58), and increased matrix accumulation is seen in most aging rats and precedes the appearance of focal sclerosis (59). In the Wistar rat, this is seen in aging males but not females and correlates with injury (60). In aging Fisher 344 rats, the major age-dependent change in renal extracellular matrix is interstitial fibrosis due mainly to accumulation of thrombospondin and fibronectin, which precedes glomerular sclerosis and tubular atrophy (31). On the other hand, age-related matrix expansion is greater in female than in male WAG/Rij rats, and is not associated with any glomerulosclerosis (14). In the Wistar/Lou strain, mesangial matrix and mesangial cellularity are barely modified with age, and no glomerular injury develops in very old rats of either gender (61). From these studies, it appears that mesangial expansion is not necessarily associated with glomerulosclerosis, but that the development of glomerulosclerosis is usually preceded by mesangial expansion, especially in males. The greater susceptibility of the old male of most strains to develop glomerular sclerosis may be related to androgens, which can increase synthesis of extracellular matrix material (54). In addition to increased synthesis, reduced rates of degradation will also cause accumulation of mesangial matrix products. As shown in Figure 3, activity of a glomerular metalloprotease responsible for degradation of mesangial matrix products is low in intact old male Munich Wistar rats that exhibit glomerular injury, but elevated in females and castrated rats of both sexes, which are protected from damage (62).

The accumulation of advanced glycation end products (AGE) within the glomeruli has also been proposed as a major cause of renal lesions in aging rats. AGE accumulate in the kidney of senescent rats, increase the synthesis of extracellular matrix, and expand the glomerular mesangium (63–69). Chronic administration of the AGE inhibitor aminoguanidine to female Sprague Dawley rats from 6 to 24 mo reduces the accumulation of AGE in the kidney and the incidence of glomerulosclerosis and nephron loss (18). Similarly, administration of aminoguanidine in male WAG/Rij rats from 24 to 30 mo reduces mesangial expansion without causing a change in the age-related renal hypertrophy (70). Because aminoguanidine has a number of other actions, however, including preferential inhibition of the inducible nitric oxide synthase (see below), the mechanism by which aminoguanidine protects the aging kidney from injury is still unclear.

Effect of Food Intake and Environment on the Development of Chronic Progressive Nephrosis

Some strains of rats develop chronic progressive nephrosis early in life, and by 24 mo exhibit severe renal disease. These strains are those in which body weight continues to increase after young adulthood, such as Sprague Dawley and Fisher 344 rats (6,12,13,16,17,25). Rats that remain small even when fed *ad libitum*, such as the Wistar, Long-Evans, or Brown Norway strains, are less susceptible to chronic progressive nephrosis (5,8,9,18,22). These observations led to the hypothesis that age-related renal lesions could be linked to overfeeding and that control of nutrition might protect the senescent kidney from disease.

The influence of nutrition on chronic progressive nephrosis has been documented in many studies since the pioneering experiments of Saxton and Kimball in 1941 (71). These investigators found that a low protein diet was protective and that
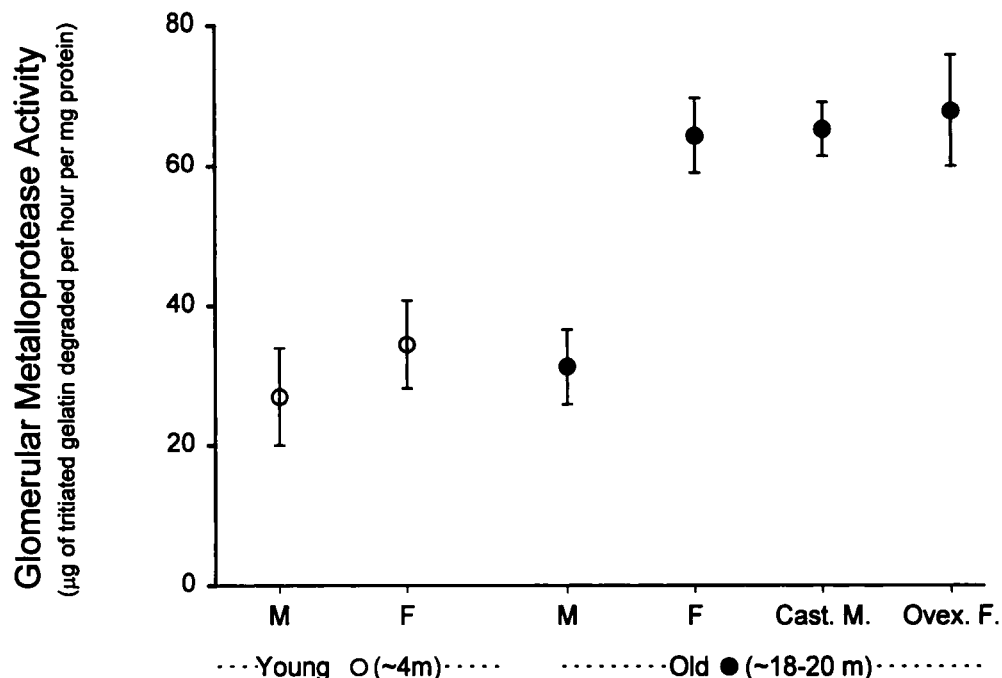

Figure 3. Glomerular metalloprotease activity in intact young adult male and female rats (aged 3 to 5 mo), in old (aged 18 to 20 mo) intact male and female rats, and in rats castrated at 10 wk of age. Data are from reference 62. Figure reproduced with permission from reference 3.

restriction of food was the most effective method of preventing chronic progressive nephrosis. These results have been confirmed and extended over the past 50 years by several authors, as reviewed recently (72). Dietary restriction consists of allowing access to approximately 60 to 70% of the ad libitum intake or, alternatively, periodic removal of food. Food restriction limits the obesity frequently reported in aging rats, with reductions in body weight up to approximately 50%. The most impressive effect is the increase in survival, since mean life span is 25 to 50% longer in food-restricted rats. This increase in survival is associated with a reduced incidence of diseases, including chronic progressive nephropathy (13,25,73–77).

The striking effect of food restriction on the prevention of renal disease in aging rats prompted investigators to test whether this was due to restriction of one element of the diet or to caloric restriction per se. Restriction of dietary salt has little effect on the progression of chronic progressive nephrosis (75,76). Restriction of dietary fat and dietary substitution of polyunsaturated fatty acids are protective in various models of underlying renal disease (72), and a deranged plasma lipid profile may contribute to age-dependent glomerulosclerosis in the female analbuminemic rat (78). However, there is little direct evidence that lipid restriction protects against kidney aging (75,76). In contrast, reducing the animal protein content of the diet delays the appearance of renal lesions. Similarly, replacement of casein by liver or vegetable proteins is protective, suggesting that the source of proteins may be important (71,79,80). Restriction of calories, however, is more powerful than any other dietary manipulation in preserving renal structure in senescent rodents. Not only does this retard the onset of chronic progressive nephrosis, but it completely prevents the development of renal failure in the oldest animals. (13,21,23,71,72,76,79–85). The conclusion from these studies is that the total amount of food ingested by the animal during its life is a determinant of the extent of renal damage. The mechanism of the beneficial effect of food restriction is not certain, although reduced generation of free radicals and protein glycation could be involved (76,86). Increased oxidants and formation of AGE, both of which accumulate in aging, have indeed been implicated in glomerular injury, possibly by enhancing extracellular matrix expression (87,88).

Environment may also play a role in the development of chronic progressive nephrosis. Maintenance of animals in a pathogen-free environment throughout their lives lowers the incidence of renal disease in ad libitum-fed animals, although this is not as efficient as food restriction (26,89). Overall, these experiments indicate that the severe chronic progressive nephrosis described in old rats is related more to disease than to true aging processes. It is clear that renal disease in aging rodents is not an obligatory event. This analysis prompted investigators to combine conditions known to minimize renal failure in their development of experimental models of kidney aging free of renal disease. Strains of rats were selected that remained lean even when fed ad libitum and that were resistant to chronic progressive nephrosis. The rats were maintained under pathogen-free conditions and fed a diet in which animal proteins were substituted with vegetable and fish proteins and that contained a moderate amount of calories. By combining these optimal conditions, it has been possible to produce extremely old rats that are free of chronic progressive nephrosis (9). This does not mean that the kidney escapes the processes of aging, but it shows that the pathologic changes are not inevitable.

Renal and Glomerular Hemodynamics

As in man, the impact of aging on GFR is quite variable in the rat, and depends on strain, gender, environmental conditions including diet, and importantly, on whether GFR is factored for body or kidney weight. Rats that become obese with age and exhibit substantial chronic progressive nephrosis, such as the male Sprague Dawley, show increases in absolute GFR up to old age (approximately 18 mo) and then GFR returns to the young adult value as senescence approaches (90). When factored for the increase in body weight or kidney weight, GFR remains unchanged up to middle age, and then declines markedly with senescence. This differs from the findings in WAG/Rij female rats, which do not increase body weight after maturation (although the kidney undergoes hypertrophy) and do not exhibit chronic progressive nephrosis. In these rats, there is little change at any age in the absolute values of filtration rate or when GFR is factored for body weight, although GFR does fall at senescence when factored for kidney weight due to renal hypertrophy (5). It is difficult to know which is the most appropriate way of expressing GFR, and we recommend that absolute values of kidney and body weights should be published, in addition to any factoring.

Sexual dimorphism in age-related changes in GFR is evident from comparison studies in the Munich Wistar and WAG/Rij rats. In the Munich Wistar strain, GFR is higher in young adult males than in females, and this gender difference gradually disappears with advancing age due to the more rapid reduction in GFR seen in the male rat (10,91). In the WAG/Rij strain, GFR measured in conscious animals is comparable to or even higher in adult females than in males when factored to kidney weight. At the end of life, this GFR/kidney weight is comparably decreased in both the male and female. However, due to the pronounced renal hypertrophy observed in the female of this strain, the absolute values of GFR decrease in the aging male but not in the female (5,8).

Several micropuncture studies have measured single nephron GFR (SNGFR) and its determinants in the aging rat. The distribution and average value of SNGFR increase with age in male Sprague Dawley rats that also develop substantial injury, and this pattern is consistent with a compensatory response to nephron loss (19,46). In contrast, female WAG/Rij rats that are free of kidney disease show no change in distribution or mean value of SNGFR up to 30 mo of age (Figure 4). In the male Munich Wistar rat, absolute values of SNGFR and GFR are similar at 8 and 19 mo of age, although when factored for the increase in kidney weight, these variables decline. Both afferent and efferent arteriolar resistances increase by 19 mo, so that glomerular blood pressure remains unchanged (10). In female Munich Wistar rats, GFR and SNGFR are constant with age, even when factored for kidney weight. The kidney is relatively vasoconstricted in the young adult female, tends to dilate with age, and at 19 mo there is no difference in afferent
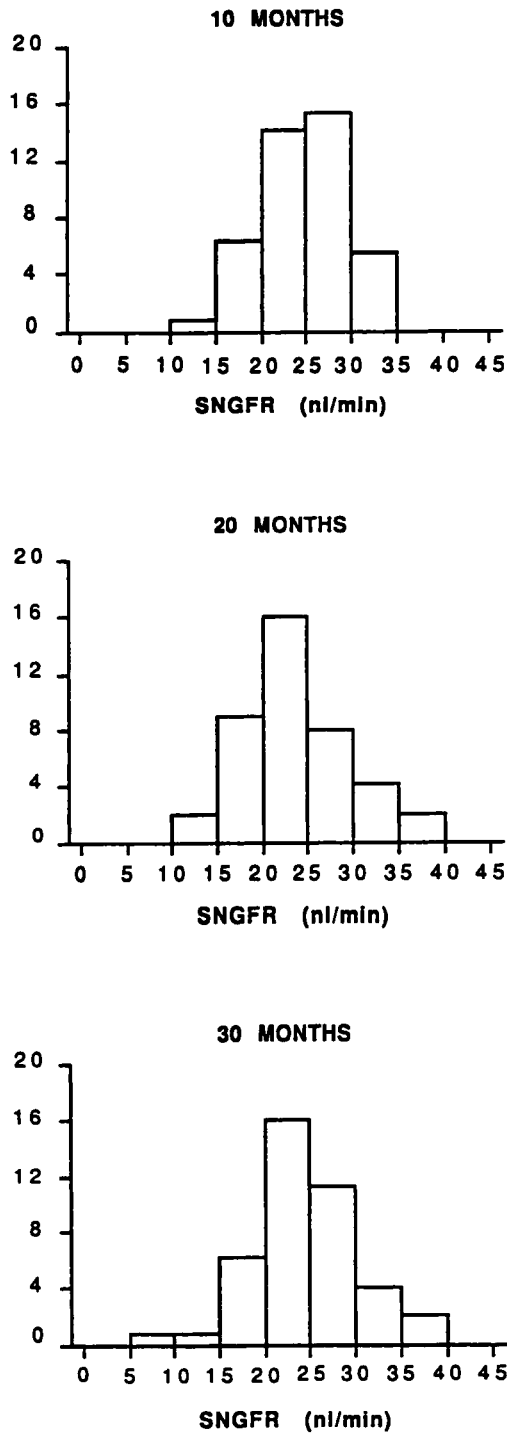
10 MONTHS

(chart: SNGFR distribution, y-axis 0 4 8 12 16 20, x-axis 0 5 10 15 20 25 30 35 40 45)

SNGFR (nl/min)

20 MONTHS

(chart: SNGFR distribution, y-axis 0 4 8 12 16 20, x-axis 0 5 10 15 20 25 30 35 40 45)

SNGFR (nl/min)

30 MONTHS

(chart: SNGFR distribution, y-axis 0 4 8 12 16 20, x-axis 0 5 10 15 20 25 30 35 40 45)

SNGFR (nl/min)

Figure 4. Distribution of single nephron GFR (SNGFR) in 10-, 20-, and 30-mo-old female WAG/Rij rats. Data are from 41 measurements in nine animals for each age group. Figure reproduced with permission from reference 61.

and efferent arteriolar resistances between the sexes. As shown in Figure 2, glomerular blood pressure remains unchanged in intact female rats as well as males and is also constant in castrated rats of both sexes (10). The glomerular capillary ultrafiltration coefficient (K_f) is also relatively constant with advancing age in both sexes, despite progressive increases in

glomerular tuft volume, which are particularly pronounced in the male of this strain (10). However, as discussed above, an increased glomerular volume does not necessarily translate into increased filtration surface area (14).

Control of the Renal Vascular Resistance
Renin-Angiotensin System

Substantial reductions in plasma renin activity (PRA) have been reported in a number of species including man, and possible clinical consequences of this reduction in the elderly have been recently reviewed (92). In the rat, a decline in PRA occurs in both sexes (93–97) in association with a fall in renal renin content (93,97,98) and a reduction in renin synthesis in individual juxtaglomerular apparatuses (94). A fall in PRA precedes glomerulosclerosis in susceptible animals and also occurs in rat strains protected from chronic progressive nephrosis (93,96–98), although severe glomerular pathology is associated with the lowest values of PRA (96). This unusual association of reduced PRA with increasing kidney damage may reflect loss of individual juxtaglomerular apparatuses secondary to loss of nephrons during injury (96).

A number of stimuli influence renin release and could be altered in aging. Of these, neither renal perfusion pressure nor macula densa delivery of solute is apparently involved, because substantial decreases occur in PRA in the absence of either increased blood pressure or alterations in the fluid composition in the distal tubules of senescent rats (93,99). Atrial natriuretic peptide (ANP) is a potent inhibitor of renin release via increased cGMP. Because ANP levels increase with age in association with cardiac hypertrophy (97), this may provide a mechanism for reduced PRA. Circulating catecholamines and renal nerve activity are important stimuli to renin secretion via a beta-adrenergic effect, and beta-adrenergic responsivity is markedly blunted with age (100). This may also provide an explanation for the fall in PRA, because under basal, unstressed conditions, PRA is similar in young and old Sprague Dawley male rats and shows a blunted response to stress in old rats (101,102). In contrast, PRA in unstressed female WAG/Rij rats indicates an age-related decrease in PRA comparable to that seen when blood samples are obtained by decapitation, suggesting that the fall in PRA must be multifactorial. Stimulation of renin release in response to angiotensin-converting enzyme inhibition (ACEI) and low sodium diet is also reduced in old rats (95,101), suggesting a global loss of responsivity to the normal stimuli.

Several studies have investigated whether the age-related fall in PRA is due to an alteration in renin gene transcription, translation, maturation, or storage of the protein. Middle-aged male Sprague Dawley rats exhibit a fall in renal renin mRNA, although PRA is not reduced (103). In contrast, renin mRNA is unchanged in male c57BL/6J mice up to 29 mo, although a fall occurs between 29 and 37 mo (104). Unfortunately, no values were reported for PRA or renal renin content and no renal histopathology was presented in this study. WAG/Rij female rats (98) do not show a change in intrarenal renin mRNA up to 30 mo, despite a 50% reduction in intrarenal renin activity (Figure 5). This suggests that transcription of the renin gene is

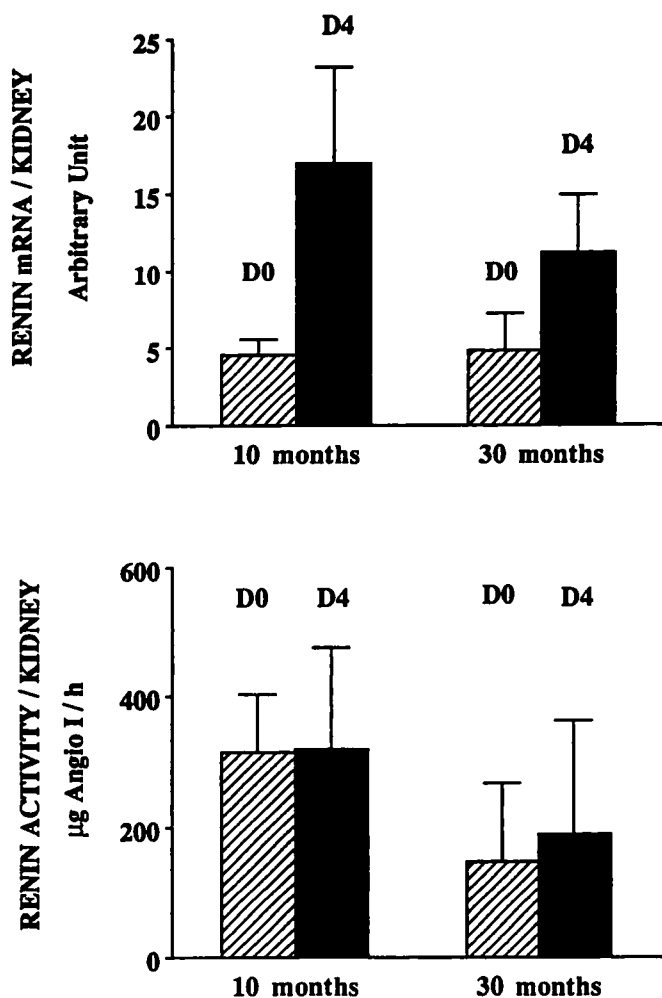## EFFECT OF SODIUM RESTRICTION
ON RENIN GENE EXPRESSION

Figure 5. Intrarenal renin mRNA and concentration in 10- and 30-mo-old female WAG/Rij rats. The animals had access to a normal diet (control) or to a salt-restricted diet for 4 d. Mean of eight animals in each group. Figure reproduced with permission from reference 98.

unchanged with age and that the fall in renin activity is linked to a posttranscriptional alteration. This idea is supported further by the increase in mRNA content of the kidney after 4 d of salt restriction in adult and senescent rats (98). It confirms that transcription of the renin gene is maintained in the aging kidney (Figure 5), whereas 6 d of salt restriction do not increase PRA in senescent rats, indicating an impaired renin release with age despite the increase in renin mRNA (95).

Other components of the renin-angiotensin system are also affected by age. Plasma angiotensinogen concentration decreased slightly in old rats (93), but this may be counterbalanced by increased local synthesis of angiotensinogen in vascular smooth muscle cells (105) and the heart (106). The activity of the plasma-soluble form of angiotensin I-converting enzyme was unaffected by age in female WAG/Rij rats and

male Fisher 344 rats, whereas in male WAG/Rij rats a moderate decrease occurred by 30 mo (93,107,108). These small changes in converting enzyme activity and angiotensinogen synthesis with age are trivial and indicate that the reduction in renin activity is the main rate-limiting step responsible for production of angiotensin II in senescent animals.

When reported, plasma values of angiotensin II (AngII) generally change in parallel to renin. In the unstressed basal state when PRA is similar in old and young Sprague Dawley rats, values for plasma AngII are also similar (101), despite an increased metabolic clearance rate in the old rat. An increased metabolic clearance rate, together with unchanged plasma AngII, suggests that overall AngII production must also be increased to keep pace with the accelerated rate of AngII breakdown. In WAG/Rij rats in which an age-related decrease in plasma renin is found in unstressed conditions, plasma AngII falls in proportion (98). The AngII receptor involved in control of renal hemodynamic and tubular transport is the AT1 receptor, and this receptor is usually upregulated by low plasma levels or local concentrations of AngII. Despite the reported decrease in PRA and AngII in aging male Wistar rats, AT1 mRNA expression is much lower in 24-mo-old versus 3-mo-old rats (109) and correlates well with the decreased maximal binding of AngII in senescent animals.

The functional impact of these changes in the renin/AngII system have been investigated by several groups with variable findings. Administered AngII is reportedly more sensitive in reducing renal plasma flow in late middle-aged Sprague Dawley rats (110). In contrast, AngII has similar renal vasoconstrictor actions in young and old conscious male Sprague Dawley rats, and the responsiveness of the afferent and efferent arterioles is also similar, although the sensitivity of K_f to AngII increases with advancing age (111,112). The renal vascular responsiveness to acute ACEI or AngII receptor blockade is enhanced in old male Sprague Dawley rats (111), not altered in the middle-aged male Sprague Dawley rat (110), and reduced in the aged female WAG/Rij rat (93). Chronic administration of converting enzyme inhibition in the normal rat may produce renal vasodilation, but this is controversial (107,113). Thus, there is no consensus on whether endogenous intrarenal AngII activity is enhanced with advancing age, and this may vary with gender, experimental preparation, and strain-dependent susceptibility to renal disease.

The role of the renin-angiotensin system in the development of age-dependent kidney damage has been assessed by studying the effect of chronic ACEI on aging processes. Treatment of normotensive mice from birth to 24 mo results in increased survival, reduced cardiac mass, and a decrease in the percentage of glomerulosclerosis (114,115). Chronic ACEI protects against glomerulosclerosis and reduced proteinuria, and lowers blood pressure in aging male Munich-Wistar rats treated from 3 to 30 mo of age (113). Treatment also prevents the increase in glomerular blood pressure and reduction in K_f while not altering the age-dependent increase in glomerular size and maintained SNGFR. Lifetime ACEI in the male WAG/Rij rat also lowers blood pressure, renal vascular resistance, proteinuria, and expansion of the mesangial matrix, without influenc-

ing glomerular volume, renal blood flow, or GFR (107). Even the parameters whose absolute values are reduced by ACEI, such as renal vascular resistance, still increase with age in parallel to the control groups, suggesting that chronic ACEI does not affect the aging processes *per se*, but simply postpones the consequences.

Sympathetic Nervous System

Alterations occur in the autonomic control of the cardiovascular system with advancing age, including a blunted responsiveness to alpha 2- and beta-adrenoceptors, and blunting of the arterial baroreflex (100). The possible implications of the blunted beta-adrenoceptor responses, in the context of control of renin release (102), were discussed above. Impairment of the arterial baroreflex leads to increased renal sympathetic nerve activity, which increases both renal vascular resistance and the sensitivity of the aging kidney to vasoconstrictor agents (116). One functional consequence is that increases in renal nerve activity appear to play a role in the blunted pressure natriuresis that occurs in the kidney of the old rat (117) and may contribute to age-related increases in salt-sensitive hypertension.

Atrial Natriuretic Peptide

Vasodilation induced by ANP is attenuated by aging in several vascular beds, including the renal arteries (118,119). This may be due to accelerated degradation of cGMP (the ANP second messenger) by upregulated phosphodiesterases in aging blood vessels (119). The renal vascular action of administered ANP in young animals depends on the preexisting level of vascular tone, because in stressed or precontracted renal vessels ANP is vasodilatory, whereas in the relaxed basal state, ANP causes efferent arteriole vasoconstriction (120). In the conscious rat, a small depressor dose of ANP has no effect on renal hemodynamics but does exhibit a potent and selective natriuretic effect on the kidney of the old rat (121), perhaps because of a decreased renal clearance of ANP (122) secondary to diminished activity of the proximal tubular ANP-degrading enzyme (123).

Endothelial Factors

Endothelin (ET) is an extremely potent vasoconstrictor synthesized by vascular endothelial cells that is normally present in extremely low concentrations in the plasma. There is little information about the activity of ET in the aging kidney, although infusion of ET produces an exaggerated fall in renal plasma flow in late middle-aged Sprague Dawley rats (110). Inhibition of endogenous ET with the mixed receptor antagonist Bosentan has no renal hemodynamic effect in young or old conscious male Sprague Dawley rats (124).

It is well established that in aging there is a widespread reduction in prostacyclin (PGI2) synthesis throughout the vascular endothelium, leading to a reduction in the PGI2/TXA2 ratio, a maladaptation that is atherogenic (125,126). This occurs in the kidney of the old rat as reflected by an elevation of the ratio of thromboxane to prostacyclin in the urine, glomeruli, and inner and outer medulla (127). This shift away from production of the vasodilatory prostaglandins puts the older

kidney at risk in any vasoconstricted state and may be responsible, in part, for the sensitivity of the kidney of the old rat to ischemic and toxic insults (33,128–131).

Nitric oxide (NO) plays a major physiologic role in the maintenance of peripheral and renal vascular tone (132,133). With aging, the peripheral vasculature has a diminished ability to produce NO (134,135) and may also exhibit an impaired vascular response to administered nitrodilators (100). The 24-h urinary excretion of NO3 + NO2 (the stable oxidation products of NO) are decreased in the old rat, supporting the notion that total NO production falls with age (136–138). This could reflect a fall in NO synthesis in the vasculature, perhaps due to reduced NO synthase (NOS) (139), reduced substrate (L-arginine) availability, although this point is controversial (136,137), and/or increased breakdown of NO by oxidants that are activated in aging (140,141). Generalized NO deficiency may also contribute to age-dependent kidney damage (142). Within the kidney vasculature, there is a reduction in the quantity of neuronal NOS with age (142), findings consistent with reduced intrarenal NO generation. However, functional studies suggest that NO is still very important in the control of renal vascular tone, because both acute and chronic NO inhibition causes exaggerated renal vasoconstriction in old rats (52,116,139). This may mean that more NO is being produced in the kidney of the old rat or, alternatively, that the NO that is present has an increased role as a counter-regulatory influence to the activated intrarenal vasoconstrictor systems.

The renal vasodilatory response to acetylcholine (Ach) is not blunted in old conscious rats (138), although *in vitro* the dose–response curve to Ach changes so that the isolated perfused kidney of the aged rat vasoconstricts to high levels of Ach (143). The renal vasodilatory response to amino acid infusion and protein feeding is mediated by both prostaglandins and NO (144,145), although the available data in aging are conflicting. Administration of the NO substrate L-arginine produces an unblunted renal vasodilatory response in old rats (138). In contrast, the renal vasodilatory response to infusion of glycine and to protein intake in the food is blunted with advancing age in the Sprague Dawley and WAG/Rij rat (34,90). Interpretation of Ach and amino acid responses is complicated because these agents use other vasodilatory pathways in addition to NO, and the contribution of these pathways may vary between species and under different experimental conditions.

There is also the issue of NO originating from constitutive NOS ("good NO" involved in controlled vasodilation, antiplatelet aggregation, etc.) *versus* NO originating from inducible NOS (iNOS; "bad NO," which is cytotoxic and causes uncontrolled vasodilation). Senescent mice exhibit an enhanced macrophage iNOS response with excessive NO generation in response to immunologic stimulation, which increases mortality (146,147). Aminoguanidine is an iNOS inhibitor, and some of the beneficial effects on the kidney of long-term treatment with this drug may reflect iNOS inhibition, as well as inhibition of AGE (18). In addition to their vasoactive actions, many of the hormones and autocoids discussed above can influence growth of glomerular mesangial cells and extracellular matrix production (148–151). Alterations in the local

renal activity of these systems probably contribute to the age-dependent expansion of the glomerular and tubulointerstitial extracellular matrix, discussed above.

Summary and Conclusions

The rat provides a useful experimental model to study of the mechanisms of kidney aging. As in man, a wide diversity in the renal response to aging occurs in the rat, and because of this variability it is important to always specify experimental conditions, i.e., strain, gender, diet, and environment. Most aging rats display chronic progressive nephrosis, although the rate at which injury develops is highly variable. There are a number of known risk factors that potentiate injury, including male gender, genetic background, obesity, high protein/high calorie diet, and environmental exposure to pathogens. The causes of age-dependent glomerulopathy are multifactorial and include an imbalance between synthesis and degradation of extracellular matrix products, as well as hemodynamic alterations. Of importance, this damage is not inevitable and can be dissociated from normal kidney aging when optimal conditions for successful aging are provided. There is complex and sometimes contradictory information on vasoactive factors. It is, likely, however, that the activity of intrarenal AngII is somehow upregulated in the aging kidney of some, but not all, strains, and α1-dependent renal nerve activity may also be enhanced. The endothelial vasodilatory prostaglandins and NO exert an increasingly important role in the maintenance of renal perfusion with advancing age, although their production may be diminished. In the future, we anticipate that comparison of rats with different genetic backgrounds will help to dissociate true aging from disease.

References

1. Epstein M: Aging and the kidney. J Am Soc Nephrol 7: 1106–1122, 1996
2. Chou SY, Lindeman RD: Structural and functional changes in the aging kidney. In: The Principles and Practice of Nephrology, 2nd Ed., edited by Jacobson HR, Striker GE, Klahr S, St. Louis, Mosby, 1995, pp 510–514
3. Baylis C, Schmidt RJ: The aging glomerulus. Semin Nephrol 16: 265–276, 1996
4. Levi M, Rowe JW: Renal function and dysfunction in aging. In: The Kidney: Physiology and Pathophysiology, edited by Seldin DW, Giebisch G, New York, Raven, 1992, pp 3433–3456
5. Corman B, Michel JB: Glomerular filtration, renal blood flow, and solute excretion in conscious aging rats. Am J Physiol 253: R555–R560, 1987
6. Corman B, Owen R: Normal development, growth, and aging of the kidney. In: Pathobiology of the Aging Rats, edited by Mohr U, Dungworth DL, Capen CC, Washington, DC, ILSI Press, 1992, pp 195–209
7. Hirokawa K: Characterization of age-associated kidney disease in Wistar rats. Mech Ageing Dev 4: 301–316, 1975
8. Heudes D, Michel O, Chevalier J, Bariety J, Zimmerman A, Corman B: Effect of chronic angiotensin I converting enzyme inhibition on the aging processes. I. Kidney structure and function. Am J Physiol 266: R1038–R1051, 1994
9. Dodane V, Chevalier J, Bariety J, Pratz J, Corman B: Longitudinal study of solute excretion and glomerular ultrastructure in an experimental model of aging rats free of kidney disease. Lab Invest 64: 377–391, 1991
10. Baylis C: Age-dependent glomerular damage in the rat: Dissociation between glomerular injury and both glomerular hypertension and hypertrophy. Male gender as a primary risk factor. J Clin Invest 94: 1823–1829, 1994
11. Corman B, Pratz J, Poujeol P: Changes in anatomy, glomerular filtration, and solute excretion in aging rat kidney. Am J Physiol 248: R282–287, 1985
12. Owen R, Heywood R: Age-related variation in renal structure and function in Sprague-Dawley rats. Toxicol Pathol 14: 158–167, 1986
13. Yu B, Masoro E, Murata I, Bertrand H, Lynd F: Lifespan study of SPF Fischer 344 male rats fed ad libitum or restricted diets: Longevity, growth, lean body mass, and disease. J Gerontol 37: 130–141, 1982
14. Francois V, Heudes D, Bariety J, Bruneval P, Corman B: Glomerular capillary network of cortical nephron is reduced in male but not in female aging rats. Mech Ageing Dev 91: 11–22, 1996
15. Gray J: Chronic progressive nephrosis in the albino rats. CRC Crit Rev Toxicol 5: 115–143, 1977
16. Gray J, Weaver R, Purmalis A: Ultrastructural observations of chronic progressive nephrosis in the Sprague-Dawley rat. Vet Pathol 11: 153–164, 1974
17. Bolton W, Sturgill B: Ultrastructure of the aging kidney. In: Aging and Cell Structure, Vol. 1, edited by Johnson JE, New York, Plenum, 1981, pp 215–250
18. Li Y, Steffes M, Donelly T, Liu C, Fuh H, Basgen J, Bucala R, Vlassara H: Prevention of cardiovascular and renal pathology of aging by the advanced glycation inhibitor aminoguanidine. Proc Natl Acad Sci USA 93: 3902–3907, 1996
19. Reckelhoff JF, Samsell L, Racusen L, Dey R, Baylis C: The effect of aging on glomerular hemodynamics in the Sprague-Dawley rat. Am J Kidney Dis 20: 70–75, 1992
20. Sato F, Tsuchihashi T, Kawashima N: Age changes in number and size of the murine renal glomeruli. Exp Gerontol 10: 325–331, 1975
21. Bertani T, Zoja C, Abbate M, Rossini M, Remuzzi G: Age-related nephropathy and proteinuria in rats with intact kidneys exposed to diets with different protein content. Lab Invest 60: 196–204, 1989
22. Bureck J: Pathology of Aging Rats, Boca Raton, FL, CRC Press, 1979
23. Everitt A, Porter B, Wyndham J: Effect of caloric intake and dietary composition on the development of proteinuria, age associated renal disease and longevity in the male rats. Gerontology 28: 168–173, 1982
24. Kreisberg J, Karnovsky M: Focal glomerular sclerosis in the Fawn-Hooded rat. Am J Pathol 92: 637–652, 1978
25. Maeda H, Gleiser C, Masoro E, Murata I, McMahan C, Yu B: Nutritional influences on aging of Fischer 344 rats. II. Pathology. J Gerontol 40: 671–688, 1985
26. Pollard M, Kajima M: Lesions in aged, germ-free Wistar rats. Am J Pathol 61: 25–36, 1970
27. Short B, Goldstein R: Nonneoplastic lesions in the kidney. In: Pathobiology of the Aging Rats, edited by Mohr U, Dungworth DL, Capen CC, Washington, DC, ILSI Press, 1992, pp 212–225
28. Walker F: The origin, turnover and removal of glomerular basement membrane. J Pathol 110: 233–244, 1973
29. Win Win Y, Takahashi S, Kawashima S: Age-related changes in sex difference in the ultrastructure of renal glomerulus in Wistar/Tw rats. Zool Sci (Tokyo) 6: 777–788, 1989

30. Greenfeld Z, Stillman IE, Brezis M, Rosen S: Medullary injury in the aging rat kidney: Functional-morphometric correlations. *Eur J Clin Invest* 27: 346–351, 1997

31. Abrass CK, Adcox MJ, Raugi GJ: Age associated changes in renal extracellular matrix. *Am J Pathol* 146: 742–752, 1995

32. Van Liew JB, Davis FB, Davis PJ, Noble B, Bernardis LL: Calorie restriction decreases microalbuminuria associated with aging in barrier-raised Fischer 344 rats. *Am J Physiol* 263: F554–F561, 1992

33. Goldstein RS, Tarloff JB, Hook JB: Age-related nephropathy in laboratory rats. *FASEB J* 2: 2241–2251, 1988

34. Corman B, Chami-Khazraji S, Schaeverbeke J, Michel JB: Effect of feeding on glomerular filtration rate and proteinuria in conscious aging rats. *Am J Physiol* 255: F250–F256, 1988

35. Baylis C, Fredericks M, Leypoldt K, Frigon R, Wilson C, Henderson L: Mechanisms of proteinuria in aging rats. *Mech Ageing Dev* 45: 111–126, 1988

36. Neuhaus OW, Flory W: Age-dependent changes in the excretion of urinary proteins by the rat. *Nephron* 22: 570–576, 1978

37. Alt JM, Hackbarth H, Deerberg F, Stolte H: Proteinuria in rats in relation to age-dependent renal changes. *Lab Anim* 14: 95–101, 1980

38. Bakala H, Verbeke P, Perichon M, Corman B, Schaeverbeke J: Glycation of albumin with aging and diabetes in rats: Changes in its renal handling. *Mech Ageing Dev* 78: 63–71, 1995

39. Casadevall G, Piera C, Setoain J, Queralt J: Age-dependent enzymuria, proteinuria and changes in renal blood flow and glomerular filtration rate in rats. *Mech Ageing Dev* 82: 51–60, 1995

40. Damsgaard EM, Froland A, Jorgensen OD: Microalbuminuria as predictor of increased mortality in elderly people. *Br Med J* 300: 297–300, 1990

41. Cheignon M, Bakala H, Geloso-Meyer A, Schaeverbeke J: Changes of glomerular filtration barrier related to aging, in the rat. *Comptes Rendus de l'Académie des Sciences Paris*, t.299, serie III, #9, 379–382, 1984

42. Anderson S, Brenner BM: Effects of aging on the renal glomerulus. *Am J Med* 80: 435–442, 1986

43. Remuzzi A, Puntorieri S, Mazzoleni A: Sex related differences in glomerular ultrafiltration and proteinuria in Munich Wistar rats. *Kidney Int* 34: 481–486, 1988

44. Reckelhoff JF, Manning RD Jr: Role of endothelium-derived nitric oxide in control of renal microvasculature in aging male rats. *Am J Physiol* 265: R1126–R1131, 1993

45. Fujihara CK, Limongi DMZP, De Oliveira HCF, Zatz R: Absence of focal glomerulosclerosis in aging analbuminemic rats. *Am J Physiol* 262: R947–R954, 1992

46. Brenner BM: Nephron adaptation to renal injury or ablation. *Am J Physiol* 249: F324–F328, 1985

47. Yoshida Y, Fogo A, Ichikawa I: Glomerular hemodynamic changes vs hypertrophy in experimental glomerular sclerosis. *Kidney Int* 35: 654–660, 1989

48. Daniels BS, Hostetter TH: Adverse effects of growth in the glomerular microcirculation. *Am J Physiol* 258: F1409–F1416, 1990

49. Zatz R, Fujihara CK: Glomerular hypertrophy and progressive glomerulopathy: Is there a definite pathogenetic correlation? *Kidney Int Suppl* 45: S27–S29, 1994

50. Remuzzi A, Puntorieri S, Alfano M, Maccioni D, Abbate M, Bertani T, Remuzzi G: Pathophysiologic implications of proteinuria in a rat model of progressive glomerular injury. *Lab Invest* 67: 572–579, 1992

51. Gafter U, Ben-Bassat M, Levi J: Castration inhibits glomerular hypertrophy and proteinuria in uninephrectomized male rats. *Eur J Clin Invest* 20: 360–365, 1990

52. Gray JE, Van Zwieten MJ, Hollandes CF: Early light microscopic changes of chronic progressive nephrosis in several strains of aging laboratory rats. *J Gerontol* 37: 142–150, 1982

53. Baylis C, Wilson CB: Sex and the single kidney. *Am J Kidney Dis* 13: 290–298, 1989

54. Lombet JR, Adler SG, Anderson PS, Nast CC, Olsen DR, Glassock RJ: Sex vulnerability in the subtotal nephrectomy model of glomerulosclerosis in the rat. *J Lab Clin Med* 114: 66–74, 1989

55. Gretz N, Zeier M, Geberth S, Stranch M, Ritz E: Is gender a determinant for evolution of renal failure? A study of autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 14: 178–183, 1989

56. West KM, Erdreich L, Stober JA: A detailed study of risk factors for retinopathy and nephropathy in diabetes. *Diabetes* 29: 501–508, 1980

57. Silbiger SR, Neugarten J: The impact of gender on the progression of chronic renal disease. *Am J Kidney Dis* 25: 515–533, 1995

58. Floege J, Johnson RJ, Couser WG: Mesangial cells in the pathogenesis of progressive glomerular disease in animal models. *Clin Invest* 70: 857–864, 1992

59. Couser WG, Stilmant MM: Mesangial lesions and focal glomerular sclerosis in the aging rat. *Lab Invest* 33: 491–501, 1975

60. Elema JD, Arends A: Focal and segmental glomerular hyalinosis and sclerosis in the rat. *Lab Invest* 33: 554–561, 1975

61. Corman B, Roinel N: Single nephron filtration rate and proximal reabsorption in aging rats. *Am J Physiol* 266: F75–F80, 1990

62. Reckelhoff JF, Baylis C: Glomerular metalloprotease activity is suppressed by androgens in the aging kidney. *J Am Soc Nephrol* 3: 1835–1838, 1993

63. Cohen M, Hud E, Van-Yu W, Ziyadeh N: Albumin modified by Amadori glucose adducts activates mesangial cell type IV collagen gene transcription. *Mol Cell Biochem* 151: 61–67, 1995

64. Doi T, Vlassara H, Kirstein M, Yamada Y, Striker G, Striker L: Receptor-specific increase in extracellular matrix production in mouse mesangial cells by advanced glycosylation end products is mediated via platelet-derived growth factor. *Proc Natl Acad Sci USA* 89: 2873–2877, 1992

65. Soulis-Liparota T, Cooper M, Papazoglou D, Clarke B, Jerums G: Retardation by aminoguanidine of development of albuminuria, mesangial expansion, and tissue fluorescence in streptozotocin-induced diabetic rat. *Diabetes* 40: 1328–1334, 1991

66. Vlassara H, Bucala R, Striker L: Pathogenic effects of advanced glycosylation: Biochemical, biologic, and clinical implications for diabetes and aging. *Lab Invest* 70: 138–151, 1994

67. Yang C, Vlassara H, Peten E, He C, Striker G, Striker L: Advanced glycation end products up-regulate gene expression found in diabetic glomerular disease. *Proc Natl Acad Sci USA* 91: 9436–9440, 1994

68. Yang C, Vlassara H, Striker G, Striker L: Administration of AGEs in vivo induces genes implicated in diabetic glomerulosclerosis. *Kidney Int Suppl* 49: S55–S58, 1995

69. Verbeke P, Perichon M, Borot-Laloi C, Schaeverbeke J, Bakala H: Accumulation of advanced glycation end products in the rat nephron: Link with circulating AGEs during aging. *J Histochem Cytochem* 45: 1059–1068, 1997

70. Corman B, Duriez M, Poitevin P, Heudes D, Bruneval P, Tedgui A, Levy BI: Aminoguanidine prevents age-related arterial stiff-

ening and cardiac hypertrophy. *Proc Natl Acad Sci USA* 95: 1301–1306, 1998

71. Saxton J, Kimball G: Relation of nephrosis and other diseases of albino rats to age and to modification of diet. *Arch Pathol* 32: 951–965, 1942

72. Zawada ET, Alavi FK, Santella RN, Maddox DA: Influence of dietary macronutrients on glomerular senescence. *Curr Nephrol* 20: 1–47, 1997

73. Corman B, Teillet L: Nutrition and kidney aging. In: *Facts and Research in Gerontology*, edited by Albarede JL, Veilas P, Garry PJ, Serdi, 1994, pp 127–137

74. Kennedy G: Effect of old age and over-nutrition on the kidney. *Br Med Bull* 13: 67–81, 1957

75. Masoro E: Food restriction in rodents, an evaluation in its role in the study of aging. *J Gerontol* 43: 59–64, 1988

76. Masoro E, Yu B: Diet and nephropathy. *Lab Invest* 60: 165–167, 1989

77. Yu B, Masoro E, McMahan C: Nutritional influences on aging of Fischer 344 rats. I. Physical, metabolic, and longevity characteristics. *J Gerontol* 40: 657–670, 1985

78. Joles JA, Goor H, Van Der Horst LC, Van Tol A, Elema JD, Koomans HA: High lipid levels in very low density lipoprotein and intermediate density lipoprotein may cause proteinuria and glomerulosclerosis in aging female analbuminemic rats. *Lab Invest* 6: 912–921, 1995

79. Iwaski K, Gleiser C, Masoro E, McMahan C, Seo EJ, Yu B: The influence of dietary protein source on longevity and age-related disease processes of Fischer rats. *J Gerontol* 43: B5–B12, 1988

80. Kalu D, Masoro E, Yu B, Hardin R, Hollis B: Modulation of age-related hyperparathyroidism and senile bone loss in Fischer rats by soy protein and food restriction. *Endocrinology* 122: 1847–1854, 1988

81. Blatherwick N, Medlar E: Chronic nephritis in rats fed high protein diets. *Arch Intern Med* 59: 572–586, 1937

82. Bras G, Ross H: Kidney disease and nutrition in the rat. *Toxicol Appl Pharmacol* 6: 247–252, 1964

83. Fujita Y, Ichikawa M, Kurimoto M, Rikimaru T: Effect of feed restriction and switching the diet on proteinuria in male Wistar rats. *J Gerontol* 39: 531–537, 1984

84. Tucker S, Mason R, Beauchene R: Influence of diet and feed restriction on kidney function of aging male rats. *J Gerontol* 31: 264–270, 1976

85. Wyndham J, Everitt A, Everitt S: Effect of isolation and food restriction begun at 50 days on the development of age-associated renal disease in the male Wistar rat. *Arch Gerontol Geriatr* 2: 317–332, 1983

86. Masoro E, Katz M, McMahan C: Evidence for the glycation hypothesis of aging from the food-restricted rodent model. *J Gerontol* 44: 20–21, 1989

87. Sterzel RB, Schulze-Lohoff E, Weber M, Goodman SL: Interactions between glomerular mesangial cells, cytokines, and extracellular matrix. *J Am Soc Nephrol* 2: S126–S131, 1992

88. Doi T, Vlassara H, Kirstein M, Yamada Y, Striker G, Striker L: Receptor specific increased mesangial cell extracellular matrix production is mediated by PDGF. *Proc Natl Acad Sci USA* 89: 2873–2877, 1992

89. Paget G, Lemon P: The interpretation of pathology data. In: *The Pathology of Laboratory Animals*, Vol. 14, edited by McCoy J, Springfield, IL, Thomas, 1965, pp 382–395

90. Baylis C, Fredericks M, Wilson C, Munger K, Collins R: Renal vasodilatory response to IV glycine in the aging rat kidney. *Am J Kidney Dis* 15: 244–251, 1990

91. Munger KA, Baylis C: Sex differences in renal hemodynamic in rats. *Am J Physiol* 254: F223–F231, 1988

92. Belmin J, Lévy BI, Michel JB: Changes in the renin angiotensin-aldosterone axis in the laterlife. *Drugs Aging* 5: 391–400, 1994

93. Corman B, Michel JB: Renin-angiotensin system, converting-enzyme inhibition, and kidney function in aging female rats. *Am J Physiol* 251: R450–R455, 1986

94. Hayashi M, Satura T, Nakamura R, Kitajima W, Kato E: Effect of aging on single nephron renin content in rats. *Renal Physiol* 4: 17–21, 1981

95. Jover B, Dupont M, Geelen G, Wahba W, Mimran A, Corman B: Renal and systemic adaptation to sodium restriction in aging rats. *Am J Physiol* 264: R833–R838, 1993

96. Magro AM, Rudofsky UH: Plasma renin activity decrease precedes spontaneous focal glomerular sclerosis in aging rats. *Nephron* 31: 245–253, 1982

97. Michel JB, Heudes D, Michel O, Poitevin P, Philippe M, Scalbert E, Corman B, Levy BI: Effect of chronic angiotensin I converting enzyme inhibition on the aging processes. II. Large arteries. *Am J Physiol* 267: R124–R135, 1994

98. Corman B, Barrault MB, Klingler C, Houot AM, Michel JB, Della Bruna R, Pinet F, Soubrier F: Renin gene expression in the aging kidney: Effect of sodium restriction. *Mech Ageing Dev* 84: 1–13, 1995

99. Corman B, Roinel N, Geelen G: Plasma vasopressin and cortical nephron function in aging rats. *Mech Ageing Dev* 62: 263–277, 1992

100. Docherty JR: Cardiovascular responses in aging: A review. *Pharmacol Rev* 42: 103–125, 1992

101. Baylis C, Engels K, Hymel A, Navar LG: Plasma renin activity and metabolic clearance rate of angiotensin II in the unstressed aging rat. *Mech Ageing Dev* 97: 163–171, 1997

102. Baylis C, Engels K, Beierwaltes WH: Airjet stress (AJS) stimulated renin release is blunted in old rats in association with diminished β-adrenoceptor responsiveness [Abstract]. *J Am Soc Nephrol* 8: 826A, 1997

103. Jung F, Kennefick T, Ingelfinger J, Vora J, Anderson S: Downregulation of the intrarenal renin-angiotensin system in the aging rat. *J Am Soc Nephrol* 5: 1573–1580, 1995

104. Hung L, Richardson A: The effect of aging on the genetic expression of renin by mouse kidney. *Aging (Milano)* 5: 193–198, 1993

105. Eggena P, Morin AM, Barett JD, Krall JF: The influence of aging on angiotensinogen production by rat vascular smooth muscle cells in vitro. *Clin Exp Hypertens [A]* 10: 597–603, 1988

106. Heymes C, Swinghedauw B, Chevalier B: Activation of angiotensinogen and angiotensin-converting enzyme gene expression in the left ventricle of senescent rats. *Circulation* 90: 1328–1333, 1994

107. Heudes D, Michel O, Chevalier J, Scalbert J, Ezan E, Bariety J, Zimmerman A, Corman B: Effect of chronic ANG I converting enzyme inhibition on aging processes. I. Kidney structure and function. *Am J Physiol* 266: R1038–R1051, 1994

108. Mooradian A, Lieberman J: Age-related decrease in serum angiotensin converting enzyme activity: The role of thyroidal status and food intake. *J Gerontol* 45: B24–B27, 1990

109. Lu X, Li X, Li L, Li L, Li C, Wang H: Variation of intrarenal angiotensin II and angiotensin II receptors by acute renal ischemia in the aged rats. *Renal Failure* 18: 19–29, 1996

110. Tank JE, Vora JP, Houghton DC, Anderson S: Altered renal vascular responses in the aging rat kidney. *Am J Physiol* 266: F942–F948, 1994

111. Baylis C: Renal responses to acute angiotensin II inhibition and administered angiotensin II in the aging, conscious, chronically catheterized rat. *Am J Kidney Dis* 22: 842–850, 1993

112. Zhang XZ, Qiu C, Baylis C: Glomerular hemodynamic responses to administered angiotensin II in the old rat. *Mech Ageing Dev* 97: 183–192, 1997

113. Anderson S, Rennke HG, Zatz R: Glomerular adaptations with normal aging and with long-term converting enzyme inhibition in rats. *Am J Physiol* 267: F35–F43, 1994

114. Ferder L, Inserra F, Romano L, Ercole L, Pszenny V: Effects of angiotensin-converting enzyme inhibition on mitochondrial number in the aging mouse. *Am J Physiol* 65: C215–C218, 1993

115. Ferder L, Inserra F, Romano L, Ercole L, Pszenny V: Decrease of glomerulosclerosis in aging by angiotensin-converting-enzyme inhibitions. *J Am Soc Nephrol* 5: 1147–1152, 1994

116. Hajduczok G, Chapleau MW: Increase in sympathetic activity with age. I. Role of impairment of arterial baroreflexes. *Am J Physiol* 260: H1113–H1120, 1991

117. Masilamani S, Baylis C: Defective pressure natriuresis in the aging kidney [Abstract]. *J Am Soc Nephrol* 4: 516A, 1993

118. Kawai Y, Ohhashi T: Age-related changes in relaxant response of vascular smooth muscles to atrial natriuretic peptide. *J Pharmacol Exp Ther* 252: 1234–1239, 1990

119. Moritoki H, Yoshikawa T, Hisayama T, Takeuchi S: Possible mechanisms of age-associated reduction of vascular relaxation caused by atrial natriuretic peptide. *Eur J Pharmacol* 210: 61–68, 1992

120. Dunn BR, Ichikawa I, Pfeffer JM, Troy JL, Brenner BM: Renal and systemic hemodynamic effects of synthetic atrial natriuretic peptide in the anesthetized rat. *Circ Res* 59: 237–246, 1986

121. DePriest D, Zimmermann C, Baylis C: Renal effects of administered atrial natriuretic peptide in the conscious, aging rat. *Life Sci* 46: 785–792, 1990

122. Tan AC, Jansen TL, Termond EFS: Kinetics of atrial natriuretic peptide in young and elderly subjects. *Eur J Clin Pharmacol* 42: 449–452, 1992

123. Reckelhoff JF, Baylis C: Proximal tubular metalloprotease activity is decreased in the senescent rat kidney. *Life Sci* 50: 959–963, 1992

124. Greenfeld Z, Engels K, Samsell L, Baylis C: Aging does not affect the role of endothelin (ET) in the rat kidney [Abstract]. *J Am Soc Nephrol* 8: 329A 1997

125. Menconi M, Taylor L, Martin B: A review: Prostaglandins, aging, and blood vessels. *J Am Geriatr Soc* 35: 239–247, 1987

126. Hornych A, Forette F, Bariety J, Krief C, Aumont J, Paris M: The influence of age on renal prostaglandin synthesis in man. *Prostaglandins Leukotrienes Essent Fatty Acids* 43: 191–195, 1991

127. Rathaus M, Greenfeld Z, Podjarny E, Brezis M, Bernheim J: Sodium loading and renal prostaglandins in old rats. *Prostaglandins Leukotrienes Essent Fatty Acids* 49: 815–819, 1993

128. Johnson AG, Day RO: The problems and pitfalls of NSAID therapy in the elderly (Part 1). *Drugs Aging* 1: 130–143, 1991

129. Zager RA, Alpers CE: Effects of aging on expression of ischemic acute renal failure in rats. *Lab Invest* 3: 290–294, 1989

130. Greenfeld Z, Peleg I, Brezis M, Rosen S, Pisanty S: Potential interaction between prolonged cyclosporin administration and aging in the rat kidney. *Ann NY Acad Sci* 717: 209–212, 1994

131. Sabbatini M, Sansone G, Uccello F, De Nicola L, Giliberti A, Sepe V, Magri P, Conte G, Andreucci VE: Functional versus structural changes in the pathophysiology of acute ischemic renal failure in aging rats. *Kidney Int* 45: 1355–1361, 1994

132. Moncada S, Palmer RMJ, Higgs EA: Nitric oxide: Physiology, pathophysiology, and pharmacology. *Pharmacol Rev* 43: 109–141, 1991

133. Kone BC, Baylis C: Biosynthesis and homeostatic roles of nitric oxide in the kidney. *Am J Physiol* 272: F561–F578, 1997

134. Tominaga M, Fujii K, Abe I, Takata Y, Kobayashi K, Fujishima M: Hypertension and aging impair acetylcholine-induced vasodilation in rats. *J Hypertens* 12: 259–268, 1994

135. Dohi Y, Thiel MA, Buhler FR, Luscher TF: Activation of endothelial L-arginine pathway in resistance arteries. *Hypertension (Dallas)* 15: 170–179, 1990

136. Sonaka I, Futami Y, Maki T: L-Arginine-nitric oxide pathway and chronic nephropathy in aged rats. *J Gerontol* 49: B157–B161, 1990

137. Reckelhoff JF, Kellum JA, Blanchard EJ, Bacon EE, Wesley AJ, Kruckeberg WC: Changes in nitric oxide precursor, L-arginine, and metabolites, nitrate and nitrite, with aging. *Life Sci* 55: 1895–1902, 1994

138. Hill C, Lateef AM, Engels K, Samsell L, Baylis C: Basal and stimulated nitric oxide in control of kidney function in the aging rat. *Am J Physiol* 41: R1747–R1753, 1997

139. Challah M, Nadaud S, Philippe M, Battle T, Soubrier F, Corman B, Michel JB: Circulating and cellular markers of endothelial dysfunction with aging in rats. *Am J Physiol* 273: H1941–H1948, 1997

140. Halliwell B: Oxidants and human disease: Some new concepts. *FASEB J* 1: 358–364, 1987

141. Ruiz-Torres P, Gonzalez-Rubio M, Lucio-Cazana J, Ruiz-Villaespesca A, Rodriguez-Puyol M, Rodriguez-Puyol D: Reactive oxygen species and platelet activating factor synthesis in age-related glomerular sclerosis. *J Lab Clin Med* 124: 489–495, 1994

142. Greenfeld Z, Dey R, Baylis C: Neuronal nitric oxide synthase (nNOS) level in macula densa (MD) of old rat kidney [Abstract]. *J Am Soc Nephrol* 8: 329A, 1997

143. Vargas F, Osuna A, Fernandez-Rivas A: Abnormal renal vascular reactivity to acetylcholine and nitroprusside in aging rats. *Gen Pharmacol* 28: 133–137, 1997

144. Ruilope L, Rodicio J, Garcia Robles R, Sancho J, Miranda B, Granger J, Romero J: Influence of a low sodium diet on the renal response to amino acid infusions in humans. *Kidney Int* 31: 992–999, 1987

145. Tolins JP, Raij L: Effects of amino acid infusion on renal hemodynamics: Role of endothelium derived relaxing factor. *Hypertension (Dallas)* 17: 1045–1051, 1991

146. Chorinchath B, Kong LY, Mao L, McCallum R: Age-associated differences in TNF-α and nitric oxide production in endotoxic mice. *J Immunol* 156: 1525–1530, 1996

147. Chen LC, Pace JL, Russell SW, Morrison DC: Altered regulation of inducible nitric oxide synthase expression in macrophages from senescent mice. *Infect Immun* 64: 4288–4297, 1996

148. Johnson A, Lermioglu F, Garg UC, Morgan-Boyd R, Hassid A: A novel biological effect of atrial natriuretic hormone: Inhibition of mesangial cell mitogenesis. *Biochem Biophys Res Commun* 152: 893–897, 1988

149. Mene P, Dunn MJ: Prostaglandins and rat glomerular mesangial cell proliferation. *Kidney Int* 37: 1256–1262, 1990

150. Garg UC, Hassid A: Inhibition of rat mesangial cell mitogenesis by nitric oxide generating vasodilators. *Am J Physiol* 257: F60–F66, 1989

151. Dubey RK: Vasodilator derived nitric oxide inhibits fetal calf serum- and angiotensin-II-induced growth of renal arteriolar smooth muscle cells. *J Pharmacol Exp Ther* 269: 402–408, 1994