Renal

PHYSIOLOGY AND PATHOPHYSIOLOGY OF THE AGING KIDNEY

Internal Medicine Grand Rounds

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Also Drug effects on ADH ⊕ + ⊖

It gives me great pleasure to converse with the aged; they have been over the road that all of us must travel, and know where it is rough and difficult and where it is level and easy.

Plato: The Republic

He that would pass the latter part of life with honor and decency, must when he is young, consider that he shall one day be old and remember when he is old that he was once young.

Samuel Johnson: The Rambler

INTRODUCTION

There are significant age-related decreases in renal blood flow, glomerular filtration rate, and tubular function. In spite of the functional and anatomical impairments, the aging kidney, under normal conditions, is remarkably capable of maintaining fluid and electrolyte balance within narrow limits. The adaptive capacity of the aging kidney, however, is quite restricted, and stress and disease can result in significant fluid and electrolyte disorders in the elderly subject.

This grand rounds will review the physiology and pathophysiology of the aging kidney, will discuss the clinical implications of the age-related renal functional impairments, and finally will describe some renal diseases that are frequently encountered in the aged population.

Of note, the term aging, as used here, refers to renal changes that occur after attainment of maturity and in the absence of superimposed medical diseases which can independently affect renal function.

RENAL ANATOMY

Advancing age is associated with progressive loss of renal mass in humans, with renal weight decreasing from 250 to 270 grams in young adulthood to 180 to 200 grams by the eighth decade (141,164) In the absence of hypertension, diabetes, or atherosclerosis, the aging kidney maintains its relatively smooth contour. The loss of renal mass is primarily cortical, with relative sparing of the renal medulla. The total number of identifiable glomeruli falls with age, in accord with the changes of renal weight (54,111,127). The number of hyalinized or sclerotic glomeruli identified on light microscopy increases from 1 to 2 percent during the third to fifth decade, to as high as 30 percent in some apparently healthy 80-year-olds, with a mean prevalence after age 70 of approximately 10 to 12 percent (89,111,162). The number of obsolescent glomeruli at postmortem does not correlate with coincident vascular abnormalities.

Aging is associated with a loss of lobulation of the glomerular tuft, thus decreasing effective filtering area. Although the total number of nuclei per glomerulus is unchanged with age, the filtering surface is further diminished by progressive increase in the number of mesangial cells after age 40 years, and a reciprocal decrease in the number and percentage of epithelial cells. The mesangium, which accounts for approximately 8 percent of total glomerular volume at age 45 years, increases to nearly 12 percent by age 70 years (156). Although the glomerular basement membrane thickens with age, studies of glomerular filtration characteristics, as estimated by dextran clearance, show no change in permeability between ages 20 and 61 (16).

Several changes have been documented in the renal tubule with age. As with the glomerulus, the tubular basement membrane thickens (46,151). In addition, diverticuli of the distal nephron, which are essentially absent in kidneys from young individuals, become increasingly prevalent with advancing age, reaching a frequency of three diverticuli per tubule at age 90 years. These diverticuli may represent the origin of the simple retention cysts commonly seen in the elderly (19,112).

Changes also occur in the intrarenal vasculature with age, independent of hypertension or other renal disease. Normal aging is associated with variable sclerotic changes in the wall of the larger renal vessels which are augmented in the presence of hypertension. Smaller vessels are spared, with fewer than 20 percent of senescent kidneys from nonhypertensive subjects displaying arteriolar changes (131,174,176).

Radiographic studies of the renal vasculature in normotensive subjects from across the adult age range demonstrate an increasing prevalance of abnormal tapering of interlobular arteries, abnormal arcuate arteries, and increased tortuosity of intralobular arteries (47,74).

Microangiographic and histologic studies have identified two very distinctive patterns of change in arteriolar-glomerular units with senescence (107,163). In one type, hyalinization and collapse of the glomerular tuft are associated with obliteration of the lumen of the preglomerular arteriole and a resultant loss in blood flow. This type of change is seen primarily in the cortical area.

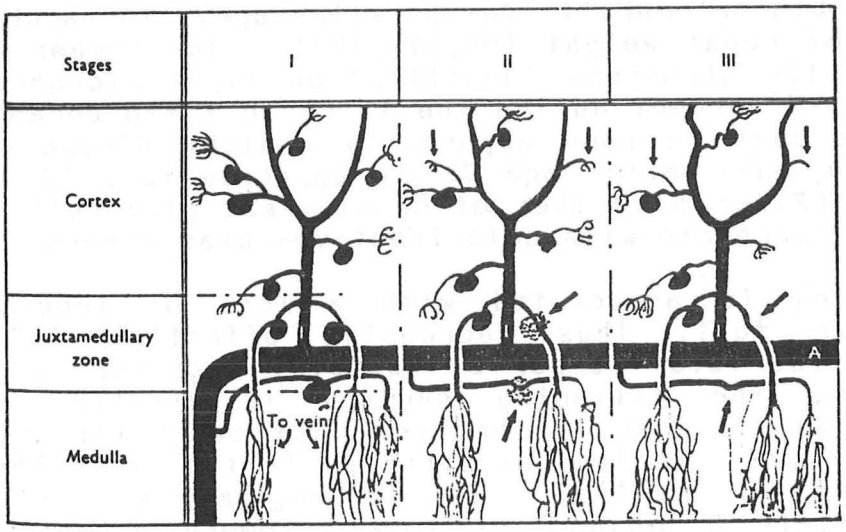
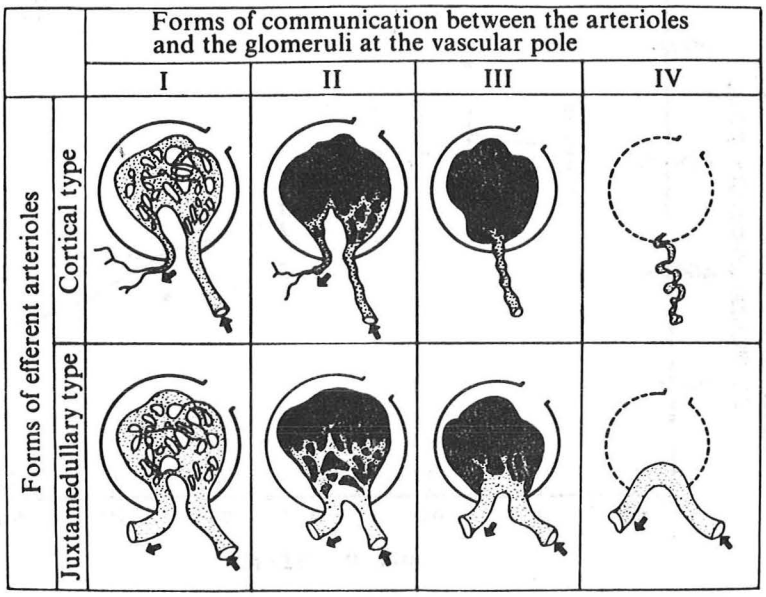


Diagram showing changes in the intrarenal arterial pattern with age. (A, arcuate artery. I, interlobular artery.) Stage I. Basic adult pattern showing glomerular arterioles. Stage II. Partial degeneration of some glomeruli. Two cortical afferent arterioles ramify into remnants of glomerular tufts (small arrows). Two juxtamedullary arterioles pass through partially degenerated glomeruli (large arrows). There is slight spiralling of interlobular arteries and afferent arterioles. Stage III. Two cortical afferent arterioles now end blindly (small arrows), and two juxtamedullary arterioles are aglomerular (large arrows). The corresponding glomerular tufts have degenerated completely. The spiralling of interlobular arteries and afferent arterioles is now more pronounced.
Ljungqvist and Lagergren, J. Anat. Lond. 96:285, 1962.

The second pattern, seen primarily in the juxtamedullary area, is characterized by the development of anatomic continuity between the afferent and efferent arterioles during glomerular sclerosis.



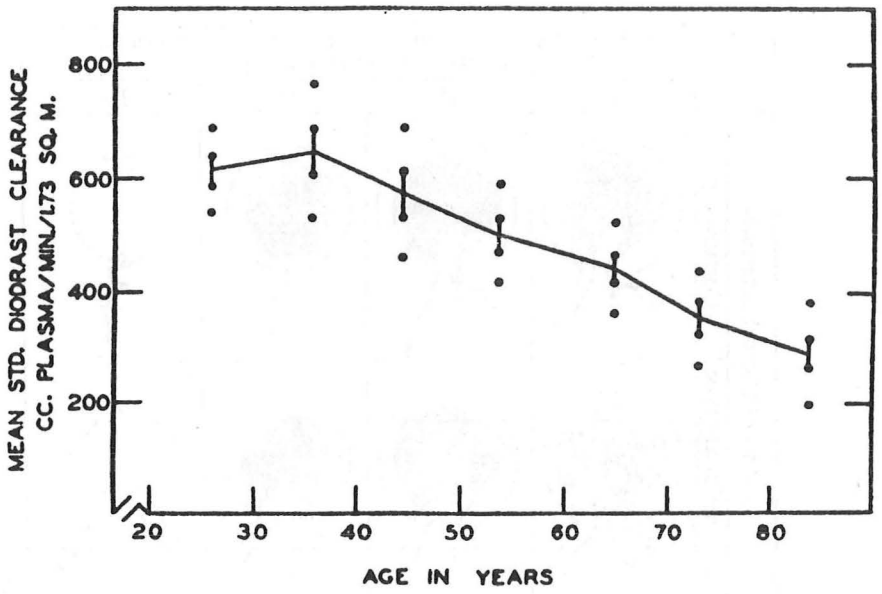
Structure and classification of the A-G units. A-G units were classified into two basic types, cortical and juxtamedullary, depending on the form of the efferent arterioles. Cortical types were arranged in various stages of degeneration terminating in complete atrophy of the A-G units. The juxtamedullary type departed from the basic pattern (Type I) to become continuous (Types II-IV) where the afferent and efferent arterioles formed a direct connection.
Takazukura, Sawabu, Handa, Takada, Shinoda, and Takeuchi. Kidney Internat. 2:224, 1972.

The end point is thus loss of glomerulus and shunting of blood flow from afferent to efferent arterioles. Blood flow is maintained to the arteriolar rectae verae, the primary vascular supply of the medulla, which are not decreased in number with age.

RENAL PHYSIOLOGY AND PATHOPHYSIOLOGY

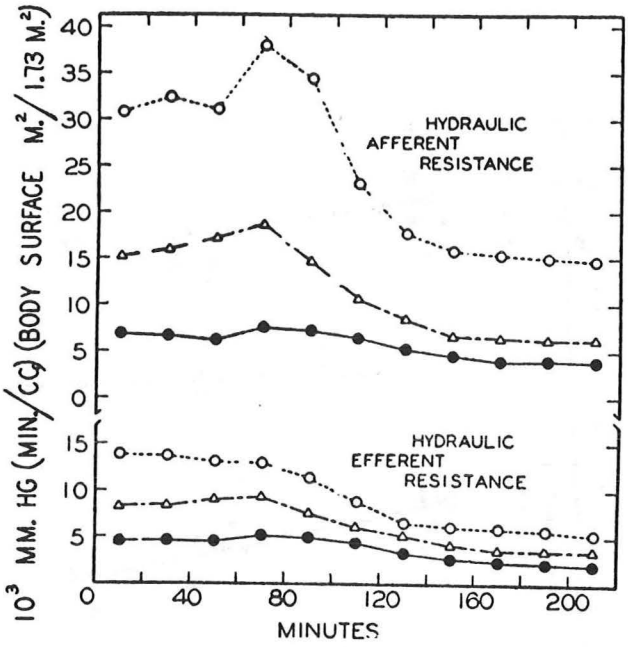
Renal Blood Flow

A progressive reduction in renal plasma flow (PAH clearance) of approximately 10 percent per decade from 600 ml/min/1.73M^2 in the 20-29 year age group to 300 ml/min/1.73M^2 in the 80-89 year age group is well known to occur (48,173).



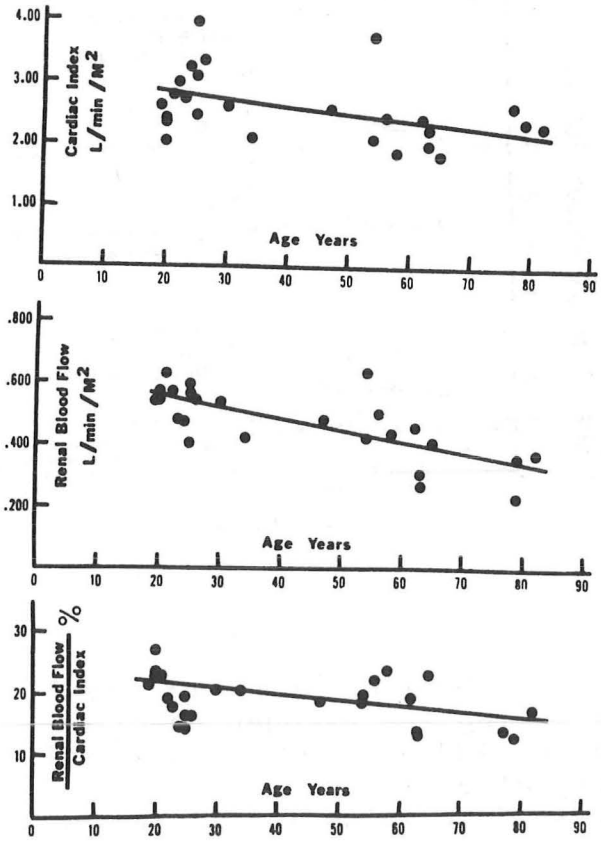
Average change in standard diodrast clearance or effective renal plasma flow with age, cc. Plasma/min/1.73 S.Q.M. body surface area.
Davies, D.F. and N.W. Shock JCI 29:496, 1950.

The decrease in renal blood flow is associated with significant increases in both the afferent and efferent arteriolar resistance (110).



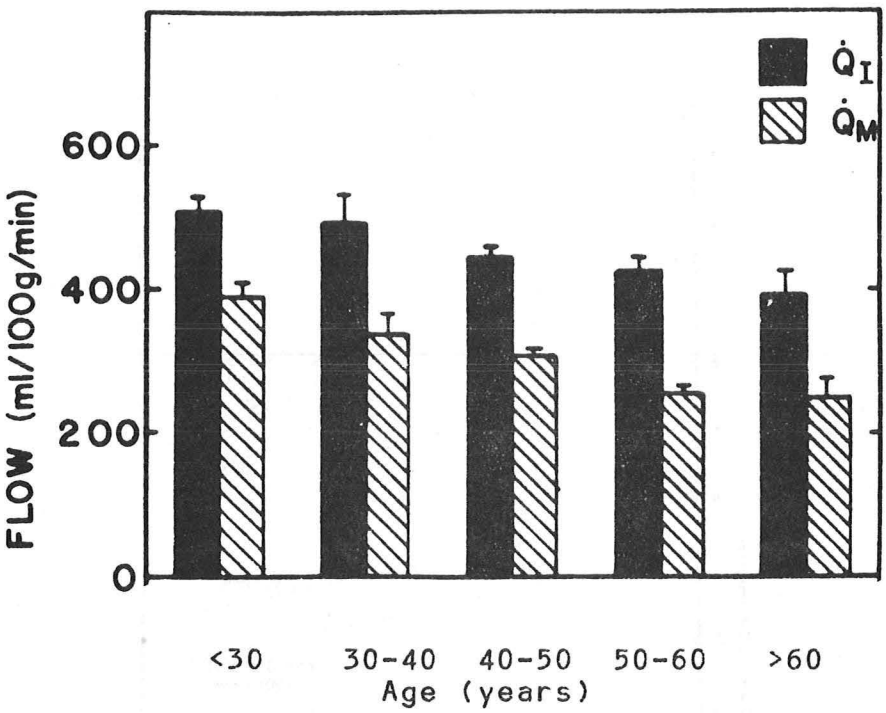
Changes in afferent and efferent renal hydraulic resistances during the pyrogen reaction.
Fifty million killed typhoid organisms were injected intravenously at 0 time.
(open circles) Mean value for 14 subjects in old age group (70-85 yrs.)
(triangles) Mean value for 20 subjects in middle age group (50-69 yrs.)
(solid circles) Mean value for 20 subjects in young age group (20-49 yrs.)
McDonald, R.K., D.H. Solomon, and N.W. Shock: JCI 30:457-462, 1951.

The increase in the efferent arteriolar resistance may explain the age-related increase in filtration fraction (48,110). The exact relationship between renal plasma flow and cardiac output as a function of aging is not well-established. Some studies have shown an age-related decrease in cardiac output (33,97), while others have shown no decrease in cardiac output with age (117,160). Furthermore, there is a small but definite decrease in the renal fraction of the cardiac ouput (RBF/CO) (100).



Cardiac index, renal blood flow per square meter body surface area, and the renal fraction of the cardiac output are plotted against age. The calculated age regression lines are drawn for each graph.
Lee, T.D., Jr., R.D. Lindeman, M.J. Yiengst, and N.W. Shock: J. Appl. Physiol. 21(1):55-61, 1966.

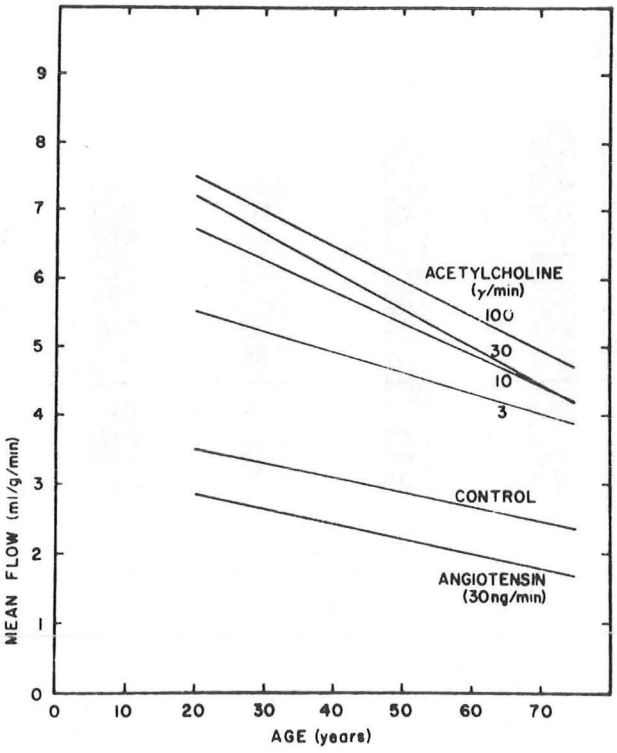
These studies suggest that the major determinant of reduced renal blood flow with age is due to functional or anatomical changes in the renal vasculature. A study using the xenon washout technique to measure renal blood flow in 207 healthy potential renal donors ranging in age from 17 to 76 years, also showed an age-related linear reduction in mean blood flow/gram kidney weight (82). There was also a parallel reduction in the rapid component flow rate as well as the percent of flow entering the rapid component.



Relationship between age, and renal perfusion rates. There is a significant reduction in mean renal blood flow (Q_M) with age ($p<0.001$): a parallel reduction in the rapid-component flow rate (Q_I) occurs with age also ($p<0.001$). Hollenberg, N.K., D.F. Adams, H.S. Solomon, A. Rashid, H.L. Abrams, and J.P. Merrill Circ. Res. XXXIV:309-316, 1974.

Since the rapid component is thought to provide an index of cortical flow, the finding of a preferential decrease in cortical blood flow as function of aging is consistent with the histologic studies showing selective loss of cortical vasculature and preservation of medullary flow. This histologic and functional demonstration of selective decrease in cortical flow may also explain the observation that filtration fraction actually increases with advancing age (48,110), as outer cortical nephrons have a lower filtration fraction than do juxtamedullary nephrons.

Whether the age-related decrease in renal blood flow is due to anatomical or functional changes in the renal vasculature has been studied by two groups of investigators who have measured renal hemodynamics following intravenous administration of pyrogen (110) and intraarterial administration of acetylcholine and angiotensin (82). During both pyrogen and acetylcholine administration, the vasodilator response was greater in the younger subjects compared to the older subjects. On the other hand, the vasoconstrictive response to angiotensin was identical in the young and old subjects.

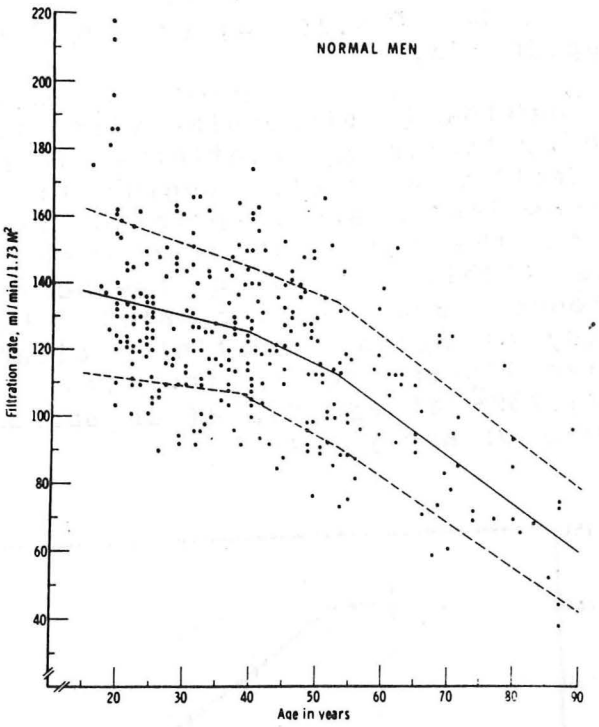


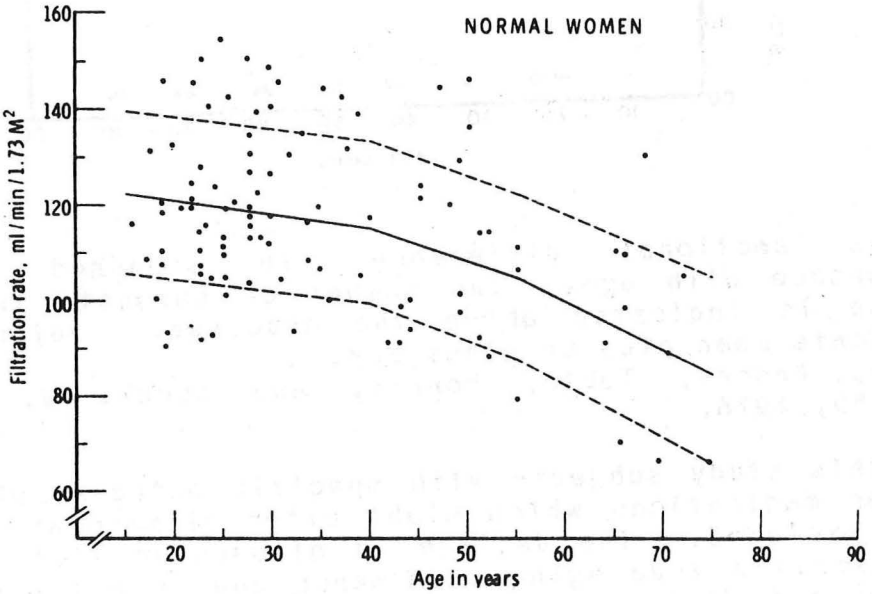
Regression relationships between age and mean blood flow during the infusion of angiotensin or graded doses of acetylcholine. The control regression relationship was identical in the two groups.
Hollenberg, N.K., D.F. Adams, H.S. Solomon, A. Rashid, H.L. Abrams, and J.P. Merrill: Circ. Res. XXXIV:309-316, 1974.

These studies suggest that while the aging renal vasculature does respond to vasoconstriction and vasodilatation, the response to vasodilatation is markedly blunted, and that anatomical changes rather than functional vasoconstriction are largely responsible for the age-related decrease in renal blood flow.

Glomerular Filtration Rate

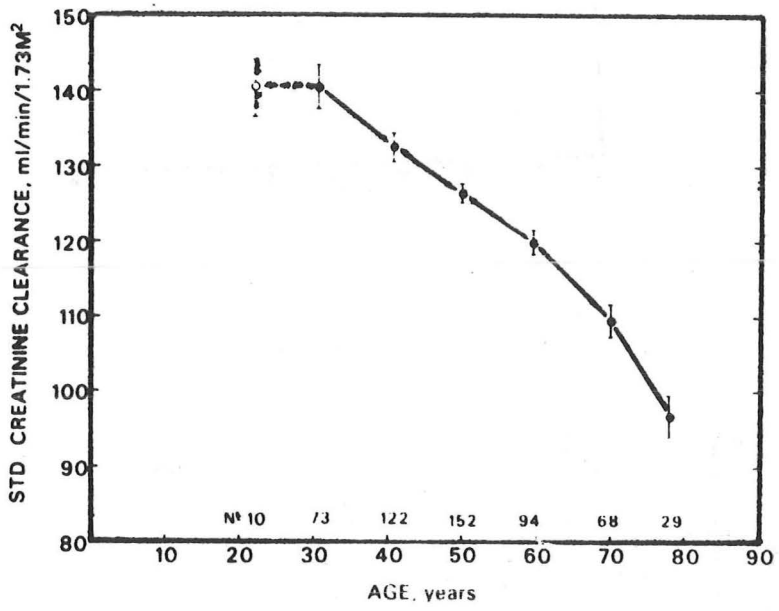
A progressive age-related decline in the glomerular filtration rate is well known to occur in men and women (48,64,82,100,106,108,110,143).


NORMAL MEN
Filtration rate, ml/min/1.73 M²
220
200
180
160
140
120
100
80
60
40
20
30
40
50
60
70
80
90
Age in years


NORMAL WOMEN
Filtration rate, ml/min/1.73 M²
160
140
120
100
80
60
20
30
40
50
60
70
80
90
Age in years

Filtration rate (inulin clearance) per 1.73 M^2 in normal men and women. Solid and broken lines represent mean value and one standard deviation.
Wesson, L.G.: in Physiology of the Human Kidney. Grune & Stratton pp.96-108.

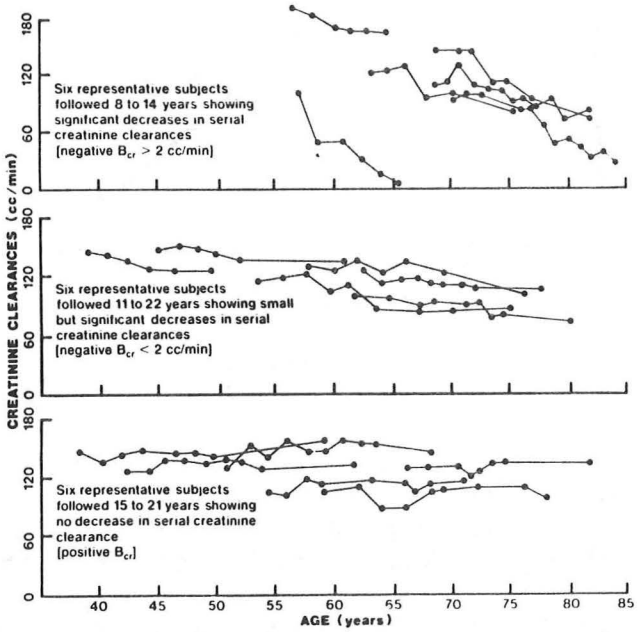
The age-related decline in glomerular filtration rate is evident whether measured by inulin or creatinine clearance. In fact, in a study in 55 healthy subjects ranging in age from 17 to 93 years, simultaneous inulin and creatinine clearances revealed no effect of age on the ratio of true creatinine clearance to inulin clearance (143). In a cross-sectional study in 548 healthy volunteers who participated in the Baltimore Longitudinal Study of Aging, creatinine clearance was found to show a progressive linear decline from 140 ml/min/1.73M^2 at age 30 to 97 ml/min/1.73M^2 at age 80, at an approximate rate of 0.8 ml/min/1.73M^2 years of age (143).



Cross sectional differences in standard creatinine clearance with age. The number of subjects in each age group is indicated above the abscissa. Values plotted indicate mean plus or minus SEM.
Rowe, Andres, Tobin, Norris, and Shock: J. Gerontol. 31:155, 1976.

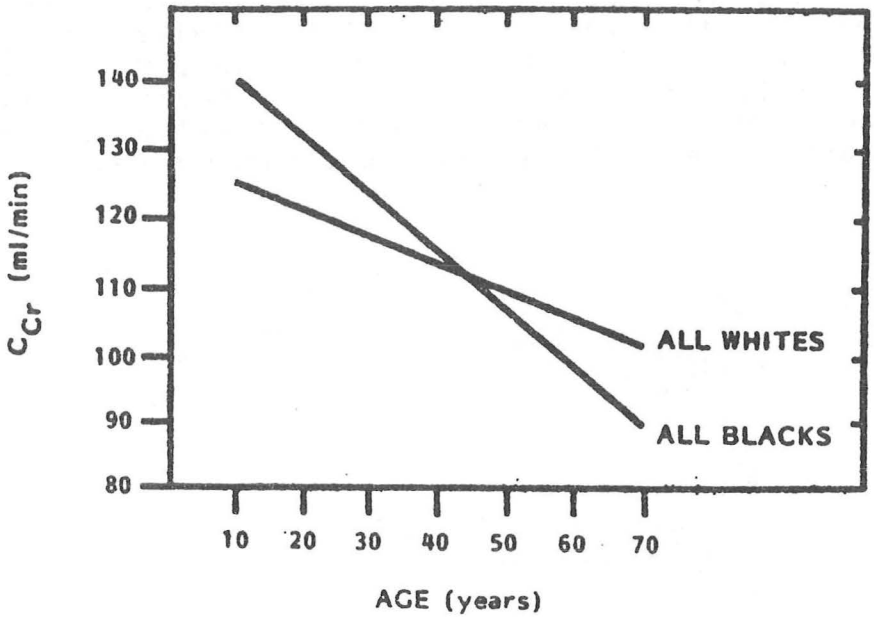
In this study subjects with specific extra-renal or renal diseases or medications which might alter glomerular filtration rate were excluded. The decline in glomerular filtration rate thus represents a true aging phenomenon and is not a reflection of superimposed disease. In this study, in addition, in 293 normal subjects three or more serial clearances were obtained at 12-18 month intervals. The longitudinal data revealed a similar age-related decline in creatinine clearance (143). Follow-up

studies in 254 normal subjects in the Baltimore Longitudinal Study on Aging with five to fourteen serial creatinine clearance determinations obtained between 1958 and 1981 also reveald a mean decrease in creatinine clearance of 0.75 ml/min/year, and an increase in the rate of loss of creatinine clearance with age (106). In this study, of interest however, 92 or 36% of the 254 subjects followed had no absolute decrease in creatinine clearance, and 7 of these subjects had actually a statistically significant increase in creatinine clearance over time (106).



Individual plots of serial creatinine clearance vs. age in years for representative subjects.
Lindeman, R.D., J. Tobin, and N.W. Shock: J of Amer. Geriat. Soc. 33:278-285, 1985.

In another study in 446 normal subjects, the age-related decline in creatinine clearance was found to be much steeper in blacks than whites (108). This may reflect on an increased propensity of glomerulosclerosis in the blacks (101).



C_{Cr} vs. age in whites and blacks. The slopes of the regression lines differ ($p<0.05$).
Luft, F.C., N.S. Finegerg, J.Z. Miller, L.I. Rankin, C.E. Grim, M.H. Weinberger: Am. J. Med. Sci. 279:15-24, 1980.

The highly significant decrease in glomerular filtration rate that occurs with age, is not usually accompanied with an elevation in serum creatinine concentration (143) (Table 1). Since muscle mass, from which creatinine is derived, falls with age at approximately the same rate as glomerular filtration rate, the rather striking age-related loss of renal function is not reflected by an increase in the serum creatinine. Thus, serum creatinine usually underestimates the decline in glomerular filtration rate in the elderly.

CROSS-SECTIONAL AGE DIFFERENCES IN CREATININE CLEARANCE, SERUM CREATININE, AND 24-HOUR CREATININE EXCRETION

Age (Years)	No. Subjects	Creatinine Clearance ml/min/1.73m^2	Serum Creatinine Concentration mg/100 ml	Creatinine Excretion mg/24hr
17-24	10	140.2	0.808	1790
25-34	73	140.1	0.808	1862
35-44	122	132.6	0.813	1746
45-54	152	126.8	0.829	1689
55-64	94	119.9	0.837	1580
65-74	68	109.5	0.825	1409
75-84	29	96.9	0.843	1259

Rowe, Andres, Robin, Norris, and Shock: J. Gerontol. 31:155, 1976.

Therefore, creatinine clearance needs to be directly measured during a 24 hour urine collection, or the creatinine clearance estimated by one of the commonly used formulae in clinical situations where the absolute value of glomerular filtration rate needs to be known, such as when adjusting the dosage of drugs whose clearance is accomplished by renal excretion. The most commonly used formulae are:

1) creatinine clearance (ml/min/1.73m^2) = 133-0.64 x age (years)

2) creatinine clearance (ml/min) (15% less in females) = $\frac{(140-age) \times wt\ (kg)}{72 \times S_{Cr}\ (mg/100\ ml)}$

Either of these two formulae yield a quite reasonable estimation of the glomerular filtration rate. In fact, in a recent study, (71), there was a very close correlation (r=0.85) between calculated (formula 2) versus measured creatinine clearance in 26 subjects.

Fluid and Electrolyte Balance

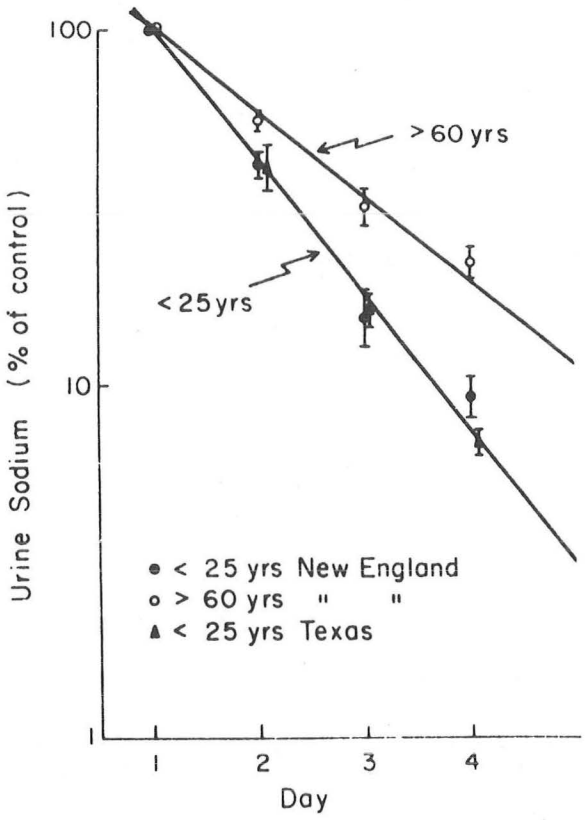
Under normal circumstances, age has no effect on the plasma sodium or potassium concentrations, on the blood pH or on ability to maintain normal extracellular fluid volume. The adaptive reserve mechanisms responsible for maintaining constancy of the extracellular fluid volume and composition in

response to stress are however, impaired in the elderly.

Sodium Balance

Sodium Conserving Ability

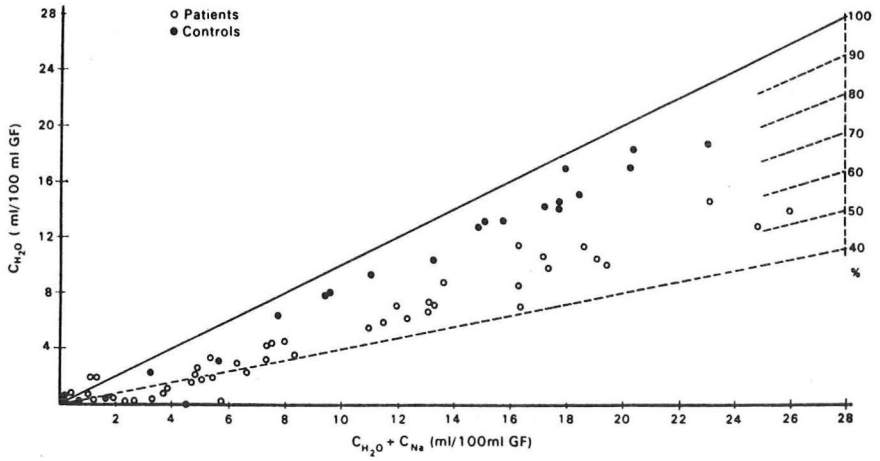
The ability of the aged kidney to conserve sodium in response to sodium deprivation is impaired. In a study of 89 normal subjects who ranged in age from 18 to 76 years, older subjects were found not to be able to conserve sodium as rapidly and efficiently as the younger subjects when dietary intake of sodium was restricted to 10 mEq per day (56). In this study, the half-time for the reduction in renal sodium excretion in subjects under 30 years was 17.6 hours, whereas in subjects over 60 years of age, the half-time was prolonged to 30.9 hours, significantly greater than that of the younger age group.



Response of urinary sodium excretion to restriction of sodium intake in normal man. The mean half-time (t 1/2) for 8 subjects over 60 years of age was -30.9±2.8 hours, exceeding the mean half-time of -17.6± 0.7 hours for subjects under 25 years of age ($p<0.01$). When the subjects under 25 years of age were separated according to geographic area, the mean half-time for the Texas group (-17.9±0.7) was similar to the New England group (-15.6±1.4;

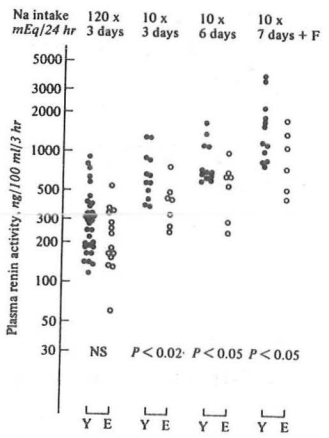
p<0.3).
Epstein, Hollenberg: J. Lab. Clin. Med. 87:411, 1976.

Clearance studies in young and elderly subjects have shown a decreased distal tubular capacity for sodium reabsorption in the elderly (114)

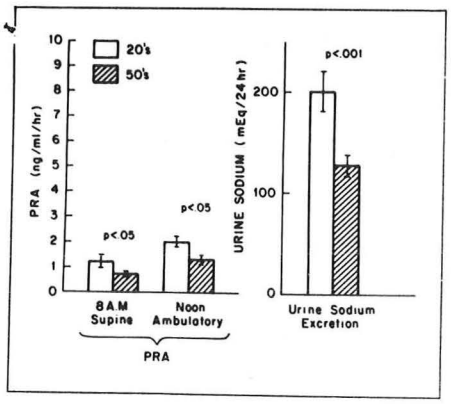


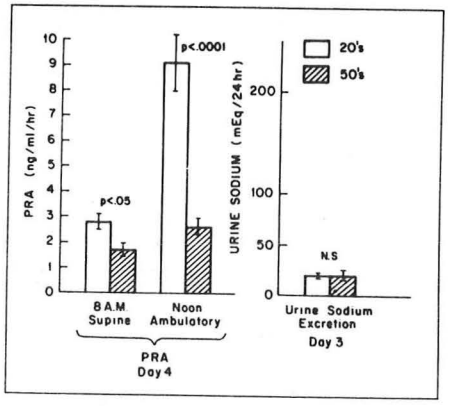
Graphic representation of distal tubular reabsorption of sodium in patients (elderly subjects) and controls (young subjects).
Macias Nunez, Garcia Iglesias, Bonda Roman, Rodriguez Commes, Corbacho Becerra, Tabernero Romo, and DeCastro del Pozo. Age and Ageing 7:178, 1978.

The distal tubular dysfunction could be caused by anatomical changes in the aging kidney such as tubulointerstitial fibrosis. Alternatively, functional and hormonal changes such as increased medullary blood flow or decreased renin-aldosterone activity could also impair distal tubular reabsorption of sodium. As discussed earlier, microangiographic and xenon washout studies reveal maintenance of medullary renal blood flow in the aging kidney in spite of a decrease in cortical blood flow (82,163). There are also important age-related alterations in the renin-aldosterone system. Basal plasma renin concentration or activity is decreased by 30 to 50 percent in elderly subjects in spite of normal levels of renin substrate. During maneuvers designed to stimulate renin secretion such as a) upright posture, b) 10 mEq/day sodium intake, and c) furosemide administration, the differences in plasma renin activity are further amplified (45,76,135,170,171)



Distribution of individual supine plasma renin before and during progressive sodium depletion in young and elderly healthy subjects. Y= young subjects; E= elderly subjects. Values indicating statistical significance refer to difference between young and elderly subjects. Weidman, P., S. DeMyttenaere-Bursztein, M.H. Maxwell, J. DeLima: Kid. Internat. 8:325,333, 1975.



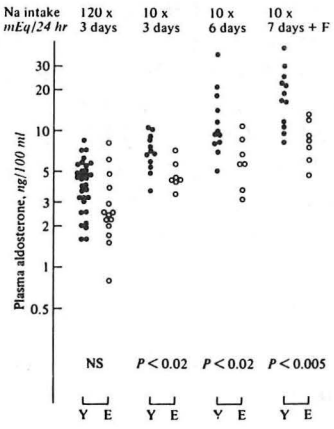


Comparison of plasma renin activity (PRA) and 24-hour urine excretion of sodium on unrestricted diet in young (20 to 29 years; n= 17) and older (50 to 58 years; n= 19) healthy normotensive volunteers.

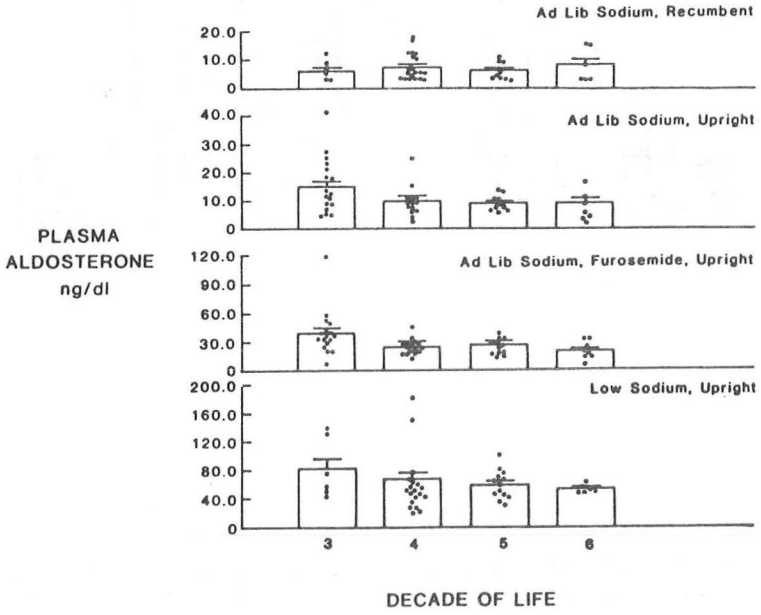
Comparison of plasma renin activity (PRA) and 24-hour urine excretion of sodium on a low-sodium (10-mEq) metabolic diet in young (20 to 29 years; n = 17) and older (50 to 58 years; n= 19) healthy normotensive volunteers.

Noth, R.H., N. Lassman, S.Y. Tan, Arturo Fernandez-Cruz, P.J. Mulrow: Arch. Intern. Med. 137:1414-1417, 1977.

There is a similar 30 to 50 percent decrease in plasma aldosterone levels in elderly subjects during recumbency and normal sodium intake which becomes more pronounced during upright posture, sodium restriction and furosemide (45,61,77,170,171).



Distribution of individual supine plasma aldosterone values before and during progressive sodium depletion in young and elderly healthy subjects. Y= young subjects; E= elderly subjects. Values indicating statistical significance refer to difference between young and elderly subjects.
Weidman, P., S. De Myttenaere-Bursztein, M.H. Maxwell, J. De Lima. Kid. Internat. 8:325-333, 1975.



Plasma aldosterone concentration in normal recumbent and upright subjects while on an ad lib sodium diet, and after sodium depletion with furosemide or a 20 meq sodium diet.
Weidman, P., S. DeMyttgnaere-Bursztein, M.H. Maxwell, J. DeLima: Kid. Internat. 8:325-333, 1975.

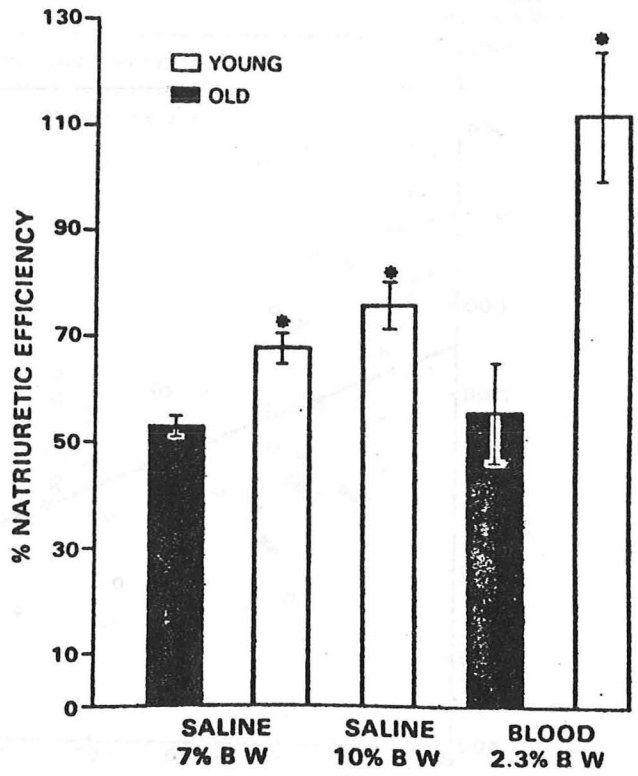
The aldosterone deficiency appears to be related to the renin deficiency, and not to intrinsic adrenal gland defects as both plasma aldosterone and cortisol responses to corticotropin (ACTH) infusion are normal in the elderly (170).

Thus, during sodium restriction, impaired renin-aldosterone response may result in decreased renal tubular reabsorption in the elderly. In fact, clearance studies in young and elderly subjects have shown marked improvement in distal tubular sodium reabsorption in the elderly following treatment with aldosterone (115). In addition, a marked decrease in Na,K-ATPase activity, which has been measured in the aging rat kidney, may also play a role in the impaired tubular adaptation to sodium restriction in the elderly (26).

Sodium Excreting Ability

Excessive sodium retention and volume overload is a commonly encountered problem in older patients. The age-related

decrease in glomerular filtration rate is probably the major factor in limiting the ability of the aged kidney in excreting an acute sodium load. The potential role(s) of additional factors, such as distribution of intrarenal blood flow, the adrenergic nervous system and other hormonal factors, and peritubular physical factors have not been studied and thus remain unknown. Controlled studies in man are lacking, but clearance studies in the aged rat confirm the clinical experience that following isotonic saline or blood expansion, the natriuretic efficiency is impaired in the aged rat (25,63).



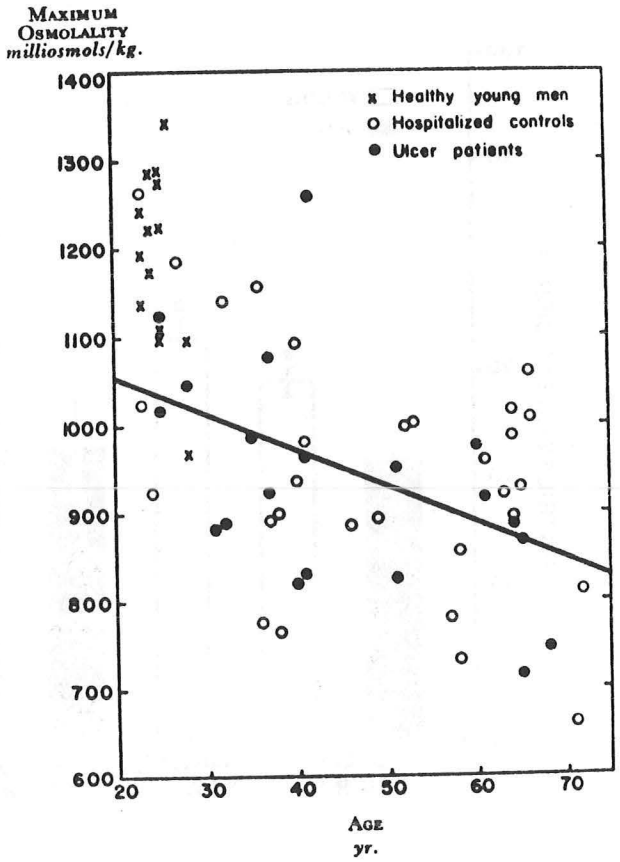
A comparison of the efficiency of the natriuretic response to the infusion of isotonic saline and blood in young and old rats. *p<0.05 young vs. old.
Bengele, H.H., R.S. Mathias, E.A. Alexander: Renal Physiol. 4:22-29, 1981.

Water Balance

Renal Concentrating Ability

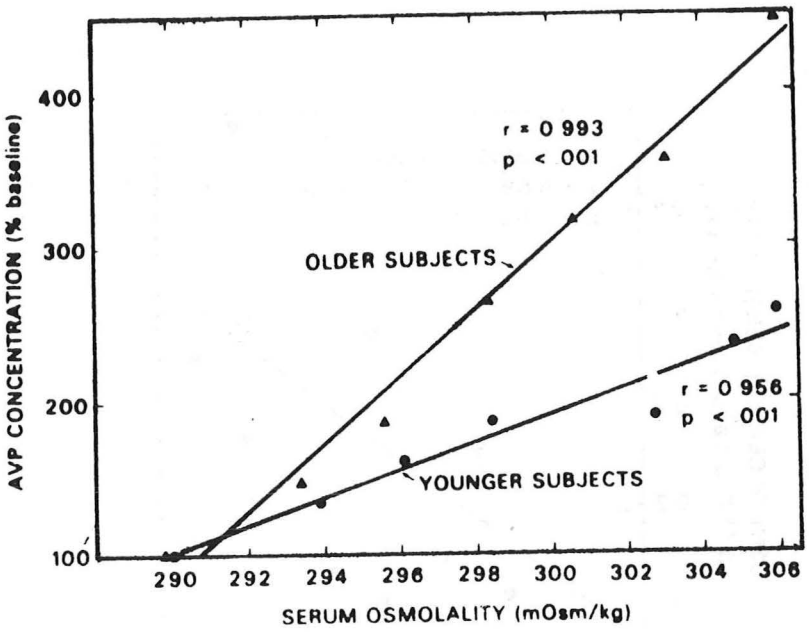
Renal concentrating ability is well-known to decline with age in man (52,102,103,104,142). In an early study, the concentrating ability of the kidneys, as measured by the urinary

specific gravity in 38 healthy men, declined from 1.030 at 40 years to 1.023 at 89 years (102). In more recent studies, the maximal urine osmolality, measured following 12-24 hours of dehydration, was inversely related to age (52,103,142). The maximal urine osmolality was 1109 mOsm/kg in 31 subjects 20-39 years old, compared to 1051 mOsm/kg in 48 subjects 40-59 years old, and 882 mOsm/Kg in 18 subjects 60-79 years old (142). The age-related decline in the concentrating defect does not correlate with the age-related decline in the glomerular filtration rate.



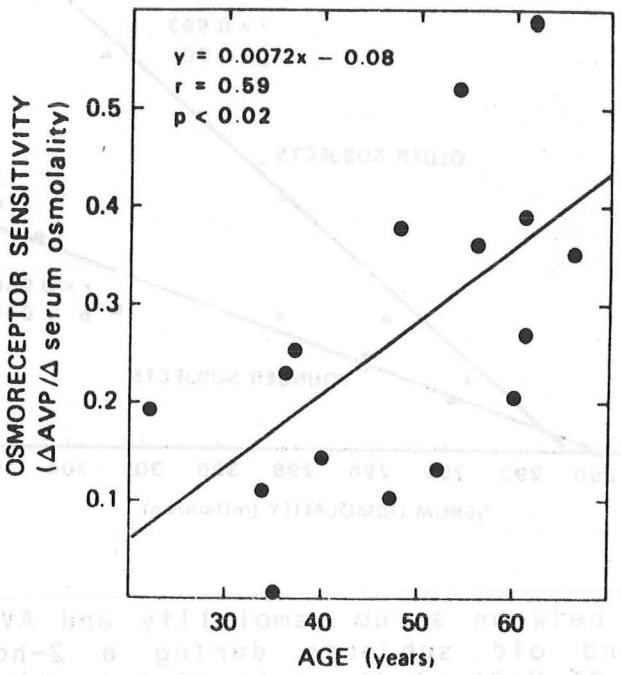
Maximum urine osmolality in healthy young men, hospitalized controls and patients with ulcer, showing a decrease with age. The solid line represents the regression slope for hospitalized patients.
Lindeman, VanBuren, and Raisz. New Engl. J. Med. 262:1306, 1960.

Studies in man suggest that the concentrating defect is due to an intrarenal defect rather than a failure in the osmotic release of arginine vasopressin (AVP) (78,104,123). In nine young (21-49 years) and thirteen old (54-92 years) subjects following intravenous infusion of hypertonic saline (3% NaCl), plasma AVP levels rose 4.5 times the baseline in the old men compared to 2.5 times the baseline in the young despite similar free water clearances (78).



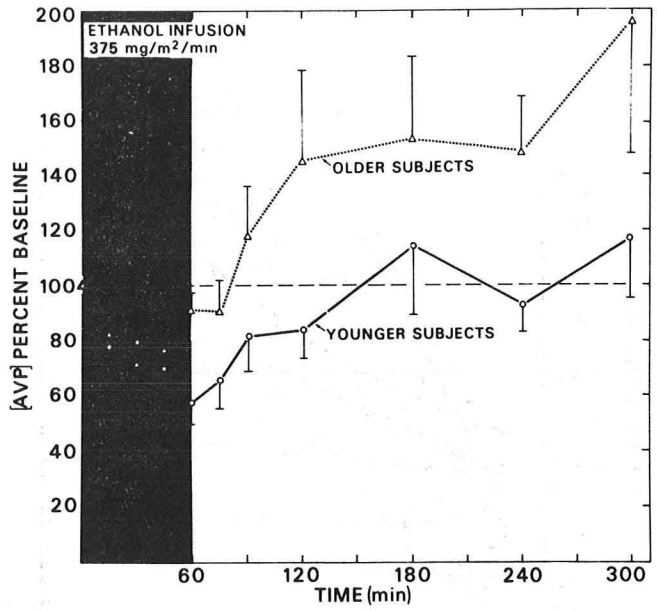
Correlation between serum osmolality and AVP concentration in young and old subjects during a 2-hour intravenous infusion of 3% NaCl at the rate of 0.1 ml/kg per min. The points represent mean values of osmolality and AVP at successive 20 min in each age group.
Helderman, Vestal, Rowe, Tobin, Andres, and Robertson. J. of Gerontol. 33:39, 1978.

The slope of the plasma AVP concentration (% baseline) versus serum osmolality, an index of the sensitivity of the osmoreceptor, was also significantly increased in the older subjects.



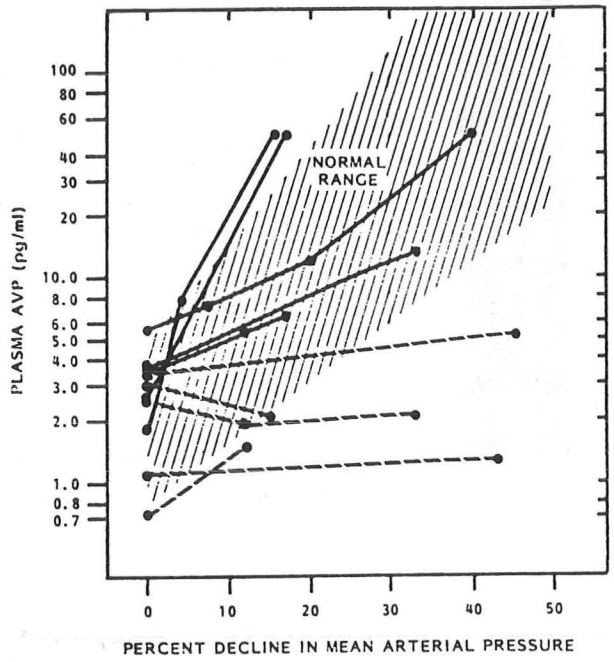
The relationship between age and osmoreceptor sensitivity (AVP/ serum osmolality). The slope of plasma AVP concentration in pg/ml on serum osmolality in mOsm/kg was computed and plotted for each subject.
Helderman, Vestal, Rowe, Tobin, Andres, and Robertson, J. of Gerontol. 33:39, 1978.

In addition, in the same study, intravenous infusion of ethanol caused a progressive decline in plasma AVP levels in the young subjects, as would be expected, but failed to have a similar effect in the older subjects. Plasma AVP levels decreased only during the initial 30 minutes in the older subjects, but then increased paradoxically despite the continuing increase in blood ethanol. Since serum osmolality increased during this period, the heightened sensitivity to hyperosmolality in the elderly probably explains this paradoxical response to ethanol (78).



Plasma arginine vasopressin response to a 1-hour intravenous ethanol infusion in young and old subjects. The AVP concentration after overnight dehydration and prior to the study is designated 100%. The AVP is significantly depressed from the baseline concentration in the young group from 15 min through 75 min ($p<0.02$, 0.05, 0.025, 0.005, 0.02, respectively). Only the 15-min and 30-min concentration in the older subjects were significantly altered ($p<0.05$).
Helderman, J.H., R.E. Vestal, J.W. Rowe, J.D. Tobin, R. Andres, and G.L. Robertson: J. Gerontol. 33:39-47, 1978.

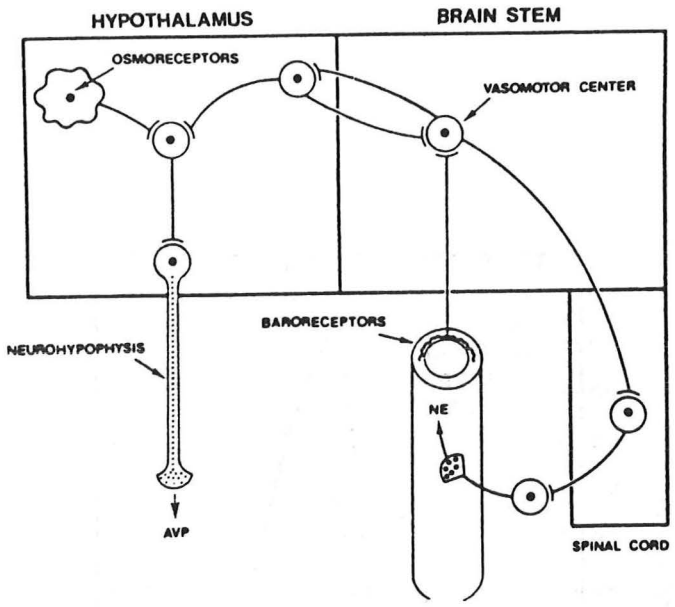
In contrast, the volume-pressure-mediated AVP release decreases with age (145). In healthy 12 young (19-31 years old) and 15 old (62-80 years old) subjects who remained recumbent overnight, the peak plasma AVP response upon assumption of upright posture was significantly higher in the younger subjects.



Plasma AVP as a function of percent decrease in mean arterial pressure in healthy adults of different ages. Hypotension was induced by orthostasis following low salt diet and prolonged bed rest. Results are depicted by solid lines for young (11 to 31 years) and broken lines for old (68 to 83 years) people. Shaded zone represents the range of values found in healthy young adults during the infusion of a ganglionic blocking drug. Note the semilog scale.
Robertson, G.L., and J. Rowe. Peptides 1:159-162, 1980.

Pulse increases and mean arterial blood pressure reductions were similar in both age groups. When categorized as responders (peak AVP response greater than 3 pg/mL) or nonresponders (peak AVP response less than 3 pg/mL), the young group included 11 responders and 1 nonresponder, while the old group included 8 responders and 7 nonresponders. In the old group, the norepinephrine response to upright posture was equal in responders and nonresponders, indicating that the baroreceptor mechanism for activation of the vasomotor center is intact regardless of the AVP response. Since the AVP response to osmolar stimuli is increased with advancing age, these findings

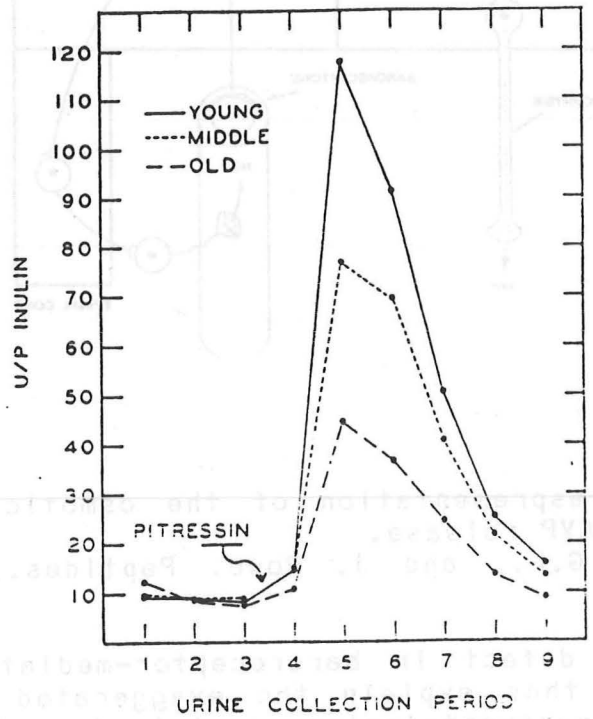
suggest an age-related defect in the afferent limb of the reflex arc, specifically at the connections between the vasomotor center and the supraoptic and paraventricular nuclei.



Schematic respresentation of the osmotic and hemodynamic control of AVP release.
Robertson, G.L., and J. Rowe. Peptides. Vol. 1:159-162, 1980.

This age-related defect in baroreceptor-mediated input to the hypothalamus may thus explain the exaggerated response of the supraoptic and paraventricular nuclei to changes in serum osmolality.

The progressive impairment in the renal concentrating ability as a function of aging is associated with a decreased response to maximal exogenous vasopressin. In water diuresing subjects urine to plasma inulin ratio following exogenous vasopressin was inversely correlated to the age of the subjects (123).



Mean values of U/P inulin ratio for each of 3 age groups before and after the intravenous administration of pitressin. Urine collection periods 1-9 represent 9 consecutive twelve minute periods. Pitressin was administered immediately after the conclusion of period 3. Miller, J.H., and N.W. Shock. J. Gerontol. 8:446-450, 1953.

Recent studies in man reveal an age-related increase in solute excretion and osmolar clearance during dehydration (142). This phenomenon which may be a reflection of an impaired solute transport by the ascending loop of Henle, may be responsible for the impairment in urine concentrating ability in elderly subjects.

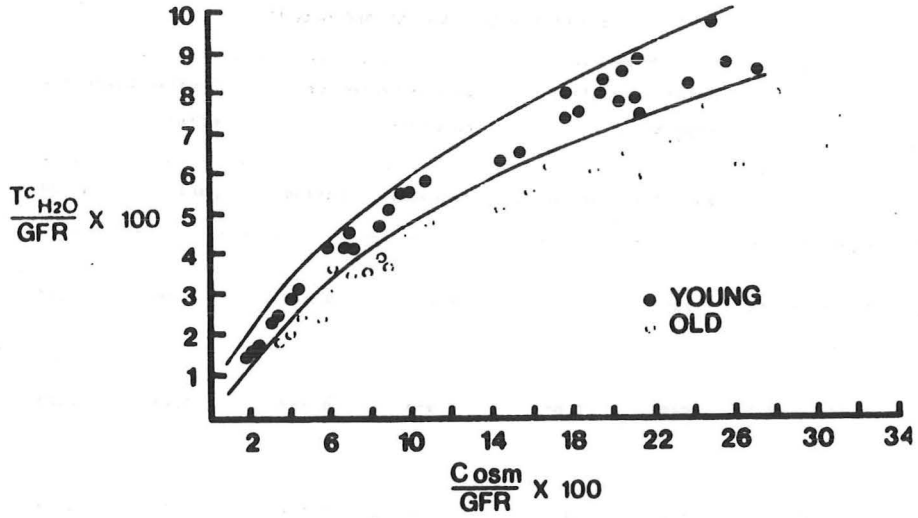
THE EFFECT OF AGE ON URINE FLOW, URINE OSMOLALITY, SOLUTE EXCREITON AND OSMOLAR CLEARANCE DURING FLUID RESTRICTION, BY AGE GROUPS

	Urine Osmolality, mosm/kg		Solute Excretion, mosm/min		Osmolar Clearance ml/min	
	period 1	period 3	period 1	period 3	period 1	period 3
Young, 20-39	969	1,109	0.988	0.543	3.40	1.87
Middle, 40-59	949	1,051	0.940	0.662	3.23	2.27
Old, 60-79	852	882	0.895	0.908	3.06	3.11

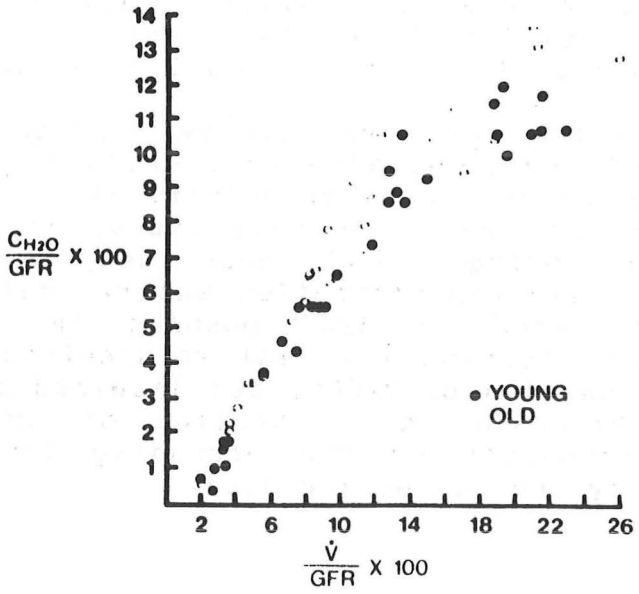
Rowe, J.W., N.W. Shock, R.A. De Fronzo: Nephron 17:270-278, 1976.

This possibility is supported by clearance studies in water diuresing subjects which demonstrate a decrease in the sodium chloride transport in the ascending loop of Henle in the elderly subjects (114,115). This defect in solute transport by the thick ascending limb of Henle's loop could diminish inner medullary hypertonicity and thereby impair urinary concentrating ability. A relative increase in medullary blood flow as suggested by the xenon washout studies (82) could also increase the removal of solutes from the medullary interstitium and thereby contribute to the decreased maximal urinary osmolality.

Studies in the aging rat however, suggest that impaired responsiveness of the collecting duct cells to AVP, rather than diminished inner medullary hypertonicity is responsible for the concentrating defect (24). In this study, the maximal urinary concentration following a 40 hour dehydration period and exogenous vasopressin administration was markedly impaired, 2550 mosm/kg when compared to 3242 mosm/kg in the young rats. Clearance studies revealed a normal solute-free water formation (CH_2O/GFR as a function of V/GFR) but impaired solute-free water reabsorption (T^CH_2O/GFR as a function of Cosm/GFR) implying normal solute transport by the ascending limb and decreased water transport by the collecting duct.

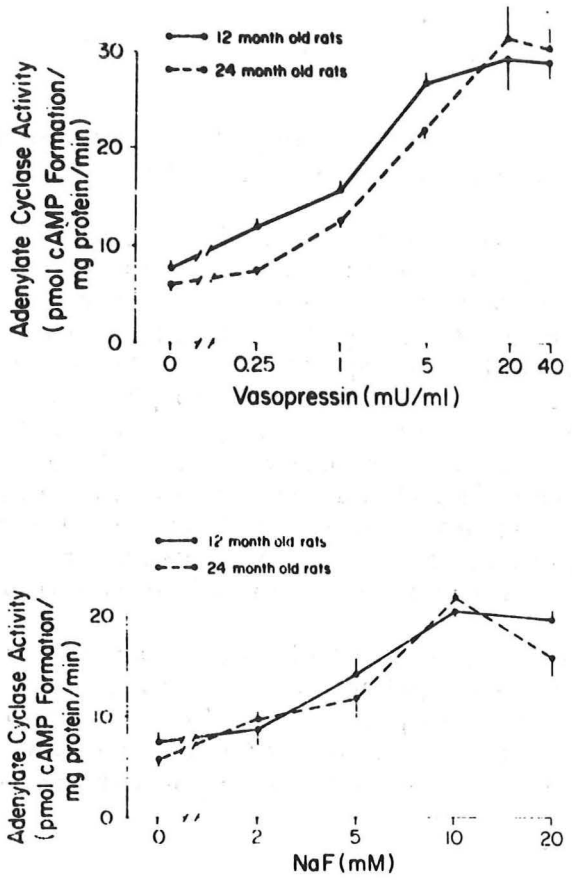


Relationship between T^C_{H2O} and C_{osmol} (both corrected for GFR) during 2.5% NaCl infusion for young (solid circle) and old (open circle) rats. Solid line curves were drawn to include all points for the young rats.
Bengele, H.H., R.S. Mathias, J.H. Perkins, and E.A. Alexander. Am. J. Physiol. 240 (Renal Fluid Electrolyte Physiol. 9):F147-F150, 1981.



Relationship between C_{H2O} and V (both corrected for GFR) during 0.4% NaCl infusion for young (closed circle) and old (open circle) rats.
Bengele, H.H., R.S. Mathias, J.H. Perkins, and E.A. Alexander. Am. J. Physiol. 240 (Renal Fluid Electrolyte Physiol. 9):F147-F150, 1981.

In fact, inner medullary solute content in the old and young rats was identical. Further studies with inner medullary slices have revealed impaired in AVP-dependent cyclic AMP generation which may be, in part, responsible for the impairment of urinary concentrating ability in old rats (22).



Dose-response curves of vasopressin and adenylate cyclase activation in renal papilla of 12- and 24-mo-old rats. Each point and vertical bar represents mean and SE (n=7).
Beck, N. and P. Yu Byung. Am. J. Physiol. 243 (Renal, Fluid, and Electrolyte Physiol. 12):F121-F125, 1982.

Renal Diluting Ability

Renal diluting ability is also impaired as a function of aging (52,104).

Age-Related Urinary Diluting Defect

	Group 1 (Ages 17-40)	Group 2 (Ages 54-64)	Group 3 (Ages 77-88)
Minimal Uosm (mOsm/kg H_2O)	52	74	92
CH_2O (mL/min)	16.2	8.4	5.9
CH_2O/Cin	10.9	9.1	9.1

Lindeman, R.D., T.D. Lee, M.J. Yiengst, N.W. Shock: J. Lab and Clin. Med. 68:206-223, 1966.

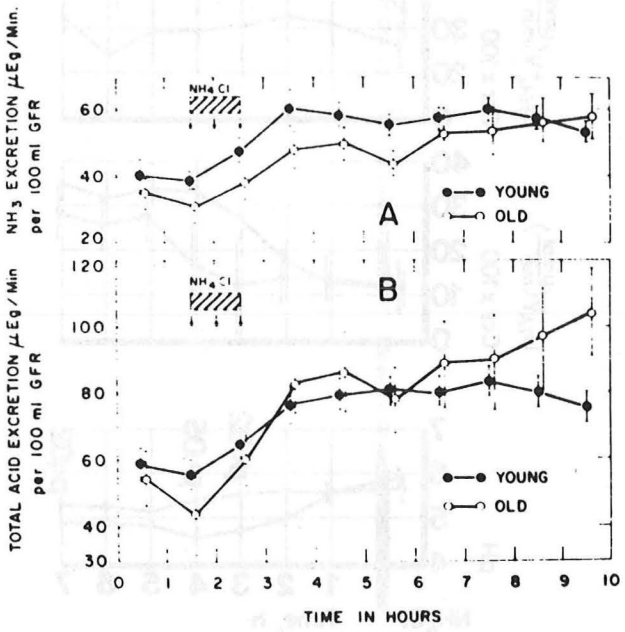
In water diuresing subjects, minimal urine osmolality was significantly higher in the older subjects (92 mosm/Kg ages 77-88), than in the younger subjects (52 mosm/Kg ages 17-40). The free water clearance (CH_2O) was also decreased, 5.9 ml/min in the older subjects compared to 16.2 ml/min in the young subjects. The impairment in CH_2O was largely due to the decrease in GFR. However, CH_2O/GFR 9.1% in the elderly was still decreased when compared to 10.9% in the young (104). Mechanisms of the impaired diluting ability in the elderly have not been well-studied; in addition to the role of impaired GFR, inadequate suppression of AVP release, and impaired solute transport in the ascending loop of Henle may also play a role.

While the age-related decrements in concentrating and diluting ability are quite significant, it should be emphasized that unless the elderly patient is stressed, such as dehydration or free water load, these defects in water metabolism do not result in significant hyper- or hyponatremia.

Acid Base Balance

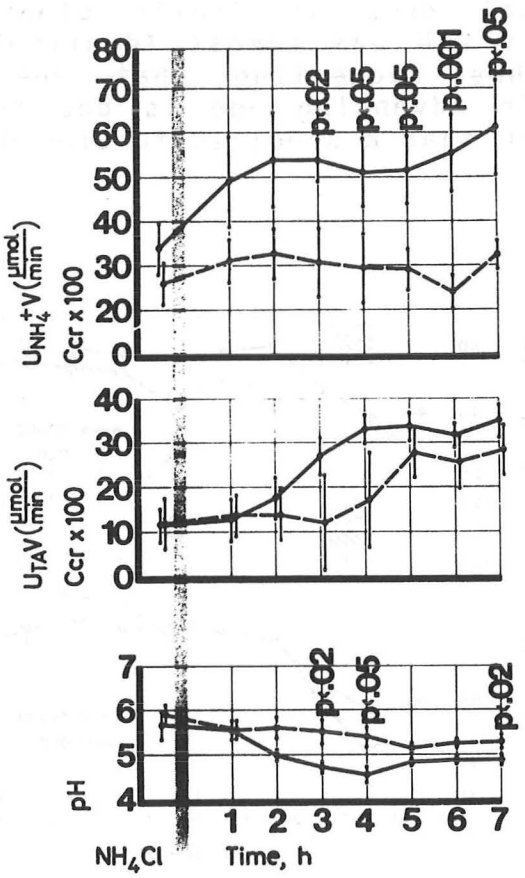
Elderly subjects can maintain the pH and bicarbonate of blood within the normal range, and their basal acid excretion is not different from that of healthy younger volunteers (2). But when elderly subjects are challenged with an acute acid load, they do not increase their acid excretion to the same degree as kidneys of younger subjects (1,2,81). In an earlier study following a standard oral ammonium chloride acid load, the older subjects (72-93 years) excreted only 19% of the acid load when compared to 35% by the younger subjects (17-35 years) over an 8 hour period (1). Urinary ammonia accounted for less of the total acid excretion in the old subjects, 59% in the old subjects when compared to 72% in the young subjects. In this study, the decrease in both of these parameters was paralleled

by a nearly equal drop in inulin clearance so that acid excretion per unit GFR was almost identical in both young and old subjects, thus suggesting that the decrease in acid excretion found in advancing age is due to a decreased renal tubular mass rather than a specific tubular defect.



Time response of ammonium and titratable acid excretion to an acute stimulus factored by the inulin clearance. Each point represents the mean of all the subjects studied in that group. Ranges shown around each point represent plus or minus one standard error of the mean.
Adler, S., R.D. Lindeman, M.J. Yiengst, E. Beard, and N.W. Shock. J. Lab. and Clin. Med. 72:278-289, 1968.

A more recent study in elderly subjects with less impaired GFR however, has arrived at a different conclusion. In this study the minimal urinary pH and net acid excretion, even when factored for GFR, were significantly decreased in the older subjects (2). There were no differences in the titratable acid excretion, but the older subjects showed a significant reduction in ammonium excretion when factored for GFR, 34 umole/min in the elderly when compared to 51 umole/min in the young subjects.



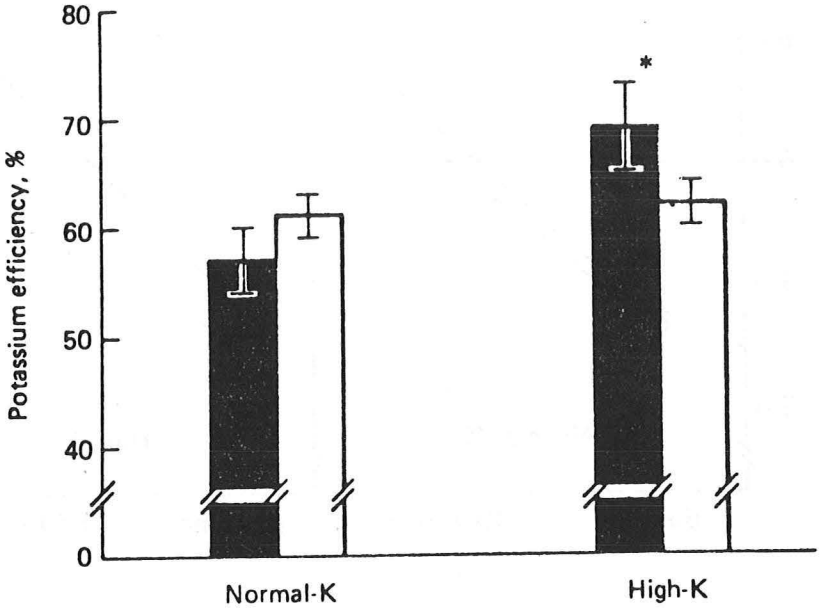
Acid excretion during the entire study in young and elderly subjects. Comparison of the ammonium ($U_{NH4}V$), titratable acid ($U_{TA}V$) excretion corrected for GFR (Ccrx100) and urinary pH in young (group I,-) and aged subjects (group III,---). Mean values (plus or minus SEM) along with p values of the difference between the two groups are shown.
Agarwal and Cabebe, Nephron 26:291, 1980.

This study therefore suggests an intrinsic tubular defect in ammonium excretion as a function of aging. It is not known whether this defect is due to anatomical changes or due to functional defects including hypoaldosteronism and impaired mitochondrial function in the aged (45,61,77,169,170).

Potassium Balance

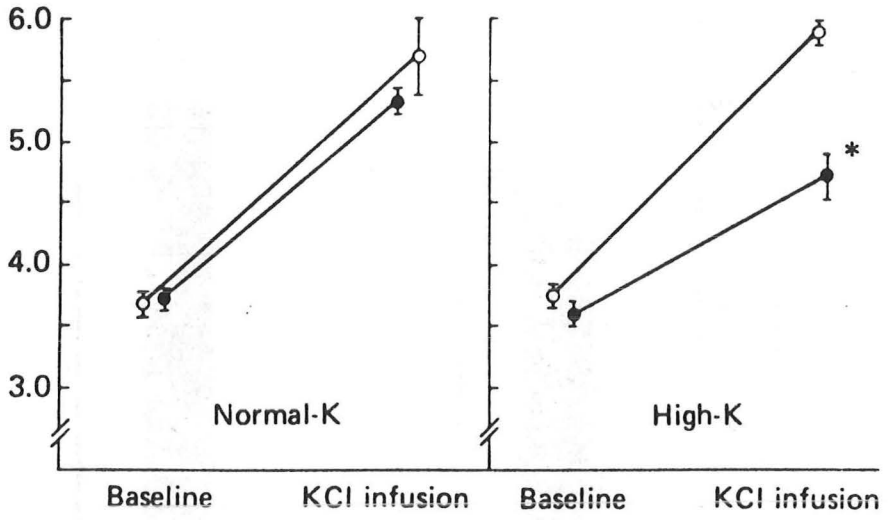
Studies on the effects of aging on renal and extrarenal adaptation to high potassium loads or dietary potassium deprivation are lacking. Two different studies conducted in the 1950's suggest that both total body potassium (4) and total exchangeable potassium (147) decreases with age in both sexes and that the decrease is more marked in women than in men. This decrease may relate to the decrease in muscle mass with advancing age.

The effects of aging on potassium adaptation has been studied in the aged rat (26). In this study, the efficiency of kaluretic response to intravenous infusion to potassium chloride and the rise in plasma potassium were identical in the young and the aged rat fed a normal potassium diet. Following a period of dietary high potassium intake however, the efficiency of kaluretic response to intravenous potassium chloride was impaired in the aged rat and also the rise in plasma potassium was significantly higher.



Efficiency of kaluretic response to a 90-min intravenous infusion of 0.143 plus or minus 0.001 M KCl (1.5% body weight per hour) for young (solid square) and old (open square) rats on a normal or high K diet. Bars are means: vertical lines show plus or minus SEM. The asterisk denotes $p<0.05$ and compares the effect of diet.
Bengele, H.H., R. Mathias, J.H. Perkins, E.R. McNamara, and E.A. Alexander. Kid. Internat. 23:684-690, 1983.

Following bilateral nephrectomy, the rise in plasma potassium concentration was also higher in the aged rats who were on a high potassium, but not normal potassium intake.



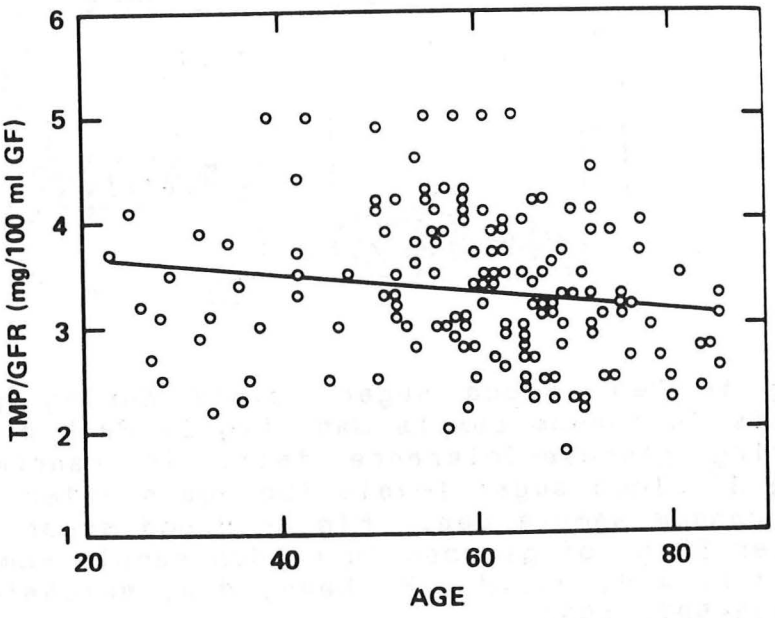
Effect of an acute potassium load (2.5 mM/kg body weight) on plasma potassium in nephrectomized young (solid circle) and old (open circle) rats fed a normal or a high K diet. Points are means; vertical lines show plus or minus SEM. The asterisk denotes $p<0.05$ and compares diet and age. Bengele, H.H., R. Mathias, J.H. Perkins, E.R. McNamara, and E.A. Alexander. Kid. Int. 23:684-690, 1983.

This renal and extrarenal impairment in potassium adaptation is thought to be due to a decrease in renal and colon Na,K-ATPase activity in the aged rat. Whether these findings also apply to human aging remains to be determined.

Calcium and Phosphorus Balance

Calcium metabolism is significantly impaired as a function of aging. In humans and in the rat, the age-related decline in renal 1 a hydroxylase activity causes in decreased levels of $1,25(OH)_2D_3$ (11,15,21,40,62,66,157,167), resulting in decreased intestinal absorption of calcium (3,10,13,14,18,37,83,86,139). Furthermore, the intestinal adaptation to dietary restriction of calcium is also impaired (10,12,14). Renal tubular reabsorption of calcium however, is not affected by the aging process and during dietary calcium restriction, almost all of the filtered calcium is reabsorbed by the tubules (10,13,14).

The age-related decrease in $1,25(OH)_2D_3$ activity also causes decreased intestinal absorption of phosphorus, as well as impaired intestinal adaptation to dietary phosphorus restriction (12). In humans and in the rat, renal tubular reabsorption of phosphate is also impaired, even when factored for the GFR, both during normal and restricted dietary phosphorus intake (1,12,14,85,98,118)



The effect of age on TmP/GFR ($r = -0.17$ $p<0.05$).
Marcus, Madvig and Young. J. Clin. Endocrinol. and Metab. 58:223, 1984.

The potential roles of decreased $1,25(OH)_2D_3$, increased parathyroid hormone activity, and/or proximal tubular membrane transport defects in the pathogenesis of the "phosphate leak" have not yet been determined.

Renal Tubular Reabsorption of Glucose

The maximal rate of renal tubular reabsorption of glucose (TmG) decreases linearly with age in male subjects at a rate of

0.684 percent of the baseline level per year (122). The decrease in TmG however, parallels the decrease in GFR so that it remains relatively constant. In contrast to this earlier American study, a more recent British study conducted in male and female subjects following an oral glucose-tolerance test, determined that the renal glucose threshold increases with age, especially in female subjects (38).

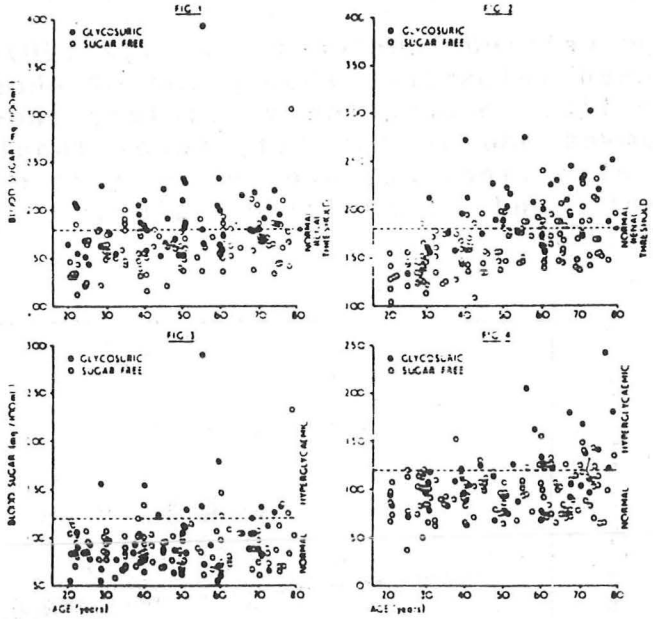


Fig 1- Peak blood sugar levels during glucose-tolerance tests in random sample men. **Fig 2-** Peak blood sugar levels during glucose-tolerance tests in random sample women. **Fig 3-** Blood sugar levels two hours after 50 g. of glucose in random sample men. **Fig 4-** Blood sugar levels two hours after 50 g. of glucose in random sample women.
Butterfield, W.J.H., H. Keen, M.J. Whichelow. Brt. Med. J. 4:505-507, 1967.

The apparent discrepancy in these two studies has not been explained and may at least in part, be due to differences in population, baseline renal function, and methodology employed.

CLINICAL IMPLICATIONS OF THE PATHOPHYSIOLOGY OF THE AGING KIDNEY

The most important clinical implication for the age-related decrease in the glomerular filtration rate is the need for adjustment of the dosage of medications that are either directly excreted by the kidney, by glomerular filtration, or tubular secretion, or whose active metabolites formed in the liver are eliminated by the kidney (72).

DRUGS WITH RENAL EXCRETION AS THE MAJOR PATHWAY OF ELIMINATION

Ampicillin	Kanamycin
Carbenicillin	Methotrexate
Cephalexin	Methyldopa
Cephalothin	Neomycin
Cephazolin	Procainamide
Colistin	Streptomycin
Cycloserine	Sulfinpyrazone
Digoxin	Tetracycline
Ethambutol	Tobramycin
5-Fluorocytosine	Vancomycin
Gentamicin	

DRUGS THAT MAY UNDERGO TUBULAR SECRETION

Acetazolamide	Methotrexate
Carbenicillin	Penicillin G
Cephalosporins	Phenylbutazone
Chlorothiazide	Probenecid
Cimetidine	Procainamide
Dopamine	Pyrazinamide
Ethacrynic acid	Salicylate
Ethambutol	Spironolactone
Fluorouracil	Sulfonamides
Furosemide	Thiazide diuretics
Guanethidine	Triamterene
Indomethacin	

WEAK ACIDS AND WEAK BASES THAT MAY BE REABSORBED BY NONIONIC BACK DIFFUSION

Weak Acids	Weak Bases
Acetazolamide	Amphetamines
Cephaloridine	Chloroquine
Ethacrynic acid	Dopamine
Furosemide	Meperidine
Hydrochlorothiazide	Morphine
Methotrexate	Neostigmine
Mersalyl	Quinine
Penicillin	Quinidine
Phenobarbital	Thiamine
Phenylbutazone	Tricyclic drugs
Probenecid	Trimethoprim
Sulfonamides	
Salicylic acid	

DRUGS THAT FORM PHARMACOLOGICALLY ACTIVE METABOLITES

Drug	Metabolite
Acetohexamide	Hydroxyhexamide
Adriamycin	Adriamycinol
Allopurinol	Oxypurinol
Azathioprine	6-Mercaptopurine
Cephalothin	Desacetylcephalothin
Chlorpropamide	2-Hydroxychlorpropramide
Clofibrate	Chlorophenoxyisobutyric acid
Daunorubicin	Daunorubicinol
Diazepam	Oxazepam
Digitoxin	Digoxin
Meperidine	Normeperidine
Methsuximide	N-desmethylmethsuximide
Primidone	Phenobarbital
Procainamide	Acetylated metabolites
Propoxyphene	Norpropoxyphene
Propranolol	4-Hydroxypropranolol
Rifampicin	Desacetylrifampicin
Sulfonamides	Acetylated metabolites

Anderson, R.J., Schrier, R.W: Mechanisms of Adverse Drug Reactions, in Clinical Use of Drugs in Patients with Kidney and Liver Disease, ed. Anderson and Schrier, W.B. Saunders Co., Philadelphia, p30-41, 1981.

When adjusting the dose of such a medication, it is very important to estimate glomerular filtration rate not only according to serum creatinine, but to either measure it or estimate it according to one of the formulae provided earlier.

The age-related decrements in hepatic blood flow and hepatocellular function also necessitate dose adjustment of drugs that normally have high hepatic first-pass metabolism, and drugs that are excreted in bile.

DRUGS BELIEVED TO HAVE HIGH HEPATIC FIRST-PASS METABOLISM

Acetylsalicylic acid	Nitroglycerin
Alprenolol	Nortriptyline
Chloropromazine	Paracetamol
Isoproterenol	Pentazocine
Lidocaine	Prazosin
Methylphenidate	Propoxyphene
Metroprolol	Propranolol
Meperidine	Salicylamide
Morphine	

DRUGS CONCENTRATED IN BILE (BILE/PLASMA RATIO >1)

Acebutolol	Doxycycline
Ampicillin	5-Fluorocytosine
Carbenoxolone	Indomethacin
Cephamandole	Metronidazole
Chloramphenicol	Pivampicillin
Chlortetracycline	Practolol
Clindamycin	Sex steroids
Demethylchlortetracycline	Spironolactone
Digoxin	Terbutaline
Doxorubicin	Vincristine

Bennett, W.M: Altering drug dose in patients with diseases of the kidney and liver. in Clinical Use of Drugs in Patients with Kidney and Liver Disease, ed. Anderson and Schrier, W.B. Saunders Co., Philadelphia, p16-29, 1981.

Additional factors that affect drug metabolism in the elderly are the age-related decrease in lean body mass, and increase in adipose-tissue mass, which can affect the volume of distribution of water and lipid soluble drugs, and the decrease in protein binding of drugs, particularly by albumin which can affect the serum concentration of the free fraction of a drug.

DRUGS WITH DECREASED PROTEIN BINDING IN RENAL AND HEPATIC FAILURE

Renal Failure	Hepatic Disease
Barbiturates	Amylbarbitone
Benzylpenicillin	Diazepam
Clofibrate	Morphine
Congo red	Phenylbutazone
Diazepam	Phenytoin
Diazoxide	Propranolol
Dicloxacillin	Quinidine
Digitoxin	Thiopentone
Furosemide	Tolbutamide
Metolazone	
Morphine	
Papaverine	
Phenylbutazone	
Phenytoin	
Salicylate	
Sulfonamides	
Thyroxine	
Triamterene	
Tryptophane	
Warfarin	

Anderson, R.W., Schrier, R.W: Mechanisms of adverse drug reactions. in Clinical Use of Drugs in Patients with

Kidney and Liver Disease, ed. Anderson and Schrier, W.B. W.B. Saunders Co., Philadelphia, p30-41, 1981.

Thus, all these factors contribute to the increased incidence of adverse drug reactions in the elderly.

MECHANISMS OF ADVERSE DRUG REACTIONS IN PATINETS WITH KIDNEY AND LIVER DISEASE

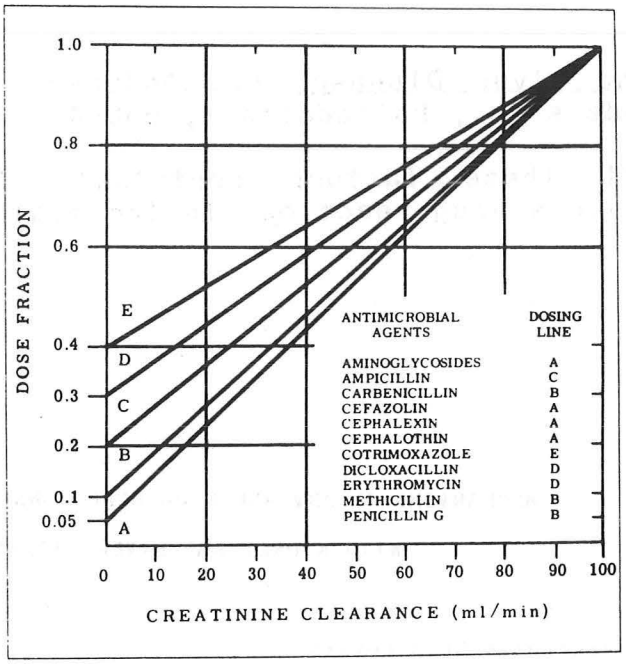
I. Increased Drug Levels
   - Decreased drug metabolism
   - Decreased elimination of parent drug
   - Decreased elimination of active metabolite

II. Increased Drug Sensitivity
   - Decreased drug-protein binding
   - Target organ alterations

III. Administration of Metabolic Loads

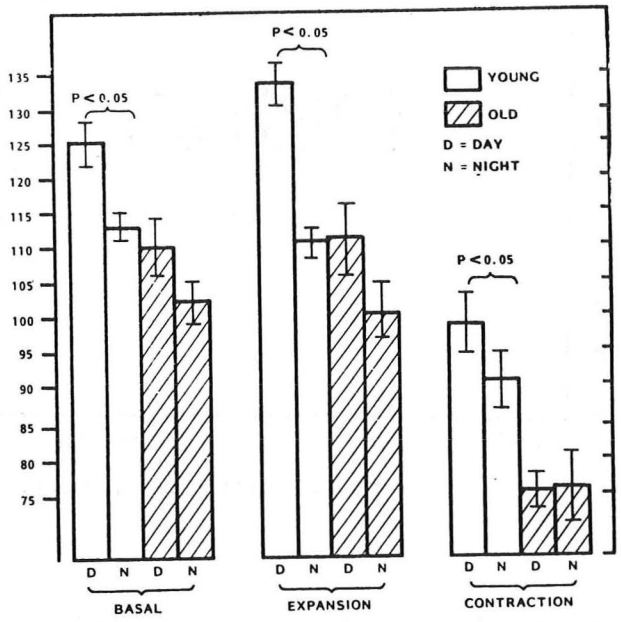
Anderson, R.J., Schrier, R.W: Mechanisms of Adverse drug reactions. In Clinical Use of Drugs in Patients with Kidney and Liver Disease, ed. Anderson and Schrier, W.B. Saunders Co., Philadelphia, p30-41, 1981.

When prescribing drugs with especially a narrow therapeutic to toxic ratio, the physician caring for the elderly patient has to consider all these factors, adjust the dose of the drugs accordingly, and when possible, carefully monitor the serum levels of these drugs.



Bennett, W.M: Altering drugs dose in patients with diseases of the kidney and liver. In Clinical Use of Drugs In Patients with Kidney and Liver Disease, ed. Anderson and Schrier, W.B. Saunders Co., Philadelphia, p16-29, 1981.

An important consequence of the age-related decrease in renal blood flow and/or glomerular filtration rate is the potential predisposition to enhanced ischemic or toxic renal injury. In addition to the absolute decrease in renal blood flow, the autoregulatory capacity of the renal vasculature is also impaired. During periods of dehydration and volume depletion, the decrease in glomerular filtration rate is markedly accentuated in elderly subjects when compared to young adult subjects.

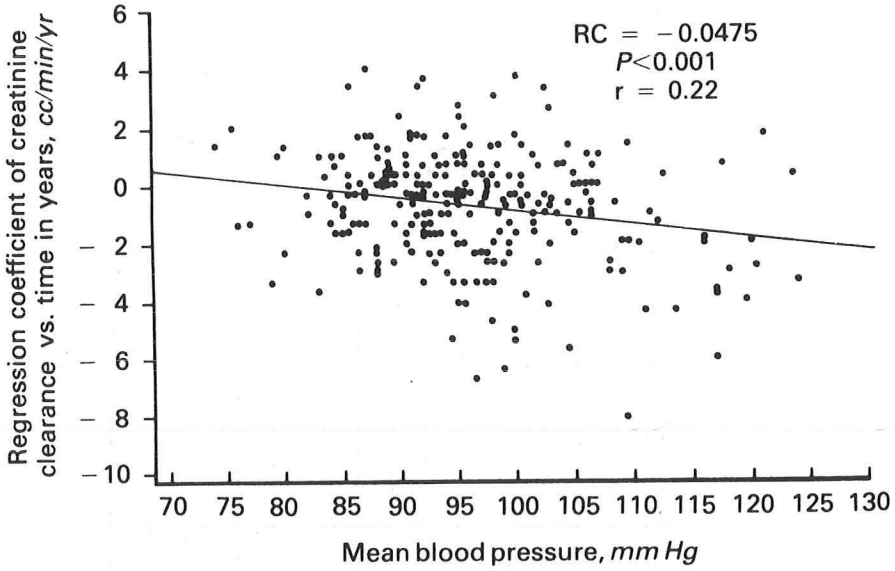


Day and night C_{Cr} values compared between whites <40 years and whites >40 years (mean plus or minus SEM).
Luft, F.C., N.S. Fineberg, J.Z. Miller, L.I. Rankin, C.E. Grim, M.H. Weinberger: Am. J. Med. Sci. 279:15-24, 1980.

The risk of hemodynamically-induced acute renal failure following severe volume depletion, septic shock, and major vascular surgery is therefore significantly increased. Failure to properly adjust the dosage of renally excreted drugs may also increase the incidence of toxin-induced acute renal failure including aminoglycoside antibiotics, nonsteroidal antiinflammatory drugs, and radiocontrast agents.

The relationship of the age-related increase in filtration fraction to the increased prevelance of glomerulosclerosis in the aging kidney has not been definitely established. In view

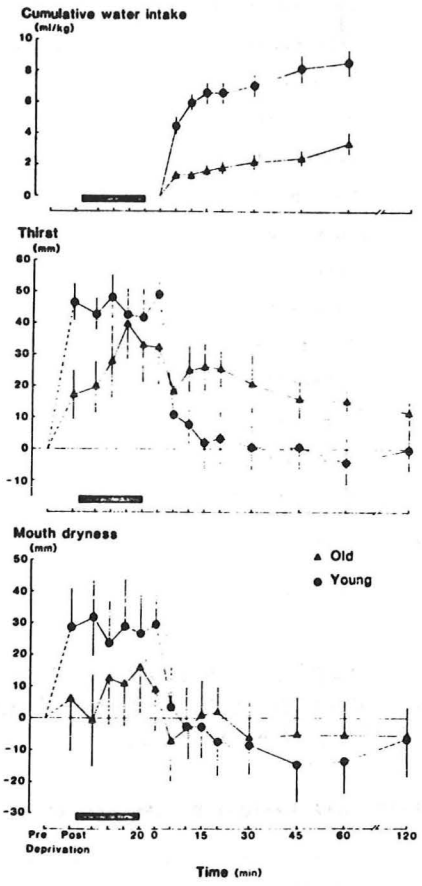
of recent interest in the possible role of hyperfiltration in the eventual glomerulosclerosis in insulin dependent diabetes mellitus, essential hypertension, and other forms of chronic renal disease, (34,35,84) a similar role for hyperfiltration in the aging kidney may also be invoked. This phenomenon may also be responsible for the acceleration of renal functional impairment in elderly patients with hypertension (105) and diabetes mellitus.



Regression coefficients (RC) plotting decline in renal function (change in creatinine clearance vs. time in years or B_{Cr}) against mean blood pressure (MB): Category 3, 254 "normal subjects".
Lindeman, Tobin, and Shock, Kid. Internat. 26:861, 1985.

Alternatively, studies in the aging rat reveal that long-term dietary sodium or protein restriction which would decrease the filtration fraction, result in significant decreases in the incidence and severity of the age-related renal lesions, renal functional impairments, and proteinuria (55,168,177). These animal studies have definite implications for the prevention or attenuation of renal disease in the elderly.

The age-related impairments in renal concentrating and sodium conserving ability are associated with increased incidence of volume depletion and hypernatremia in the elderly. Under normal physiological conditions, increased thirst and fluid intake are natural defense mechanisms against volume depletion and hypernatremia. The apparent deficit in thirst and regulation of fluid intake in the elderly however (124,137), may further contribute to the increased incidence of dehydration and hypernatremia.



Cumulative water intake and changes in thirst and mouth dryness in the old (N=7) and young (N=7) groups. Symbols represent mean values, and bars SEM. Changes in thirst and mouth dryness were measured on a visual-analogue rating scale. The hatched rectangle represents the single-blind sham infusion.
Phillips, P.A. B.J. Rolls, J.G.G. Ledingham, M.L. Forsling, J.J. Morton, M.J. Crowe, and L. Wollner. New Engl. J. Med. 12:753-759, 1984.

In practice, drugs that inhibit the thirst mechanisms and the synthesis and release of AVP, including most of the sedatives and major tranquillizers, and that inhibit the renal tubular action of AVP, especially lithium and demeclocycline, are therefore best avoided.

DRUGS AND HORMONES THAT INHIBIT VASOPRESSIN SECRETION

Norepinephrine
Fluphenazine
Haloperidol
Promethazine
Oxilorphan
Butorphanol
Morphine (low doses)
Alcohol
Carbamazepine
Glucocorticoids
? Phenytoin
Clonidine
Muscimol
Cisplatinum

Levi, M., T. Berl: Water Metabolism. In Current Nephrology, H.C. Gonick ed., Year Book Medical Publishers, Chicago, Vol 9, 1986, in press.

AGENTS THAT INHIBIT PERIPHERAL ACTION OF VASOPRESSIN

Lithium
Demeclocycline
Colchicine
Vinblastine
Methoxyflurane
Glyburide, acetohexamide, and tolazamide
Amphoteracin B
Methicillin
Gentamicin
Isophosphamide
Propoxyphene
Furosemide and ethacrynic acid
Angiographic dyes
Osmotic diuretics
Cisplatinum
CCNU

Levi, M., T. Berl: Water Metabolism in Current Nephrology, H.C. Gonick, ed., Year Book Medical Publishers, Chicago, Vol. 9, 1986, in press.

The use of osmotic diuretics, high protein and glucose containing enteral feeding, and bowel cathartics should also be carefully monitored in the elderly.

The incidence of severe hypernatremia among the elderly exceeds one case per hospital per month (116,176). Hypernatremia in the elderly may present with primary neurological or psychiatric symptoms and delay the diagnosis (87). The loss of volume and shrinkage of brain cells associated with the hypoosmolar states cause tearing of cerebral vessels leading to capillary and venous congestion, subcortical and subarachnoid bleeding, and venous thrombosis. These anatomical changes are associated with symptoms of restlessness, irritability, ataxia, tremulousness, and spasticity. If not promptly diagnosed and treated, hypernatremia leads to coma, seizures, and death (9). In fact, in adults acute elevation of serum sodium above 160 meq/L is associated with a 75% mortality rate. Even in the absence of death, the neurological sequlae can be severe in the elderly.

The age-related impairment in maximal diluting ability and the enhanced osmotic release of AVP are associated with a high incidence of hyponatremia in the elderly. A random sampling of 160 patients in a chronic disease facility showed that 36 patients had hyponatremia, with a mean serum sodium of 120 meq/L, and 27 of these patients were symptomatic (94). In another study a survey of hospitalized patients in a geriatric unit during a 10 month period revealed that 77 patients or 11% had plasma sodium concentration below 130 meq/L (161). Diuretics, especially the combination of hydrochlorothiazide/amiloride, and hypotonic intravenous fluid administration was determined to cause the hyponatremia in 56 of these patients. 47 of these patients were symptomatic and the mortality rate for the hyponatremic patients was twice the overall rate for the geriatric unit. Other reports also confirm that thiazide diuretics are a major cause of hyponatremia in the elderly (31). The well known effect of thiazide diuretics to impair the renal diluting ability under normal physiological conditions seems to be compounded in the elderly with a preexisting renal diluting defect. In practice, drugs or agents that stimulate the nonosmotic release of AVP, or potentiate the renal tubular action of AVP, including chlorpropamide (172) have to be used with extreme caution in the elderly.

DRUGS AND HORMONES THAT STIMULATE VASOPRESSIN SECRETION

Acetylcholine
Nicotine
Apomorphine
Morphine (high doses)
Epinephrine
Isoproterenol
Histamine
Bradykinin
Prostaglandins
B-Endorphin
Cyclophosphamide I.V.
Vincristine
Insulin
2-deoxyglucose
Angiotensin
Lithium
? Chlorpropamide
? Clofibrate

Levi, M., T. Berl: Water Metabolism. In Current Nephrology, H.C. Gonick ed., Year Book Medical Publishers, Chicago, Vol. 9, 1986, in press.

AGENTS THAT POTENTIATE PERIPHERAL ACTION OF VASOPRESSIN

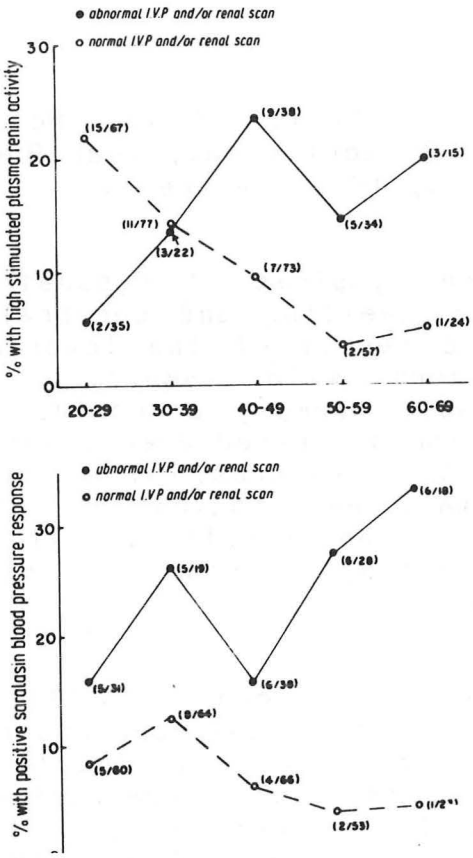
Nonsteroidal anti-inflammatory agents (short-term)
Acetaminophen
Chlorpropamide
Tolbutamide

Levi, M., T. Berl: Water Metabolism. In Current Nephrology, H.C. Gonick ed., Year Book Medical Publishers, Chicago, Vol. 9, 1986, in press.

The signs and symptoms of hyponatremia are most likely related to cellular swelling and cerebral edema caused by the water movement as a result of the lowering of ECF osmolality. Patients may present with symptoms of lethargy, apathy, disorientation, muscle cramps, anorexia, nausea, or agitation, and signs ranging from depressed deep tendon reflexes to pseudobulbar palsy and seizures (9). Differentiation of these symptoms from primary neurological or psychiatric disease is important so that one can promptly institute appropriate therapy and avoid severe neurological sequelae, including central pontine myelinolysis (121).

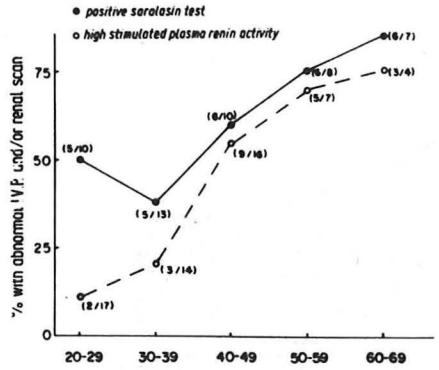
The presence of a renal acidification defect, and a decreased activity of the renin-angiotensin-aldosterone system may be the cause of the increased incidence of Type 4 RTA, or the syndrome of hyporeninemic hypoaldosteronism in the elderly (50,95). In fact, in a recent large clinical series the mean age of the patients was 65 years (50). In addition, the elderly are also at increased risk for developing hyperkalemia with potassium sparing diuretics, including aldactone and amiloride (168), as well as drugs that inhibit the renin-angiotensin systems, especially indomethacin (119,130), B-blockers, and converting enzyme inhibitors.

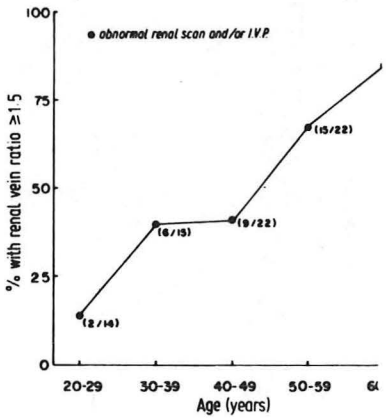
Decreased activity of the renin-angiotensin system also has implications for the diagnosis of renin-dependent hypertension, especially renovascular hypertension. A high furosemide-stimulated plasma renin activity or a positive saralasin test is more likely to indicate the presence of renal vascular hypertension in the elderly than in the young (6).



High stimulated plasma renin activity or positive saralasin test in relation to age. Open circles represent those with a normal IVP and/or renal scan; closed circles those with an abnormal IVP and/or renal scan. Nos. in parentheses are the number of patients with a high SPRA or positive saralasin divided by the number of patients tested.

Anderson, G.H., J. Springer, P. Randall, D.H.P. Streeten, and N. Blakeman. The Lancet 10:821-824, 1980.



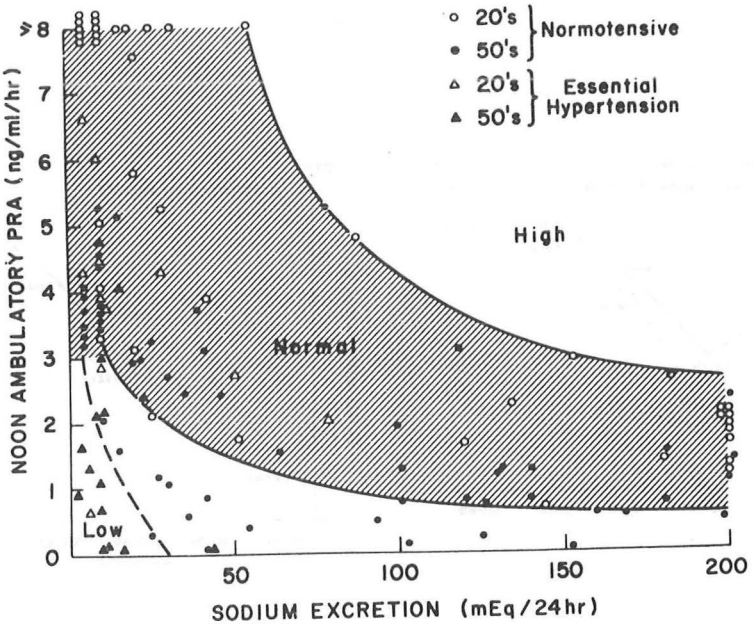


Percentage of patients with an abnormal IVP and/or renal scan in relation to a positive saralasin test (closed circles) or a high stimulated plasma renin activity (open circles), and to age.

Percentage of all patients with an abnormal IVP and/or renal scan in relation to age and renin vein renal ratio >1.5.

Anderson, G.H., J. Springer, P. Randall, D.H.P. Streeten, N. Blakeman. The Lancet 10:821-824, 1980.

On the other hand, because of the low renin profile in the aged, renal vascular hypertension may be underdiagnosed in elderly patients, especially by routine screening tests.



Age and plasma renin activity (PRA), classification, method 2. Shaded area indicates "normal" PRA-sodium excretion relationship as defined by including all values from young (20s) normotensive volunteers (n=17; 41 determinations). Dashed line indicates limit of PRA in older (50s) normotensives (n=19; 55 determinations.
Noth, R.H., N. Lassman, S.Y. Tan, A. Fernandez-Cruz, P.J. Mulrow. Arch. Intern. Med. 137:1414-1417, 1977.

The decreased activity of the renin-angiotensin system in the elderly may also have implications for the treatment of hypertension, although controlled studies in this area are lacking.

The age-related impairment in intestinal calcium absorption, caused by decreases in $1,25(OH)_2$ vitamin D_3 level and activity, is probably associated with the pathogenesis of osteoporosis and osteomalacia, one of the most common, serious, and expensive health problems in the elderly. The ensuing secondary hyperparathyroidism (67,175) may complicate the picture by futher increasing calcium release from the bone. In addition, the impairment in intestinal as well as renal tubular absorption of phosphorus may be also an important cofactor in the pathogenesis of osteoporosis and osteomalacia in the elderly.

The altered renal tubular threshold for glucose makes monitoring of urinary glucose less reliable both in the diagnosis and treatment of diabetes mellitus in the elderly. Whether the tubular threshold for glucose is increased (38) or decreased (122), it is clear that the threshold has to be carefully determined for each patient and the urine glucose monitoring has to be supplemented with frequent blood glucose determinations.

SPECIFIC RENAL DISEASES IN THE AGED

Renal Vascular Disorders

A major cause of vascular disease of the kidney in the elderly is atheroembolism which occurs when cholesterol crystals and other forms of atheromatous debris are dislodged from eroded aortic atherosclerotic plaques occluding the arcuate and intralobular arteries of the kidney (90,92,155). Renal cholesterol embolization has been reported to occur after abdominal trauma, aortic catheterization, surgery for aortic aneurysm, and abdominal, coronary or carotid angiography. The patients may present with a combination of symptoms including lower extremity focal digital necrosis, gastrointestinal bleeding, pancreatitis, myocardial infarction, retinal ischemia, cerebral infarction, hypertension, and uremia. It may be associated with fever, increased erythrocyte sedimentation rate, eosinophilia, and hematuria without casts. Episodic and labile hypertension due to renal artery emboli is a common finding. Renal cholesterol embolization results in a major reduction in glomerular filtration rate within one to four weeks (155). This helps differentiate it from radiocontrast-induced acute renal failure, which usually occurs within one to four days after the angiographic procedure (39). The renal insufficiency usually progresses to end stage renal disease, but in a recent report of five patients, only two of the patients developed end stage renal disease. Three patients developed moderate renal insufficiency with eventual recovery of renal function. In addition, in one of the patients who initially required dialysis, there was a partial recovery of renal function after four months of dialysis (155). Since renal cholesterol embolization occurs most commonly in men over 60 years of age with severe atherosclerotic disease, angiographic procedures should be replaced with noninvasive radionuclear studies in the elderly patients, unless when the clinical condition warrants otherwise. Cholesterol embolization should be considered in the differential diagnosis of acute renal failure in the elderly patients, especially when it occurs after major vessel surgery or angiography.

Another major cause of renovascular disease in the elderly is renal artery thrombosis, also occurring in patients with severe and generalized atherosclerotic disease. It may present as unilateral disease causing renovascular hypertension, or as bilateral disease causing denovo acute renal failure, or acute worsening of chronic renal failure.

Glomerulonephritis

Acute glomerulonephritis is receiving increased attention as a disease in which the presentation and prognosis are clearly age-related. Acute glomerulonephritis in the elderly usually presents as congestive heart failure rather than hypertension, hematuria, and proteinuria (8,99,126,133,148,149). Often the presenting symptoms of acute glomerulonephritis in the elderly are ascribed to coexistent disease, and unless one maintains a

high index of suspicion, the diagnosis can be overlooked (32).

A disease that appears to be more prevalent in the elderly is rapidly progressive or idiopathic cresentic glomerulonephritis (129,138,159). In an autopsy series of 44 elderly patients dying of renal disease, 28 patients (138), and in an analysis of 115 patients older than 60 years who had renal biopsy, 19 patients (129) had the diagnosis of idiopathic cresentic glomerulonephritis. The elderly patient with idiopathic cresentic glomerulnephritis appears to have a different disease from that seen in younger patients. Hemoptysis is rare and circulating anti-GBM antibodies are not often detected. Glomerular immunofluorescence studies reveal either granular deposits of IgG or are negative (23,159). The disease usually progresses to end stage renal disease and it is not clear whether the elderly respond to treatment with steroids, immunosuppressives, anticoagulants, and plasmapheresis.

Another important cause of acute glomerulonephritis in the elderly is diffuse proliferative glomerulonephritis which usually occurs in association with a major infection, especially post-streptococcal glomerulonephritis (PSGN) from pyodermal infections (138). In PSGN occurring after pyodermal infections anti-deoxyribonuclease B (anti-DNAase B) titers are increased more often than antistreotolysin (ASO) titers. In the elderly patients oliguria and volume overload are the most common presentation of PSGN and hence it is easily confused with congestive heart failure. The outcome of the disease is similar to that in the younger groups in that most patients recover renal function (129).

When compared to patients younger than 60 years the elderly also have a higher incidence of vasculitis and Wegener's granulomatosis, whereas the incidence of systemic lupus erythematosus is significantly lower (129).

COMPARATIVE INCIDENCE OF THE DIFFERENT RENAL DISEASES IN THE 115 ELDERLY PATIENTS AND 455 PATIENTS YOUNGER THAN 60 YEARS

Diagnosis	Elderly adults (60 years and older)	Other patients (<60 years)
Idiopathic crescentic glomerulonephritis	16.5%	4.0%
Membranous glomerulonephritis	13.0%	4.6%
Minimal change nephrotic syndrome	7.8%	7.0%
Focal proliferative/mesangiopathic glomerulonephritis	6.0%	10.5%
Diffuse proliferative glomerulonephritis	4.0%	2.2%
Chronic glomerulonephritis	4.0%	7.0%
Membranoproliferative glomerulonephritis	1.7%	9.2%
Glomerulosclerosis	13.0%	10.5%
Vasculitis	5.0%	3.0%
Amyloidosis	4.0%	1.0%
Wegener's granulomatosis	3.0%	0.2%
Systemic lupus erythematosus	1.7%	13.8%
Other systemic diseases	8.6%	12.0%
Miscellaneous	8.6%	15.0%

Moorthy and Zimmerman. Clin. Nephrol. 14:223, 1980.

Nephrotic Syndrome

Nephrotic syndrome is a commonly diagnosed renal disease in the elderly. In contrast to the traditional teaching that the likelihood of membranous glomerulonephritis increases and minimal change disease decreases with age, several clinical series report an equal incidence of minimal change disease in the elderly when compared to the young (760,129), although membranous glomerulonephritis is still the most commonly diagnosed cause of nephrotic syndrome in the elderly (109). In a series of 25 patients with nephrotic syndrome older than 60 years of age, 6 had minimal change disease, and 5 had membranous glomerulonephritis, an incidence similar to that seen in 75 patients with nephrotic syndrome between the ages of 15-59 (60). In another series membranous glomerulonephritis was diagnosed in 15 patients, and minimal change disease in 9 patients (129). Thus, renal biopsy seems to be essential to establish the correct histological diagnosis in the elderly patient with nephrotic syndrome. This is especially true because of the high frequency of minimal change disease in the

elderly which responds equally well to steroids and immunosuppressives as in the younger patients (60,129). A certain subset of the elderly patients with membranous glomerulonephritis also responds to steroid therapy (109,129). A limited course of alternate day steroid therapy seems to be worthwhile in the elderly patient with glomerulonephritis, although because of the potential complications such as diabetes, hypertension, and aseptic necrosis of the hip, cyclophosphamide could be considered for use as either primary or "steroid sparing" agent.

Another cause of the nephrotic syndrome in the elderly is focal glomerulosclerosis (FGS). The histologic findings in FGS include focal segmental and global glomerulosclerosis affecting especially the juxtamedullary glomeruli. Immunofluorescence generally reveals granular deposits of IgM and C_3 in the areas of segmental sclerosis. Although FGS usually occurs as a separate and distinct entity, it may also occur as the end result of various other glomerulopathies or systemic diseases, including diabetes and hypertension (166). Recently the entity of physiologic hyperfiltration has been proposed to be the precursor of FGS in these disease entities (34,35,84). In addition, FGS may also be related to the increased age-related incidence of global sclerosis (89,111,126). Interestingly, the otherwise normal and healthy aged rat also has a histologic renal lesion very similar to that of human FGS with IgM and C_3 deposition, which is accompanied by significant proteinuria (28,29,30,43,44,55). In the rat, hemodynamic rather than immunologic factors seem to be responsible for this entity (55). In the human, the age-related increase in the filtration fraction of the juxtamedullary glomeruli may also be responsible for the age-related development of glomerulosclerosis, but it remains to be established. Nevertheless, this is an important issue to consider in interpreting renal biopsies from elderly individuals. Clinically, FGS and the glomerulosclerosis of aging can usually be distinguished on the basis of the nonselective and significant proteinuria and hematuria which accompanies FGS.

Urinary Tract Infections

Urinary tract infections are an important problem in the elderly population. The reasons for the increase in the prevelance of urinary tract infections with advancing age are not known, but may include changes in bladder function, pelvic musculature, prostate size, and impaired immune response, as well as concomitant illness. While bacteriuria is found in less than 20 percent of middle-aged men, 20 percent of healthy men over the age of 65 have bacteriuria. The prevalence of bacteriuria in elderly men and women increases further to 25 percent in extended care facilities, to 30 percent in acute care hospital admissions, and to over 35 percent in nursing facility admissions (153). The increased prevalence of dementia and urinary incontinence further complicates the picture. The elderly patients with bacteriuria have a further significant

decrease in creatinine clearance when compared to age-matched patients without bacteriuria (52,53). The reason for the worsening of renal function is not clear, but may indicate the presence of chronic pyelonephritis which eventually may be associated with focal segmental glomerulosclerosis (166). Bacteriuria is also associated with a significant reduction in survival rate of the elderly subjects (52) although other associated factors also must be playing a role as the antibiotic treatment of asymptomatic bacteruria did not result in a significant improvement in the 2 year mortality in institutionalized elderly male patients (134). In fact, in the absence of renal disease, urinary tract abnormalities, or clinical evidence of sepsis, most agree that asymptomatic bacteriuria in the elderly should not be treated, as the incidence of treatment failure and relapse is high (134). The efficacy of chronic suppressive therapy has not been determined, but one might anticipate problems with emergence of highly resistant gram negative infections especially in the institutionalized and debilitated elderly patients.

Acute Renal Failure

The age-related impairments in renal blood flow, glomerular filtration rate and tubular transport of sodium and water make the elderly more susceptible to acute renal failure.

A major cause of acute renal failure in the elderly is prerenal failure, i.e., decreased perfusion of the kidney leading to a functional and potentially reversible type of acute renal failure. A decrease in cardiac output, gastrointestinal losses due to vomiting, diarrhea, or bleeding, renal losses due to glycosuria, or diuretics may all result in prerenal failure. It is not known whether the urinary indices, including fractional excretion of sodium (58,125), are reliable indicators of a prerenal state vs intrinsic acute renal failure in the elderly, due to the age-related impairments in tubular transport of sodium and water.

The elderly are also predisposed to intrinsic acute renal failure, i.e. vasomotor nephropathy or acute tubular necrosis. Complications of major surgery accounts for about 30 percent of cases of acute renal failure in the elderly (96). Hypotension during or after surgery, postoperative fluid loss due to gastrointestinal or fistulous drainage, anesthetic toxicity, arrhythmias and myocardial infarction are common post surgical complications in the elderly which may result in acute renal failure. Complications of major infections account for another 30 percent of cases of acute renal failure in the elderly (96).

CAUSE OF RENAL FAILURE

Etiology	Males	Females	Total
Multi-factorial acute renal failure			
Dehydrationn and electrolyte imbalance	30	29	59
Major surgery	17	21	38
Hypotension	13	20	33
Bronchopneumonia	7	6	13
Antibiotics	5	4	9
Jaundice	2	4	6
Septicemia	2	4	6
Diuretics	3	1	4
Contrast media	2	0	2
Primary renal disease			
Pyelonephritis	1	5	6
Acute glomerulonephritis	0	1	1
Acute polyarteritis	0	1	1
Focal embolic nephritis	1	0	1
Renal-vein thrombosis	1	0	1
Obstructive renal failure			
Enlarged prostate	18		18
Bladder retention	4	5	9
Acute obstructive pyelonephritis	2	5	7
Calculus anuria	1	3	4
Carcinoma bladder	1	3	4
Carcinomatosis (ureteric obstruction)	0	2	2
Carcinoma ovary		2	2
Fibroid		1	1

Kumar, R., C.M. Hill, M.G. McGeown. The Lancet. 1:90-91, 1973.

Gram negative infections are associated with endotoxin-induced reduction in renal blood flow, whereas gram positive infections are associated with immune complex-induced glomerulonephritis. In addition, most of the antibiotics used to treat serious in-hospital infections are associated with a high incidence of acute tubular necrosis or acute interstitial nephritis. Age is a well-known risk factor for developing aminoglycoside nephrotoxicity (128), and the reasons may include overdosage due to inaccurate estimation of the glomerular filtration rate, and preexistant age-related decrease in renal blood flow and tubular damage which may enhance the hemodynamic and tubular toxic effects of aminoglycoside antibiotics. The elderly are also at increased risk for radiocontrast-induced renal failure (39). The mechanisms of radiocontrast-induced renal injury are not completely understood, but include hemodynamic effects as well as direct tubular toxic effects, which because of preexistant renal defects predispose the elderly to enhanced renal toxicity. Another major cause of intrinsic renal failure in the elderly are the nonsteroidal antiinflammatory drugs (NSAIDs)

(79). This is of special concern because Ibuprofen, a NSAID, has recently become available as an over-the-counter-medication. Inhibition of renal vasodilatory prostaglandin biosynthesis caused by the NSAIDs potentiates the renal vasoconstrictive effects of endogenous a-adrenergic system, angiotensin II and vasopressin. In the presence of an already reduced renal blood flow, this may result in acute renal failure.

One of the most significant causes of renal failure in the elderly is urinary obstruction (96). A deficiency of bladder sensation plays a major role in the renal consequences of prostatic hypertrophy in the elderly (132). The symptoms of prostatism such as urinary frequency, difficulty in starting or stoping micturition, and nocturia are often inapparent to the patient. A significant number of patients may thus present with symptoms of end stage renal disease rather than prostatism (51,59). In addition, in clinically significant prostatism, the residual urine is often infected, which may potentiate the impairments in tubular function and reduction in renal blood flow and glomerular filtration rate caused by the obstruction. Prompt diagnosis and treatment are therefore necessary to prevent significant renal damage.

Most elderly patients respond well to treatment of acute renal failure. As in the adult population, prompt initiation of hemodialysis or peritoneal dialysis may alleviate the uremic symptoms and may prevent uremic complications such as infection, gastrointestinal bleeding, and cardiac failure, which are the major causes of increased mortality in the elderly patient with acute renal failure. Although the chances for recovery of renal function in the elderly patient with acute renal failure would be predicted to be markedly decreased, recent British study, more than 50 percent of patients aged 65 years or over who were treated with hemodialysis or peritoneal dialysis for acute renal failure eventually recovered sufficient renal function not needing further dialysis (136).

Chronic Renal Failure

Many forms of chronic renal failure are more commonly seen late in life because the renal disease is secondary to other age-dependent medical diseases. Atherosclerotic disease of the renal vasculature causing renovascular hypertension and renal ischemia, glomerulosclerosis caused by diabetes, hypertension, or chronic glomerulonephritis, and prostatic hypertrophy leading to hydronephrosis are the most common causes of chronic renal failure in the elderly. The clinical presentation of chronic renal failure in the elderly is often quite different than in the adult patient population. The elderly often present with decompensation of preexistant medical conditions such as congestive heart failure, hypertension, peptic ulcer disease or dementia, rather than with specific symptoms of uremia. In addition, the level of serum creatinine may underestimate the actual renal reserve, as in the presence of decreased muscle

mass, serum creatinine does not rise in direct proportion to the reduction in the glomerular filtration rate (143). If the renal failure is advanced and no reversible causes can be identified, then early dialysis is advisable to prevent the disabling symptoms of uremia and organ dysfunction that may become irreversible. Age per se should not be the sole criteria for selection for dialytic therapy. In the absence of major extrarenal organ dysfunction, the elderly adjust to dialysis quite well and their longevity rate, although not as favorable as the younger patients, is not markedly reduced as a result of end stage renal disease (20,36).

Summary

It is clear that aging is associated with significant changes in renal anatomy and function. The decreases in renal blood flow, glomerular filtration rate, and tubular function is usually of no consequence to an otherwise healthy elderly individual, but they do have important implications for drug therapy and diagnostic tests, and may predispose the elderly patients to life-threatening fluid and electrolyte disordrs during stress and disease.

The important questions that need to be addressed in the future are as to whether the increase in the age-related incidence of hypertension, glomerulosclerosis, and bacteriuria are responsible for progression of renal disease in the elderly and if appropriate, life-long intervention can attenuate the renal structural and functional impairments in the aging kidney.

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