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A Urologist's View of Renal Pathophysiology
Part I

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Lesson 25

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The nephron, the functional unit of the kidney, consists of a glomerular capillary network, proximal convoluted tubule, loop of Henle, distal convoluted tubule, and a collecting duct. There are approximately two to three million nephrons within two adult human kidneys. At rest, only one tenth of this amount is required to maintain homeostasis; therefore, a large reserve exists. It is the precise quantification of this reserve that enables decisions regarding therapy to be made when renal dysfunction occurs.

This lesson will examine the impact of alterations in renal function on urology. We will also discuss the limitations of various quantitative methods while presenting several "bedside techniques" for the assessment of renal function.

Historical Perspective

The evaluation of renal function dates back to the early 1800s. As described by Haycock,[1] it was John Bostock[2] working as a lecturer in clinical chemistry in London, who first demonstrated an impaired concentrating ability in a group of Richard Bright's patients with advanced renal disease. It wasn't until almost a decade later in 1917 that Van Slyke and his co-workers introduced and defined the term "renal clearance,"[3] the central concept in the measurement of renal function. Although Rehberg in 1926[4] was the first to measure and equate the clearance of creatinine with glomerular filtration rate, it was Homer Smith[5] who delineated the full potential of clearance measurements in the evaluation of renal function.

Basic Renal Pathophysiologic Processes

The myriad of alterations in homeostasis that occur with renal dysfunction can be best understood by considering **six** basic pathologic processes that alter renal function: 1) alterations in renal blood flow (RBF), 2) alterations in the glomerular filtration rate (GFR), 3) adaptation to a change in the **number** of nephrons, 4) impaired **tubular** function, 5) acute renal failure, and 6) obstruction to urine flow.

The first three will be discussed in this lesson, Part I, while the others will be discussed in the subsequent lesson, Part II.

ALTERATIONS IN RENAL BLOOD FLOW

Anatomy

The renal artery divides before entering the parenchyma of the kidney into two major branches — anterior and posterior. These subsequently divide into a variable number of segmental vessels. These in turn branch into *interlobar* arteries which extend toward the cortex in between the columns of Bertin. *Arcuate* arteries are the next division lying at the cortical-medullary junction. The arcuate arteries give rise to the *interlobular* arteries which extend to the cortical surface (Figure 1). The smaller branches of the interlobular arteries give rise to the *afferent* arteriole which leads to the glomerular capillary. The bridge to the postglomerular (i.e., peritubular capillary) circulation is via the *efferent* arteriole. It is the efferent arteriole of the juxtamedullary glomeruli which give rise to the vasa recti, important in the counter-current multiplication system. In addition, it is both the afferent and efferent arterioles which are under neural/humoral control that regulate the filtration fraction (GFR/RPF). It should be noted that some interlobular arteries also anastomose directly with the venous system.

Unlike the arterial system which has no collateral pathway, the renal venous system anastomose at various levels. The veins essentially follow the course of the arterial system, converging at the arcuate/interlobar level to form several main trunks that join to form the renal vein.

Measurement of Renal Blood Flow

Para-aminohippurate (PAH) a non-endogenous organic acid is the most commonly used injectable agent for the measurement of renal blood flow. Its usefulness stems from the fact that at *low plasma concentrations* it is filtered at the glomerulus and secreted by the tubules such that whatever enters the kidney leaves in the urine. This is then a direct application of the Fick principle, in that: 1) the amount entering kidney = amount leaving kidney where: 2) the amount entering kidney (mg/min) = Ppah x RPF and the amount leaving kidney (mg/min) = (amount excreted) + (amount leaving via renal vein) + (amount sequestered by kidney).

Since we are assuming that the amount leaving via the renal vein and the amount sequestered by the kidney is negligible, then amount entering kidney = amount leaving kidney
or:

$$Ppah \times RPF = Upah \times V$$

rearranging,

$$RPF = \frac{Upah \times V}{Ppah}$$

where;

Ppah = plasma PAH concentration (mg/ml)
Upah = urine PAH concentration (mg/min)
RPF = renal plasma flow (ml/min)
V = urine flow (ml/min)

The conversion of RPF to RBF (renal blood flow) is given by the following equation:

$$RBF = \frac{RPF}{(1 - Hematocrit)}$$

Total RBF estimated by this method is approximately 1200 ml/min/1.73m^2, a value that has been confirmed by several other methods.

Since extraction of PAH (or for that matter any similar indicator) is never complete, the term "effective renal plasma flow" (ERPF) has been used. In diseased states where tubular function is compromised, venous sampling must be performed to determine PAH concentration. The equation thus becomes:

$$RPF = \frac{Upah \times V}{(Ppah - RVpah)}$$

where;

RVpah = renal venous PAH concentration (mg/min)

The technical complexities involved in the measurement of RBF by PAH infusion has led to the search for alternative techniques. The most frequently used include the use of radionuclides and non-invasive scanners for calculation of differential RBF from each kidney.

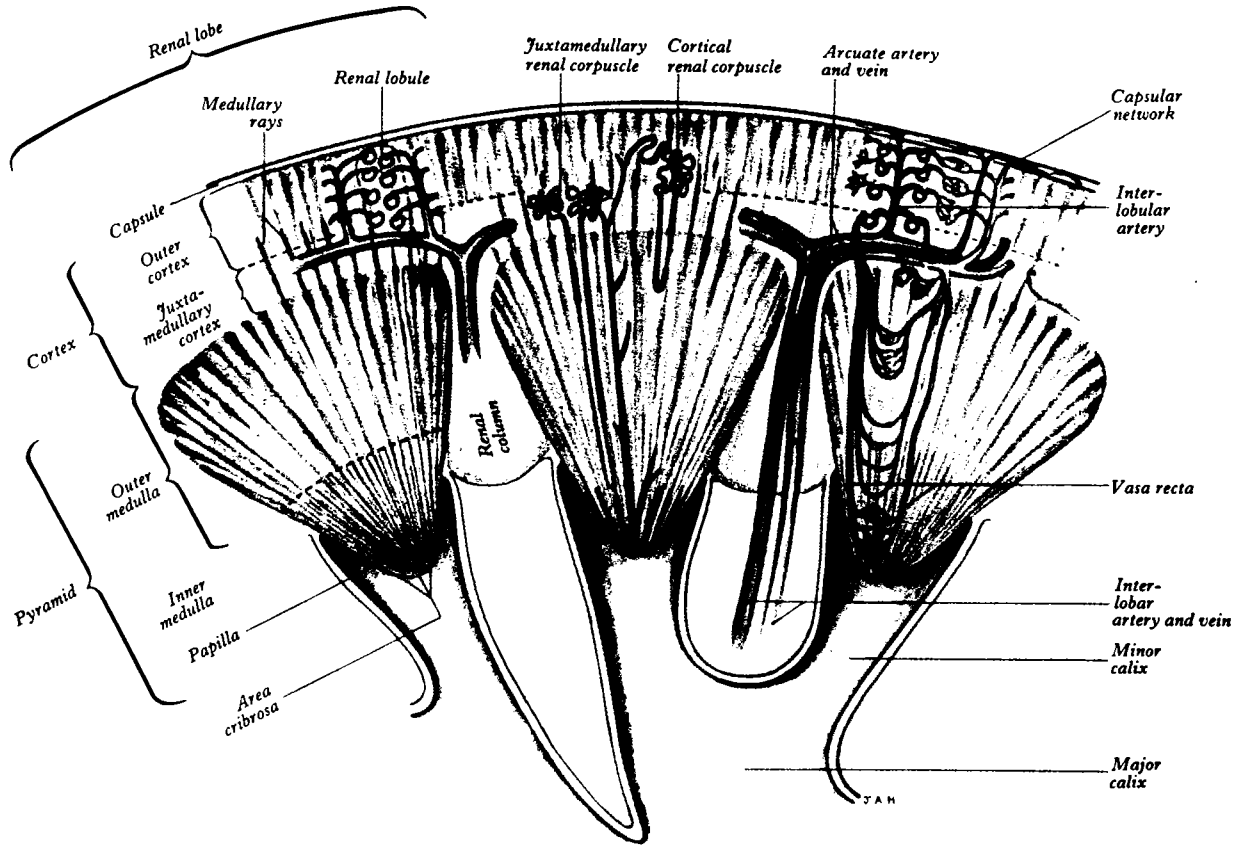

Figure 1

The major structures in the renal cortex and medulla (left), the position of the cortical and juxtamedullary nephrons (middle), and the major blood vessels (right) are shown here. (From Williams PL and Warwick R (eds): **Gray's Anatomy.** *36th ed, Philadelphia, WB Saunders Co, 1980).*

Renal Artery Stenosis

It has been shown that there has to be a 40 mmHg gradient across a renal artery stenosis before there is a fall in RBF and GFR with subsequent renin release and systemic hypertension. Thus with physiologically significant renal artery stenosis, the critical change is the decrease in RBF, afferent arteriolar pressure, and effective filtration pressure, resulting in reduced GFR. The lower volume of filtrate results in increased sodium reabsorption and water reabsorption resulting in a urine characterized by low sodium, high osmolality, and low volume when compared to the opposite kidney. The term nephron *underperfusion* can be utilized to describe this situation and the urinary findings serve as indicators of renovascular hypertension in split renal function tests.

In addition, the low afferent arteriolar pressure and the decrease in sodium or chloride at the level of the macula densa portion of the distal tubule leads to renin release, angiotensin II (AII) formation, and systemic hypertension.

There is considerable evidence that the intrarenal generation of AII produces a selective *efferent* arteriolar vasoconstriction to increase the glomerular capillary hydrostatic pressure and thus maintain GFR. Accordingly treatment of patients (see reference 6 for specific references and details) with RVH with antihypertensive agents can lead to renal infarction by two mechanisms, despite control of blood pressure. First, when diastolic pressure is lowered to normal (e.g. 80 mmHg) and there is a 40 mm gradient at the stenosis, then the pressure is below autoregulatory range (60 to 160 mmHg) and RBF and GFR drops further. Secondly, if an angiotensin converting enzyme inhibitor such as captopril is used, there may be even further fall of GFR due to loss of efferent arteriolar tone (secondary to the decreased production of AII). **Accordingly medical antihypertensive management in patients with renovascular hypertension may lead to renal functional impairment and renal loss.**

'Warm' and 'Cold' Ischemia

Over the past century multiple clinical and experimental studies have attempted to delineate the effect of renal ischemia occurring with intraoperative arterial occlusion.[7,8] **The consensus appears to be that with periods of warm ischemia exceeding 30 minutes, histologically documented irreversible damage to proximal tubular epithelium occurs.** Warm ischemia times over 60 minutes result in almost complete irreversible renal damage. The mechanism of tubular damage appears to be related to the depletion of cellular membrane stores of ATP and a concomitant decrease in the normal active transport processes. This results in an intracellular influx of salt and water followed by cell swelling and cell death.[9,10]

Recent studies on the effects of acute ischemia on renal function have delineated the effects of warm ischemia time on renal function in the human kidney. Jrgensen, et al[11] have evaluated 289 uncomplicated cadaveric renal transplants by I^{131}-hippurate renography postoperatively. They have found

normal or only slightly decreased phase one (which represents appearance of nuclide in renal vessels and early uptake of tracer into renal tubular cell during the first minute after tracer injection) and phase two (which occurs within three to five minutes when the tracer reaches the renal tubule) in 65 percent of renograms if warm ischemia time was less than 15 minutes and if the cold ischemia time was less than ten hours. Their conclusion was that warm ischemia times less than 15 minutes and cold ischemia times less than ten hours resulted in minimal renal functional impairment. Conversely, warm ischemia times greater than 15 minutes and cold ischemia times greater than ten hours were associated with an almost linear decrease in renal function. The renograms correlated well with the onset of function after transplant.

In a retrospective study Van et al[12] have found that one year survival of grafts with warm ischemia time longer than 50 minutes was only 40 percent. When warm ischemia time was less than 50 minutes, there was a direct correlation between warm ischemia time and graft survival. For each minute of warm ischemia time graft survival was decreased by one percent.

It is known that renal cooling during periods of ischemia preserves renal function.[13,14] This is related in part to the decreased metabolic needs of the tubular epithelium. It appears that a renal core temperature of 15 to 20 degrees Celsius provides maximal protection.[15] Both cooling of the perfusate and external cooling solutions (iced normal saline slush) appear to be of equal efficacy in achieving this temperature, although transarterial perfusion appears to be the most efficient in providing a rapid and homogenous cooling.

Various pharmacologic agents such as the purine nucleotide inosine have been utilized to preserve renal function during periods of ischemia up to 90 minutes.[16] This agent most likely works by maintaining a high intrarenal level of ATP precursors.

ALTERATIONS IN THE GLOMERULAR FILTRATION RATE

Whole Kidney Glomerular Filtration Rate

Glomerular filtration rate (GFR) is the volume of fluid traversing the glomerular membrane in a given period of time. The units are always referred to as volume/unit time; typically ml/min. This value is occasionally normalized to body surface area in an attempt to compare GFR in kidneys of varying sizes.

GFR can be calculated from measurable serum constituents. The equation for GFR is a subset of the generalized equation for clearance, which is the central equation used to describe renal function. In brief, the renal clearance (Cx) of any substance dissolved in plasma (Px) is the rate of excretion in urine (Ux *V),

This is given by the expression,

$$Cx = (Ux * V)/Px$$

where: Cx is the clearance of substance x (ml/min)
Px is the plasma concentration of x (mg/ml)
Ux is the urine concentration of x (mg/ml)
V is the urine flow (ml/min)

Cx is considered to be the "virtual" volume of plasma cleared of a substance in a given period of time. It is a "virtual" volume and not an actual volume since the kidney does not in general remove all solute from a given aliquot of plasma in a given pass through the kidney. Note that clearance is in units of ml/min. Although seemingly illogical to describe the excretion of a solute in terms of volume flow, it indeed describes the *volume* of plasma which contained the amount of solute excreted in the designated time period. As we develop our equations for GFR, RPF, and free water clearance, it will become apparent that it is this seemingly illogical use of units for renal clearance that allows a qualitative as well as a quantitative evaluation of renal function.

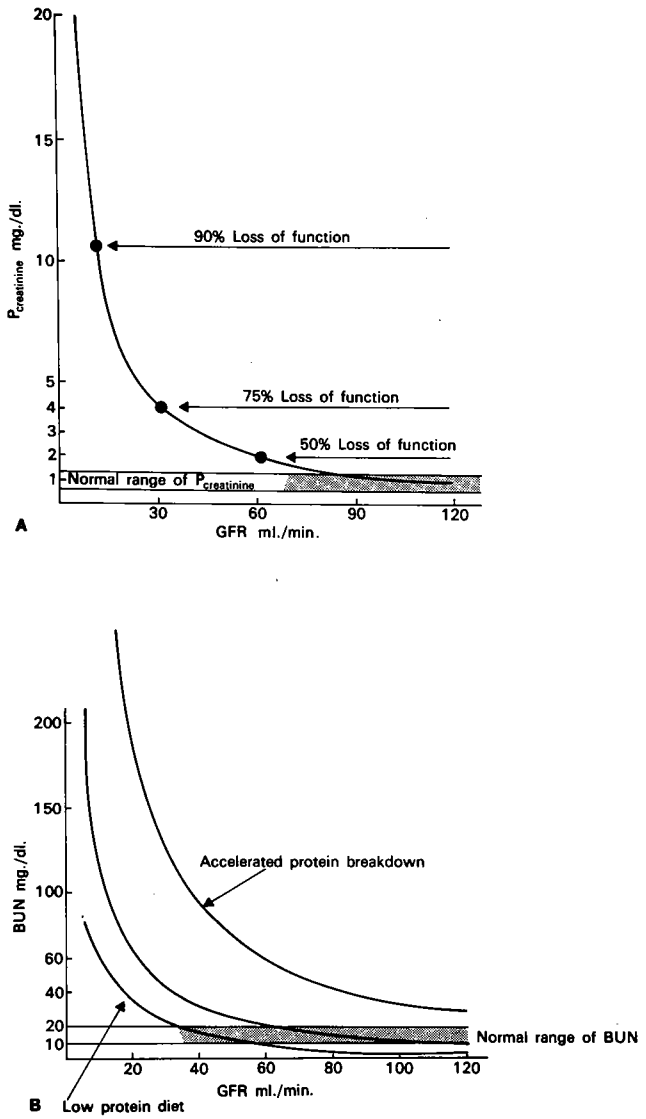

Figure 2

A) *Progressive increase in plasma creatinine concentration resulting from a declining GFR in an individual who originally had a GFR of 120 ml/min and a plasma creatinine of 1 mg/dl.* **B)** *The increment in BUN in the same patient. Note the marked effects of accelerated protein breakdown and low protein diet on BUN at any given value of GFR.*[31]

Inulin, a fructose polysaccharide with a molecular weight of 3000 to 4000, is one of the best substances used for measurement of GFR. It is non-metabolizable, not protein bound, freely filtered at the glomerular membrane and unable to cross the renal tubular epithelium in either direction. Thus the amount excreted in a given period of time (excreted load;mg/min) is equal to the amount filtered across the glomerular membrane during that same period (filtered load;mg/min). Thus the volume of plasma which contained the excreted inulin is the same volume which was filtered across the glomerular capillary. This is described by the following well known equation:

Filtered load = Excreted load

$$C(inulin) * P(inulin) = U(inulin) * V$$

(ml/min) * (mg/ml) = (mg/min) * (ml/min)

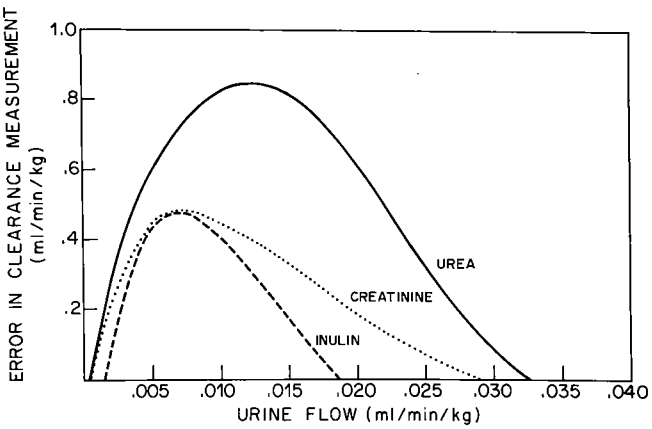

Figure 3

Intestinal reabsorption of urea, creatinine, and inulin results in error in determination of renal function by urea, creatinine, and inulin clearances. This error is urine flow dependent. At high urine flow rates, reabsorption and error resulting from it are minimized.[23]

or by rearranging;

C(inulin) = GFR (ml/min) = [U(inulin)*V]/ P(inulin)

With renal dysfunction, creatinine and urea are selectively retained by the kidney. Endogenous creatinine is a metabolic product of muscle metabolism. Its plasma concentration is maintained in a narrow range (0.6-1.2 mg/dl), since its value is a function of muscle mass which is a relatively stable parameter. Creatinine, like inulin, is filtered but not reabsorbed by the nephron. It is however *secreted* to a certain extent and thus tends to *overestimate* GFR. This discrepancy is most apparent in end stage renal disease where there is marked tubular hypertrophy of residual nephrons. This slight overestimation of GFR is, in part, compensated for by the underestimation occurring secondary to technical considerations in the analytical assay for creatinine.

Thus, since production is constant and the excreted load is essentially equal to the filtered load, it follows that a fall in GFR will cause serum levels of creatinine to rise until the filtered load is restored to its original value.

Example:

A normal man (72kg) has a plasma creatinine concentration of 1 mg/dl (10 mg/l) and a daily GFR of 180 1/24 hour. Therefore:

filtered load = 10 mg/l * 180 1/24 h=
1800 mg/24 hour = excreted load

If GFR is reduced in half (surgical extirpation or medical renal disease) to 90 1/24 h and muscle mass remains constant, then plasma creatinine concentration would have to double to maintain the same filtered load.

filtered load = 20 mg/dl * 90 1/24 hour =
1800 mg/24 h = excreted load

Therefore halving the GFR doubles the plasma creatinine concentration. Quartering the GFR would quadruple the creatinine plasma concentration. Plasma creatinine concentration is thus inversely proportional to GFR (Figure 2). **Note that plasma creatinine concentration rises steeply when nephron loss is greater than 75 percent.**

Urea concentration (normally 10 to 20 mg/dl) rises in parallel with the creatinine concentration as GFR falls. Urea is partially reabsorbed from the glomerular filtrate. Additionally, its metabolism varies to a greater extent than that of creatinine (Figure 2). **Therefore, the BUN/Creatinine ratio is greater than 20 in conditions associated with accelerated protein breakdown (trauma, infection, steroid therapy, gastrointestinal bleeding, or high protein diet) or when increased fractional urea reabsorption occurs with a decrease in GFR (e.g., prerenal failure). Conversely a decrease in the BUN/Creatinine ratio occurs with a low protein diet or when reabsorption of urea is minimized (e.g., obstruction, renal tubular damage, elevated GFR).**

Often the need arises to be able to accurately predict the creatinine clearance without awaiting the results of a 24 hour urine, for example, to adjust the dose of various potentially toxic drugs when beginning therapy. Several investigators have devised formulae to do this utilizing serum creatinine, body weight, age, and sex as variables. The most widely used of these is that described by Crockcroft and Gault.[17]

Estimated GFR is given by the following equation:

$$\frac{(140 - \text{age})\,(\text{weight})}{72\ \text{SCr}} \quad \text{ml/min}$$

(multiply the equation by 0.85 for women)

where SCr is serum creatinine (mg/dl)
Age is in years
weight is in kg

The major prerequisite is that renal function be at its steady state (as defined by a stable serum creatinine). Their study group consisted of 249 patients ranging in age from 18 to 92 years old with measured mean creatinine clearances from 37.4 to 114.9 ml/min. Their correlation coefficient between measured and calculated creatinine clearance was 0.84, a value not significantly different than the correlation between two measured creatinine clearance determined on the same individual on a hospital ward.

Example:

A 70-year-old female weighing 60 kg having a serum creatinine of 2.0 mg/dl would have an estimated creatinine clearance of:

$$\frac{(140-\text{age})*(\text{weight})}{72\ \text{SCr}}*0.85 = \frac{(140-70)*60}{72*2.0}*0.85 = 25\ \text{ml/min}$$

An interesting problem occurs with the *measurement* of renal function when an intestinal segment is used as a replacement for part or all of the lower urinary tract. Most studies[21-23] have utilized a canine model. A recent study by Koch and McDougal[23] quantitates the effect on the measurement of renal function when an intestinal segment (ileum) substitutes for one of the ureters. In their study the contralateral ureter was used as a control. Inulin, urea, and creatinine clearances as well as osmolality were determined at varying urine flows from both the control and substituted side. The results shown in Figure 3 suggest that:

1) Urea clearances, especially under conditions of hydropenia, do not reflect true renal function when there is urinary diversion through an ileal segment.

2) Creatinine clearance in a diuretic state is an accurate assessment of true renal function.

3) Inulin clearance in moderate degrees of diuresis gives the most accurate indication of renal function. It, however, is the most difficult to employ.

Therefore to obtain an accurate assessment of renal function with intestinal replacements, one must ensure at least a moderate degree of diuresis with hydration for the duration of the collection period.

Single Nephron GFR

Glomerular filtration at the level of the nephron, is determined by the driving forces of oncotic (OP) and hydrostatic

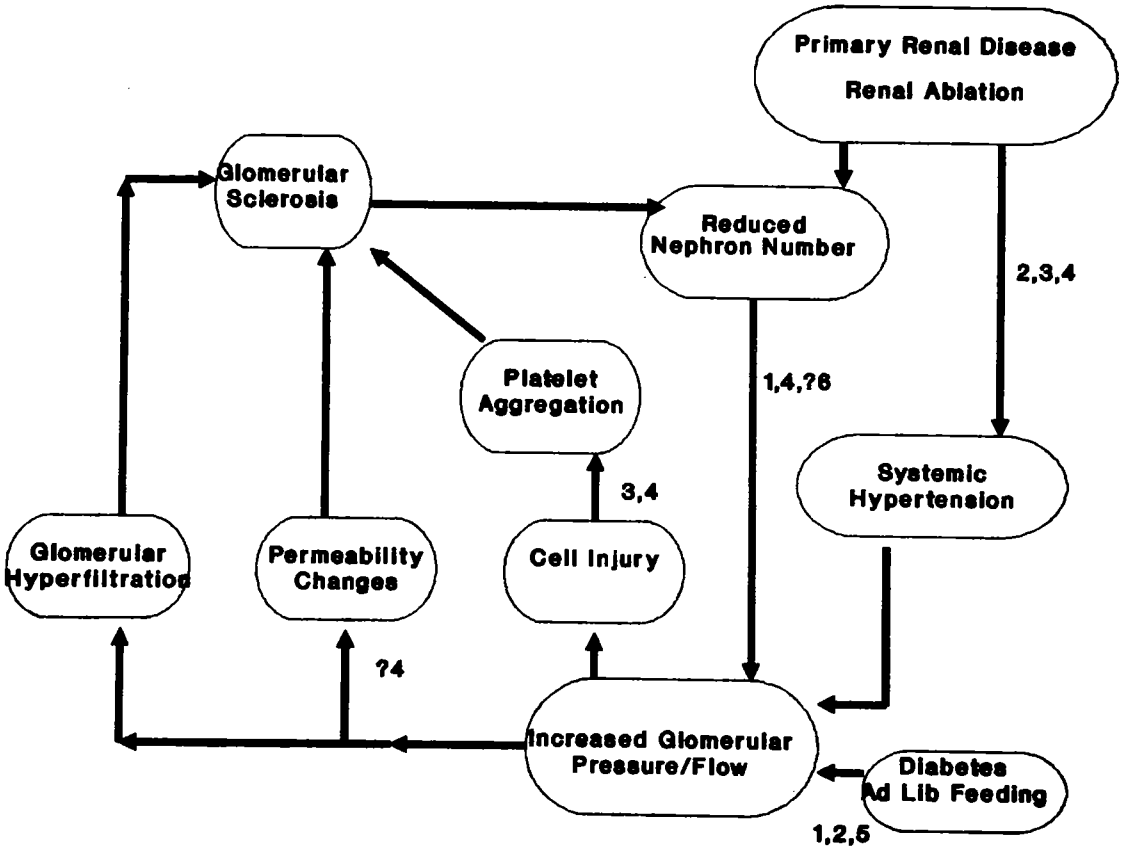

Figure 4

Schema depicting the role of hemodynamic factors in initiation and progression of glomerular sclerosis. Possible therapeutic interventions and their likely loci of action are indicated: 1) dietary protein restriction; 2) aggressive antihypertension therapy; 3) anticoagulant/antiplatelet drugs; 4) cyclooxygenase inhibitors; 5) strict blood glucose control; and 6) phosphorous restriction.[24]

(HP) pressure. The OP is primarily a function of the plasma albumin concentration and the permeability characteristics of the glomerular membrane. The hydrostatic pressure is a function of the systemic arterial pressure as well as the afferent and efferent arterial resistances. Fluid movement across the glomerulus is then a passive process approximated by the following equation:

$$Jv = k (HP - COP)$$

where:

1) Jv is the fluid flux from glomerular capillary to Bowman's space.

2) k is the effective hydraulic permeability of the capillary wall.

3) HP is the hydrostatic pressure gradient across the glomerular capillary (HP = glomerular capillary hydrostatic pressure —Bowman's space hydrostatic pressure).

4) COP is the capillary colloid osmotic pressure gradient across the glomerular capillary (COP = Bowman's space colloid osmotic pressure — glomerular capillary colloid osmotic pressure).

The effective hydraulic permeability (k) of the capillary membrane is known to vary with pore size, ratio of total pore cross-sectional area to pore length and charge selectivity of the glomerular capillary wall.[24]

Thus a decrease in GFR can result from a change in the hydrodynamic (Starling) forces present across the glomerular membrane as well as from a decrease in the number of functioning nephrons.

ADAPTATION TO A CHANGE IN THE NUMBER OF NEPHRONS

No matter what factors may contribute to reduce the function of individual nephrons, it is abundantly clear that the remaining nephrons attempt to make up for the loss. They have a high solute load and undergo a degree of hypertrophy and hyperplasia; appearing as if they are undergoing an osmotic diuresis. This occurs whether nephron loss occurs secondary to medical renal disease or due to surgical extirpation.

In a way that is not completely understood, functional adaptation to a loss of renal mass appears to be related to dietary protein.[24] Accumulated evidence suggests that a circulating hormone is responsible for the increased renal perfusion and filtration induced by dietary protein, since this effect can be blocked by somatostatin.[25,26] A schema proposed by Brenner et al[24] (Figure 4) shows a reduction in renal mass, systemic hypertension, conventionally treated diabetes, and ad libitum feeding (as opposed to the intermittent feeding of primitive man) leading to unrelenting vasodilation via some unknown circulating hormone. The consequent elevations in glomerular capillary pressures and flows promote hyperfiltration and impairment of the permselective properties of the glomerular wall. This results in glomerulosclerosis which in turn causes nephron loss with compensatory adaptation and therefore continuation of the destructive cycle. **Of particular interest to urologists is the relatively high incidence of hypertension and proteinuria found in donors ten or more years after uninephrectomy,[27] suggesting the destructive functional adaptation that can occur with nephron loss.** It should be emphasized that Brenner's thesis suggests that these destructive changes can be avoided by the use of a low protein diet postoperatively.

In assessing renal functional alterations with disease, it must be kept in mind that although we commonly view the kidney as one large nephron, it is in fact a composite of *heterogeneic nephron populations* that differ in *structure* and *function*.

Heterogeneity is typically broadly divided into *vascular*

heterogeneity or *tubular heterogeneity*, and subdivided as to the location of the glomeruli; cortical, mid-cortical, juxta-medullary. Vascular (including glomerular) size increases from cortex to medulla. Tubular length also increases; the shortest nephrons having cortical glomeruli. Functionally, GFR and RPF (renal plasma flow) are also increased in the more medullary located nephrons while FF (GFR/RPF) is usually decreased in these deeper regions. This fall in FF in the deep nephons likely plays an important role in the natiuretic response to volume expansion and to certain vasoactive agents. The mechanism being related in part to a "medullary washout" effect. It appears from studies on acutely volume expanded rats,[28] that natiuresis results from the delivery of salt to the distal collecting ducts of the *juxtamedullary nephrons*. This apparently is the result of increased medullary blood flow which in turn "washes out" the medullary concentration gradient. Since this effect can be reproduced with the infusion of drugs such as bradykinin and acetylcholine, it is apparent that a neuro-humoral control of renal function exists that is dependent on the existing nephron heterogeneity.

A reduction in nephron filtration rate as described above usually doesn't alter tubular transport process unless the viability of the tissue is affected secondary to poor perfusion. There are however several substances whose *renal excretion* is affected by a reduced nephron GFR.

With a decrease in nephron filtration or vascular perfusion, a greater fraction of filtered sodium and water is reabsorbed. This is in part due to the activation of the renin-angiotensin-aldosterone system and volume receptor-ADH system; these are considered to be the *extrinsic factors*. *Intrinsic mechanisms* are also important. With a decrease in RPF, GFR tends to be well maintained throughout a wide range of renal perfusion pressure (autoregulation). Thus the filtration fraction (FF = (GFR/RPF)) increases. As discussed above, the glomerular membrane is a selective membrane that under normal conditions effectively excludes protein from the glomerular filtrate. With an increase in FF the protein concentration and hence the protein colloid osmotic pressure of fluid leaving the glomerulus is significantly elevated. This occurs since more fluid without protein is filtered at the glomerulus leaving a relative hyperoncotic post glomerular pericapillary fluid thus providing a "physical" driving force for bulk flow of salt and water across the proximal tubule. It has been suggested that this might be the modulating factor for as much as 25 percent of fluid movement in the proximal tubule.[29,30]

With a decrease in GFR, a disproportionate lowering of the urea clearance occurs. This is due to both the *decrease* in filtered urea as well as the *increase* in passive reabsorption resulting from increased fractional fluid reabsorption. Thus the BUN/Creatinine ratio increases with factors that change the renal hydrodynamics (prerenal failure) and in states of accelerated protein breakdown. In addition, for substances such as glucose, the renal plasma threshold (i.e., the plasma concentration at which a substance first appears in the urine) is defined by the filtered load (GFR x plasma glucose concentration). A decrease in GFR would mean, therefore, that a higher plasma concentration would be required before "spillage" occurs in the urine. Therefore, measurement of urinary glucose concentration ("urine fractionals") under conditions of lowered GFR could grossly underestimate the serum glucose concentration.

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Study Questions Volume VII Lesson 25

1. For a substance which is filtered but neither secreted or reabsorbed by the renal tubule, the excreted load is:
   a) proportional to the plasma concentration.
   b) equal to the filtered load.
   c) inversely proportional to the glomerular filtration rate.
   d) the concentration in the urine.
   e) equal to the GFR.

2. A 60-year-old, 80 kg man with a serum creatinine of 1.0 mg/dl and urine creatinine of 50 mg/dl has a measured GFR of 130 ml/min. The filtered load of creatinine is:
   a) 1.3 mg/min.
   b) 13 mg/min.
   c) 50 mg/min.
   d) 130 mg/min.
   e) cannot be determined from the information given.

3. A 60-year-old 80 kg man with a serum creatinine of 1.0 mg/dl and urine creatinine of 50 mg/dl has a measured GFR of 130 ml/min. The calculated urine flow would be:
   a) 130 ml/min.
   b) 1.3 ml/min.
   c) 2.6 ml/min.
   d) cannot be determined from the information given.
   e) < 1.0 ml/min.

4. The estimated creatinine clearance of a 50-year-old woman weighing 60kg with a solitary kidney and having a serum creatinine of 1.5 mg/dl is approximately:
   a) 120 ml/min.
   b) 90 ml/min.
   c) 50 ml/min.
   d) 40 ml/min.
   e) cannot be determined from the information given.

5. A 50-year-old woman weighing 60kg with a solitary kidney presents with hematuria and flank pain. Her serum creatinine is 3 mg/dl which is increased from her baseline of 1 mg/dl. Her estimated creatinine clearance has changed by the following:
   a) increased by 33 percent.
   b) decreased by 33 percent.
   c) increased by 66 percent.
   d) decreased by 66 percent.
   e) unchanged.

6. The most accurate means of assessing renal function in a patient in whom an intestinal segment has been used for urinary diversion is:
   a) measurement of urea clearance.
   b) measurement of creatinine clearance during hydropenia.
   c) measurement of creatinine clearance during diuresis.
   d) measurement of changes in serum creatinine.
   e) measurement in changes of serum urea.

7. The diuresis seen in acute volume expansion is in part related to:
   a) release of ADH.
   b) decreased GFR and RPF to cortical nephrons.
   c) decreased GFR and RPF to more medullary located nephrons.
   d) increased filtration fraction in more medullary located nephrons.
   e) decreased RPF secondary to catecholamine release.

8. In which of the following situations would the BUN/creatinine ratio be expected to be less than 20?
   a) infection
   b) gastrointestinal bleeding
   c) steroid therapy
   d) bilateral ureteral obstruction
   e) high protein diet

9. Which of the following is most characteristic of pre-renal failure?
   a) increased sodium reabsorption
   b) decreased BUN reabsorption
   c) BUN/creatinine ratio less than 20
   d) hypokalemia
   e) decreased renal plasma threshold for glucose

10. According to the hyperfiltration theory of Brenner, which of the following factors is important in the genesis of glomerular sclerosis?
    a) renal vasoconstriction
    b) systemic hypotension
    c) intermittent feeding
    d) unrelenting renal vasodilation
    e) low protein diet

Fill in answers on answer sheets provided.