Pathophysiology of Renal Disease

Second Edition

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PREFACE

The aim of this book is to teach medical students, house officers, and practicing physicians the basic aspects of intrinsic renal disease and hypertension. Although the basic outline is similar to that of the first edition, so many new advances have been made in the past six years in both pathophysiology and clinical management that the text has essentially been completely rewritten. As an example, Chapter 4 is new, dealing with the mechanisms responsible for the progression of renal disease. This exciting area offers hope in the therapy of many disorders, such as diabetic nephropathy, in which reduction of the intraglomerular pressure may prevent progressive glomerular injury, even in the absence of strict glycemic control.

The material that is presented reflects the core of information that I believe the clinician should possess. I have tried, wherever possible, to include discussions both of the mechanisms of disease and of how to derive a differential diagnosis based upon the findings present at initial evaluation. Thus, there are separate chapters reviewing the pathogenesis and approach to glomerular disease and to essential hypertension. In addition, the first two chapters present a broad overview of renal disease, including the common laboratory tests used to assess renal function (creatinine clearance, urinalysis, and urine sodium and osmolality) and a general diagnostic approach to help determine what kind of renal disease is present.

There are also certain areas that are not covered. Renal physiology and fluid and electrolyte disorders are presented in my other book, *Clinical Physiology of Acid-Base and Electrolyte Disorders, 2d. ed.* (McGraw-Hill, 1984). Space limitations and a desire to emphasize those problems that are most commonly seen by the nonnephrologist have led to the omission of chapters on urinary tract infections (other than chronic pyelonephritis), chronic renal failure, dialysis and transplantation, renal stones, and renal neoplasms.

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CONTENTS

1

CLINICAL ASSESSMENT OF RENAL FUNCTION

Burton D. Rose

The evaluation of the patient with kidney disease involves two basic steps: (1) establishing the correct diagnosis and (2) estimating the degree of renal dysfunction. Although the history and physical examination are frequently helpful, laboratory tests play a central role in this process. The most important of these tests are estimation of the glomerular filtration rate (GFR), examination of the urine, radiologic studies, and renal biopsy. This chapter reviews in some detail the meaning of these tests and the kinds of information that they can provide. The following chapter then discusses their specific use in the patient with renal disease.

MEASUREMENT OF GFR

The GFR is the best clinical estimate of functioning renal mass. To appreciate why this relationship is true, it is first necessary to briefly review normal renal physiology.

The basic unit of the kidney is the nephron, with each kidney in humans containing approximately 1.0 to 1.3 million nephrons. Each nephron consists of a glomerulus, which is a tuft of capillaries interposed between two arterioles (the afferent and efferent arterioles), and a series of tubules lined by epithelial cells (Fig. 1–1). As with other capillaries, an ultrafiltrate of plasma is formed across the glomer-

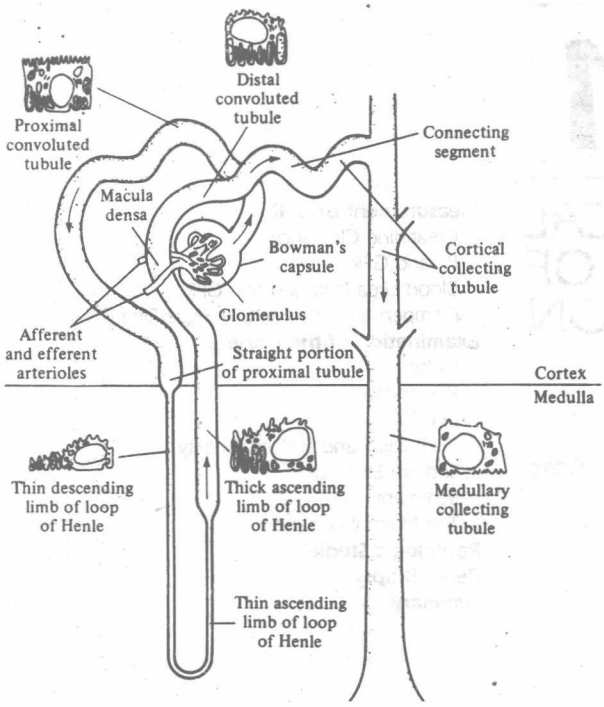

FIG. 1-1. Relationships of the component parts of the nephron. (*Adapted from R. Vander, Renal Physiology, 2d ed., McGraw-Hill, New York, 1980.*)

ulus. The filtrate is then altered by the tubules which reabsorb and, to a lesser degree, secrete solutes and water. The normal GFR is 135 to 180 L/day, an amount roughly equal to 10 times the extracellular volume. To prevent excessive fluid losses, 98 to 99 percent of the filtrate undergoes net reabsorption, resulting in a urine output of only 1 to 2 L/day.

These nephrons perform a variety of essential functions*[1]:

1. They participate in the maintenance of the constant extracellular environment that is required for adequate functioning of the cells. This is achieved by excretion of some of the waste products of metabolism (such as urea, creatinine, and uric acid, as well as many drugs) and by specific adjustment of the urinary excretion of water and electrolytes to match intake and endogenous production. To attain the latter goal, the kidney is able to regulate individually the excretion of solutes (such as sodium, potassium, and hydrogen) and water, largely by changes in tubular reabsorption or secretion. For example, water excretion appropriately increases after a water load. This change is mediated by reduced secretion of antidiuretic hormone (ADH) from the posterior lobe of the pituitary. The relative absence of ADH diminishes the permeability of the collecting tubules to water, thereby lowering water reabsorption and promoting water excretion.

*The specific mechanisms by which these functions are performed, including the role of hemodynamic and neurohumoral factors in the regulation of the GFR, are generally beyond the scope of this discussion but are reviewed in detail in Ref. 1.

2. The nephrons secrete hormones that participate in the regulation of systemic and renal hemodynamics (renin, prostaglandins, and bradykinin), red blood cell production (erythropoietin), and calcium, phosphorus, and bone metabolism (1,25-dihydroxycholecalciferol, the most active form of vitamin D).
3. The nephrons perform such miscellaneous functions as catabolism of peptide hormones and synthesis of glucose (gluconeogenesis) in fasting conditions.

When renal disease is present, one or more of these functions may be impaired. For example, the kidney is resistant to the effects of ADH in patients with nephrogenic diabetes insipidus, resulting in an inappropriate increase in water excretion. However, all other renal functions are normal in this disorder. In contrast, there is a generalized decrease in all kidney functions in patients with advanced renal failure. Waste product excretion is reduced, producing elevations in the concentrations of urea and creatinine in the blood; edema, hyperkalemia, and acidemia may result from decreased excretion of water and electrolytes; and anemia and bone disease may occur because of diminished production of erythropoietin and the active form of vitamin D.

However, not all renal functions are impaired with lesser degrees of renal disease. Even if two-thirds of the nephrons are not functioning, clinically significant changes in electrolyte and water balance usually do not occur because of a series of specific adaptations that result in increased solute and water excretion in each of the remaining nephrons. For example, although less sodium is filtered (owing to the decrease in the number of functioning nephrons), sodium excretion remains equal to intake because of an appropriate reduction in tubular reabsorption. Similarly, renal hormone secretion also may be relatively well maintained. In this setting, determination of the GFR and examination of the urine may be the only ways to detect the presence of kidney disease, such as a reduction in functioning renal mass. Since the total GFR is equal to the sum of the filtration rates from each of the functioning nephrons, the loss of two-thirds of the nephrons will lead to a decrease in total GFR, although the net reduction will be less than two-thirds, due to compensatory hyperfiltration in the remaining nephrons (see "Compensatory Glomerular Hyperfiltration," below). Thus, *the GFR can be used to document the presence, estimate the severity, and follow the course of kidney disease.* A decrease in GFR implies either progression of the underlying disease or the development of a superimposed problem such as volume depletion or urinary tract obstruction.

Estimation of the GFR is also helpful in determining the proper dosage of those drugs that are excreted by the kidney. For example, digoxin, used in the treatment of heart failure, and the antibiotic gentamicin are excreted in the urine, primarily by glomerular filtration. When the GFR is reduced, drug excretion will decrease. If the dosage is not appropriately diminished, the drug will accumulate in the body, reaching potentially toxic levels (see Chap. 13).

CREATININE CLEARANCE

The clinical determination of the GFR involves measurement of the rate of urinary excretion of certain compounds. For example, the exogenously administered polysaccharide inulin has the following properties:

1. It is freely filtered at the glomerulus.
2. It is able to achieve a stable plasma concentration.
3. It is not reabsorbed, secreted, or metabolized by the kidney.

In this situation,

$$\text{Filtered inulin} = \text{excreted inulin}$$

The filtered inulin is equal to the GFR times the plasma inulin concentration (P_{in}), and the excreted inulin is equal to the product of the urine inulin concentration (U_{in}) and the urine flow rate (V, in milliliters per minute or liters per day). Therefore,

$$GFR \times P_{in} = U_{in} \times V$$

$$GFR = \frac{U_{in} \times V}{P_{in}}$$

The term $(U_{in} \times V)/P_{in}$ is called the clearance of inulin and is an accurate estimate of the GFR. The inulin clearance, in milliliters per minute, refers to that volume of plasma cleared of inulin by renal excretion. For example, if 1 mg of inulin is excreted per minute ($U_{in} \times V$) and the P_{in} is 1.0 mg/dL (or to keep the units consistent, 0.01 mg/mL), then the clearance of inulin is 100 mL/min; that is, 100 mL of plasma has been cleared of the 1 mg of inulin that it contained.

Despite its accuracy, the inulin clearance is rarely performed clinically because it involves both an intravenous infusion of inulin and an assay for inulin that is not available in most laboratories. Similar technical considerations limit the use of radiolabeled compounds such as iothalamate.[2]

The most widely used method to estimate the GFR is the endogenous creatinine clearance.[3-5] Creatinine is derived from the metabolism of creatine in skeletal muscle and is released into the plasma at a relatively constant rate. As a result, the plasma creatinine concentration (P_{cr}) is very stable, varying less than 10 percent per day in serial observations in normal subjects, even with marked variations in dietary intake.[6] Like inulin, creatinine is freely filtered across the glomerulus and is neither reabsorbed nor metabolized by the kidney. However, a small amount of creatinine enters the urine by tubular secretion in the proximal tubule.[3] Because of this tubular secretion, the amount of creatinine excreted exceeds the amount filtered by 10 to 20 percent in patients with relatively normal renal function. Therefore, the creatinine clearance (C_{cr}),

$$C_{cr} = \frac{U_{cr} \times V}{P_{cr}}$$

will tend to exceed the inulin clearance by 10 to 20 percent. Fortuitously, this is balanced by an error of almost equal magnitude in the measurement of the P_{cr}. The most commonly used method involves a colorimetric reaction after the addition of alkaline picrate. The plasma, but not the urine, contains noncreatinine chromagens (acetone, proteins, ascorbic acid, pyruvate), which account for approximately 10 to 20 percent of the normal P_{cr}.[3] Since both the U_{cr} and P_{cr} are elevated to roughly the same degree, the errors tend to cancel and the C_{cr} is a reasonably accurate estimate of the GFR, particularly if the GFR is greater than 40 mL/min (normal in adults is 95 to 120 mL/min).

However, as renal failure progresses and the total GFR falls, less creatinine is filtered and proportionately more of the urinary creatinine is derived from tubular secretion. As a result, urinary creatinine excretion is much higher than it would be if creatinine were excreted only by glomerular filtration, and the C_{cr} can exceed that of inulin by 10 to 40 percent or more.[3] This error, however, does not substantially detract from the clinical usefulness of the C_{cr}. For example, a C_{cr} of 35 mL/min indicates the presence of moderately severe renal disease. The fact that the GFR (as measured by the inulin clearance) may actually be only 20 to 25 mL/min is not so important since knowledge of the exact GFR is usually not necessary.

The normal values for the creatinine clearance are[3,5]:

1. In men, 120 ± 25 mL/min (about 175 L/day).
2. In women, 95 ± 20 mL/min (about 135 L/day).
3. The creatinine clearance normally declines with age, falling almost 1 mL/min per year over the age of 40.[7]
4. In infants, 17 mL/min per 1.73 m^2 body surface area (the size of the average adult) at birth, increasing to 50 mL/min per 1.73 m^2 by 4 weeks, and to adult levels by 1 year of age (about 100 mL/min per 1.73 m^2).[8,9]

The C_{cr} is usually determined in the following way. Venous blood is used for the P_{cr}. Urinary excretion ($U_{cr} \times V$) is concomitantly measured on a 24-h collection since shorter collections tend to give less reliable results.[10] For example, a 30-year-old woman who weighs 60 kg is being evaluated for possible kidney disease and the following results are obtained:

$$P_{cr} = 1.5 \text{ mg/dL}$$
$$U_{cr} = 100 \text{ mg/dL}$$
$$V = 1080 \text{ mL/day}$$

and

$$\frac{1080 \text{ mL/day}}{1440 \text{ min/day}} = 0.75 \text{ mL/min}$$

Thus

$$C_{cr} = \frac{U_{cr} \times V}{P_{cr}}$$

$$= \frac{100 \times 0.75}{1.5} = 50 \text{ mL/min}$$

Since this is roughly one-half the normal C_{cr}, this patient has lost approximately one-half of her GFR.

The major error involved in the determination of the C_{cr} is an incomplete urine collection. For this reason, it is important to know the normal values for creatinine excretion. In adults under the age of 60, daily creatinine excretion should be 20 to 25 mg/kg lean body weight in males and 15 to 20 mg/kg in females.[3,11] From the ages of 60 to 90, there is a progressive 50 percent reduction in creatinine excretion (from 20 to 10 mg/kg in males), probably due to a decrease in skeletal muscle mass.[11] If creatinine excretion is found to be much less than these values, an incomplete collection should be suspected. In the patient described above, creatinine excretion was 18 mg/kg per day (1080 mg/60 kg), suggesting that a complete collection was obtained.

P_{cr} AND GFR

Changes in, and estimation of, the GFR also can be ascertained from measurement of the P_{cr}, a simpler test to perform than the C_{cr}. In a subject in the steady state,

Creatinine excretion
= creatinine production

Creatinine excretion is roughly equal to the amount of creatinine filtered ($GFR \times P_{cr}$), whereas the rate of creatinine production is relatively constant. If these substitutions are made in the above equation,

$$GFR \times P_{cr} = \text{constant}$$

Thus, *the P_{cr} varies inversely with the GFR.* If, for example, the GFR falls by 50 percent, creatinine excretion also will be reduced. As a result, newly produced creatinine will accumulate in the plasma until the filtered load again equals the rate of production. This will occur when the P_{cr} has doubled,

$$\tfrac{1}{2} GFR \times 2P_{cr} = GFR \times P_{cr} = \text{constant}$$

In adults, the normal P_{cr} is 0.8 to 1.3 mg/dL in men and 0.6 to 1.0 mg/dL in women.*[,3]

*Since children are growing and have an increasing muscle mass, the P_{cr} increases with age. From the ages of 1 to 20, the normal P_{cr} can be estimated from the following formulas[12]:

$$P_{cr} = 0.35 + \text{age (years)}/40 \quad \text{(boys)}$$
$$= 0.35 + \text{age (years)}/55 \quad \text{(girls)}$$

The reciprocal relationship between the GFR and the P_{cr} is depicted in Fig. 1–2. There are three important points to note about this relationship. First, this curve is valid *only in the steady state.* If a patient develops acute renal failure with a sudden drop in the GFR from 120 to 12 mL/min, the P_{cr} on day 1 will still be normal since there will not have been time for creatinine to accumulate in the plasma. After 7 to 10 days, the P_{cr} will stabilize roughly at 10 mg/dL, a level consistent with the reduced GFR. A clinical application of this concept is seen with the use of drugs that are excreted in the urine. When given to patients with renal insufficiency, they should be administered in reduced dosage (see Chap. 13). Nomograms have been devised which relate drug dosage, e.g., for gentamicin, to the P_{cr} on the assumption that the latter is a reflection of the GFR.[13] However, this is true *only* in the steady state. If the above patient with acute renal failure were given gentamicin in full dosage because of the normal P_{cr}, toxic levels would ensue.

It should be remembered that the steady state can be disturbed by changes in creatinine production as well as in GFR. When creatinine production is acutely increased, as with severe muscle breakdown, the P_{cr} can increase out of proportion to any change in GFR.[14] For similar reasons, the P_{cr} should be measured when the patient is fasting, since cooked meat and its broth contain enough creatinine to transiently raise the P_{cr} by as much as 1.0 mg/dL.[15] This can result in a doubling of the P_{cr} and an apparent 50 percent reduction in GFR in a subject with normal renal function.

Second, it is important to note the *shape* of the curve. In a patient with normal renal function, *an apparently minor increase in the* P_{cr} *from 1.0 to 2.0 mg/dL can represent a marked fall in the GFR from 120 to 60 mL/min.* In contrast, in a patient with advanced renal failure, a marked increase in the P_{cr} from 6.0 to 12.0 mg/dL reflects a relatively small reduction in the GFR from 20 to 10 mL/min. Thus, the initial elevation of the P_{cr} represents the major loss in GFR.

Third, the relationship between the GFR and the P_{cr} is dependent upon the rate of creatinine production, which is largely a function of muscle mass. In Fig. 1–2, a normal GFR of 120 mL/min is associated with a P_{cr} of 1.0 g/dL. Although this may be true for a 70-kg man, a similar GFR in a 50-kg woman

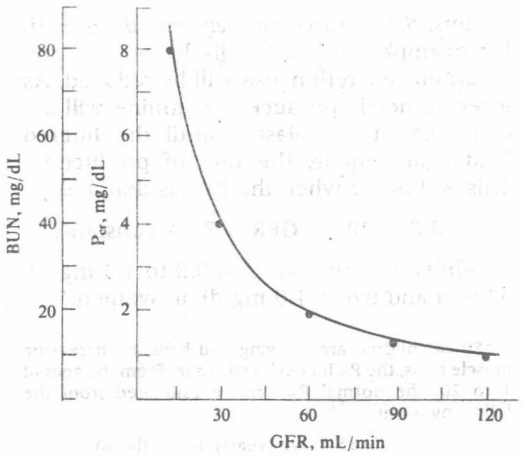

FIG. 1–2. Steady-state relationship between the plasma creatinine concentration (P_{cr}), blood urea nitrogen (BUN), and GFR.

might be associated with a P_{cr} of only 0.6 mg/dL. In this setting, a P_{cr} of 1.0 mg/dL is not normal and reflects a 40 percent fall in GFR.

To account for the effects of body weight, age, and sex on muscle mass, the following formula has been derived to estimate the C_{cr} from the P_{cr} in the steady state in adult men[16]:

$$C_{cr} \cong \frac{(140 - \text{age}) \times \text{lean body weight}}{P_{cr} \times 72}$$

This value should be multiplied by 0.85 in women since a lower fraction of the body weight is composed of muscle. The units of measure used in this formula are: C_{cr}, mL/min; age, years; lean body weight, kg; and P_{cr}, mg/dL.

The results obtained with this formula appear to correlate fairly well with a simultaneously measured C_{cr}. Its usefulness can be illustrated by the observation that a P_{cr} of 1.4 mg/dL represents a C_{cr} of 101 mL/min in an 85-kg, 20-year-old man,

$$C_{cr} \cong \frac{(140 - 20) \times 85}{1.4 \times 72}$$

but a C_{cr} of only 20 mL/min in a 40-kg, 80-year-old woman,

$$C_{cr} \cong \frac{(140 - 80) \times 40}{1.4 \times 72} \times 0.85$$

This example calls attention to the danger of overdosing elderly patients who have seriously impaired renal function despite a relatively normal P_{cr}. The use of this simple formula, while not absolutely accurate, will help to avoid this problem.

In summary, the P_{cr} varies inversely with the GFR in the steady state. Because of this relationship, serial measurements of the P_{cr} can be used to look for disease progression in patients with kidney dysfunction. The loss of functioning nephrons usually is associated with a reduction in the GFR and should result in an increase in the P_{cr}

PREDICTING THE COURSE OF RENAL FAILURE

In many patients with progressive renal disease, the rate of progression is relatively constant. As a result, the GFR should decrease linearly with time. Since the GFR varies inversely with the P_{cr}, the reciprocal of the P_{cr} ($1/P_{cr}$) should also decline at a relatively uniform rate. This prediction has been verified in patients with a variety of chronic renal diseases.[6,17] The manner in which this relationship can be used clinically is illustrated in Fig. 1–3. During the first 2 years of observation, this patient had a progressive reduction in renal function. Maintenance dialysis is usually required shortly after the P_{cr} reaches 10 mg/dL ($1/P_{cr} = 0.1$). By extrapolation, this should have occurred within

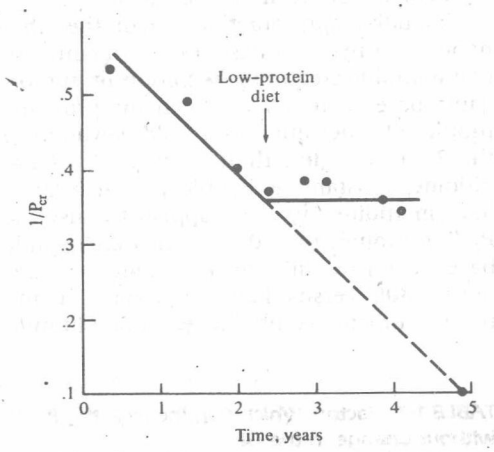

FIG. 1–3. Plot of the reciprocal of the P_{cr} versus time in a man with chronic pyelonephritis. There was a progressive and uniform decline in renal function during the first 2 years of observation. If this course had continued (dashed line), end-stage renal disease ($P_{cr} = 10$ mg/dL, $1/P_{cr} = 0.1$) would have occurred within the next 3 years. However, the institution of a low-protein diet (see "Compensatory Glomerular Hyperfiltration," below) resulted in stabilization of the P_{cr} and, since muscle mass was constant, the total GFR.

the ensuing 2 to 3 years. However, effective therapy was begun at this time, resulting in prolonged stabilization of the P_{cr}.

POTENTIAL ERRORS IN INTERPRETATION OF THE P_{cr}

In a variety of circumstances, the P_{cr} may be elevated without change in the GFR. This can result from increased creatinine production, decreased creatinine secretion, or the presence of compounds in the plasma, which may be measured as creatinine in certain assays (Table 1–1).[14,15,18–23]

Acetoacetic acid, for example, is measured as a noncreatinine chromagen by the alkaline picrate method. This can raise the measured P_{cr} by 0.5 to 2 mg/dL or more in patients with ketoacidosis.[20,21] This effect is rapidly reversed with correction of the ketoacidosis.

Cimetidine and trimethoprim, on the other hand, are organic bases which can competitively inhibit creatinine secretion by the organic base secretory pump in the proximal tubule. The net effect is a mild elevation in the P_{cr} (usually less than 0.5 mg/dL).[18,19] Ranitidine, a histamine (H_2)-receptor antagonist like cimetidine, does not appear to raise the P_{cr}.[24] Although ranitidine is also an organic base, it is generally given in much smaller doses (300 versus 1200 mg/day). The net result is much less tubular secretion of ranitidine and little interference with that of creatinine.[24]

TABLE 1–1. Factors Which Can Increase the P_{cr} without Change in the GFR

Increased creatinine production
Massive rhabdomyolysis[14]
Ingestion of cooked meat and its broth[15]
Compounds which decrease creatinine excretion by competing for secretion by organic base secretory pump
Cimetidine[18]
Trimethoprim[19]
Compounds measured as creatinine in certain assays
Acetoacetic acid in ketoacidosis[20,21]
Cefoxitin[22]
Flucytosine[23]

BLOOD UREA NITROGEN AND GFR

Changes in the GFR also can be detected by changes in the concentration of urea in the blood, measured as the blood urea nitrogen (BUN). Like creatinine, urea is excreted primarily by glomerular filtration and the BUN tends to vary inversely with the GFR (Fig. 1–2).

However, two factors can alter the BUN without change in the GFR or P_{cr}. First, urea production may not be constant. Urea is formed by the hepatic metabolism of amino acids not utilized for protein synthesis. As amino acids are deaminated, ammonia is produced. The development of toxic levels of ammonia in the blood is prevented by the conversion of ammonia (NH_3) into urea in a reaction that can be summarized by the following equation:

$$2NH_3 + CO_2 \rightarrow \underset{\text{Urea}}{H_2N - \overset{\overset{O}{\|}}{C} - NH_2} + H_2O$$

Thus, urea production and the BUN are increased when more amino acids are metabolized in the liver. This may occur with a high-protein diet, enhanced tissue breakdown (due to trauma, gastrointestinal bleeding, or the administration of corticosteroids), or decreased protein synthesis (due to tetracycline).[25] On the other hand, urea production and the BUN are reduced by severe liver disease or a low protein intake.

Second, urea excretion is not determined solely by glomerular filtration. Approximately 40 to 50 percent of the filtered urea is normally reabsorbed by the tubules. The reabsorption of urea tends to follow passively that of sodium and water. Thus, in states of volume depletion in which proximal sodium reabsorption is increased, urea reabsorption