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GOLDMAN'S
CECIL MEDICINE

西氏内科学

第24版

泌尿生殖系统疾病分册

LEE GOLDMAN
ANDREW I. SCHAFER

北京大学医学出版社

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24TH EDITION

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（第24版）

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LEE GOLDMAN, MD

Dean of the Faculties of Health Sciences and Medicine
Executive Vice President for Health and Biomedical Sciences
Harold and Margaret Hatch Professor of the University
Professor of Medicine and of Epidemiology
Columbia University
New York, New York

ANDREW I. SCHAFER, MD

Chairman, Department of Medicine
The E. Hugh Luckey Distinguished Professor of Medicine
Weill Cornell Medical College
Physician-in-Chief
New York-Presbyterian Hospital/Weill Cornell Medical Center
New York, New York

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主　　编： Lee Goldman，Andrew I. Schafer

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ASSOCIATE EDITORS

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PREFACE

The 24TH Edition of *Goldman's Cecil Medicine* symbolizes a time of extraordinary advances in medicine and in technological innovations for the dissemination of information. This textbook and its associated electronic products incorporate the latest medical knowledge in formats that are designed to appeal to learners who prefer to access information in a variety of ways.

The contents of *Cecil* have remained true to the tradition of a comprehensive textbook of medicine that carefully explains the *why* (the underlying normal physiology and pathophysiology of disease, now at the cellular and molecular as well as the organ level) and the *how* (now frequently based on Grade A evidence from randomized controlled trials). Descriptions of physiology and pathophysiology include the latest genetic advances in a practical format that strives to be useful to the nonexpert. Medicine has entered an era when the acuity of illness and the limited time available to evaluate a patient have diminished the ability of physicians to satisfy their intellectual curiosity. As a result, the acquisition of information, quite easily achieved in this era, is often confused with knowledge. We have attempted to counteract this tendency with a textbook that not only informs but also stimulates new questions and gives a glimpse of the future path to new knowledge. Grade A evidence is specifically highlighted in the text and referenced at the end of each chapter. In addition to the information provided in the textbook, the Cecil website supplies expanded content and functionality. In many cases, the full articles referenced in each chapter can be accessed from the Cecil website. The website is also continuously updated to incorporate subsequent Grade A information, other evidence, and new discoveries.

The sections for each organ system begin with a chapter that summarizes an approach to patients with key symptoms, signs, or laboratory abnormalities associated with dysfunction of that organ system. As summarized in Table 1-1, the text specifically provides clear, concise information regarding how a physician should approach more than 100 common symptoms, signs, and laboratory abnormalities, usually with a flow diagram, a table, or both for easy reference. In this way, *Cecil* remains a comprehensive text to guide diagnosis and therapy, not only for patients with suspected or known diseases but also for patients who may have undiagnosed abnormalities that require an initial evaluation.

Just as each edition brings new authors, it also reminds us of our gratitude to past editors and authors. Previous editors of *Cecil Medicine* include a short but remarkably distinguished group of leaders of American medicine: Russell Cecil, Paul Beeson, Walsh McDermott, James Wyngaarden, Lloyd H. Smith, Jr., Fred Plum, J. Claude Bennett, and Dennis Ausiello. As we welcome new associate editors—Wendy Levinson, Donald W. Landry, Anil Rustgi, and W. Michael Scheld—we also express our appreciation to Nicholas LaRusso and other associate editors from the previous editions on whose foundation we have built. Our returning associate editors—William P. Arend, James O. Armitage, David Clemmons, Jeffrey M. Drazen, and Robert C. Griggs—continue to make critical contributions to the selection of authors and the review and approval of all manuscripts. The editors, however, are fully responsible for the book as well as the integration among chapters.

The tradition of *Cecil Medicine* is that all chapters are written by distinguished experts in each field. We are also most grateful for the editorial assistance in New York of Theresa Considine and Silva Sergenian. These individuals and others in our offices have shown extraordinary dedication and equanimity in working with authors and editors to manage the unending flow of manuscripts, figures, and permissions. We also thank Faten Aberra, Reza Akari, Robert C. Brunham, Ivan Ciric, Seema Daulat, Gregory F. Erikson, Kevin Ghassemi, Jason H. Huang, Caron Jacobson, Lisa Kachnic, Bryan T. Kelly, Karen Krok, Heather Lehman, Keiron Leslie, Luis Marcos, Michael Overman, Eric Padron, Bianca Maria Piraccini, Don W. Powell, Katy Ralston, James M. Swain, Tania Thomas, Kirsten Tillisch, Ali Turabi, Mark Whiteford, and Y. Joseph Woo, who contributed to various chapters. At Elsevier, we are most indebted to Dolores Meloni and Linda McKinley, and also thank Cathy Carroll, Taylor Ball, Virginia Wilson, Linda Van Pelt, Suzanne Fannin, and Steve Stave, who have been critical to the planning and production process under the direction of Mary Gatsch. Many of the clinical photographs were supplied by Charles D. Forbes and William F. Jackson, authors of *Color Atlas and Text of Clinical Medicine*, Third Edition, published in 2003 by Elsevier Science Ltd. We thank them for graciously permitting us to include their pictures in our book. We have been exposed to remarkable physicians in our lifetimes and would like to acknowledge the mentorship and support of several of those who exemplify this paradigm—Robert H. Gifford, Lloyd H. Smith, Jr., Frank Gardner, and William Castle. Finally, we would like to thank the Goldman family—Jill, Jeff, Abigail, Mira, Daniel, and Robyn Goldman—and the Schafer family—Pauline, Eric, Pam, John, Evan, and Kate—for their understanding of the time and focus required to edit a book that attempts to sustain the tradition of our predecessors and to meet the needs of today's physician.

LEE GOLDMAN, MD
ANDREW I. SCHAFER, MD

CONTENTS

SECTION XI: RENAL AND GENITOURINARY DISEASES

XI

RENAL AND GENITOURINARY DISEASES

116 APPROACH TO THE PATIENT WITH RENAL DISEASE

DONALD W. LANDRY AND HASAN BAZARI

DIAGNOSIS

The prominent functions of the kidney include the excretion of nitrogenous waste; the regulation of the excretion of sodium, potassium, and acid; and the synthesis of a variety of hormones, including 1,25-dihydroxyvitamin D, erythropoietin, and renin. A patient can have an isolated failure in a particular function, such as in acid excretion (Chapter 120), in which case the "approach to the patient" is distinct for the isolated defect. First and foremost, however, the kidney is a filtration organ, and acute kidney injury (Chapter 122) and chronic kidney disease (Chapter 132) refer specifically to defects in the filtration function of the kidney. In the context of impaired filtration, many of the individual functions may fail.

The approximately 2 million renal glomeruli normally filter about 180 L/day. The renal glomerulus is not simply a filter, but rather a size- and charge-dependent ultrafilter that excludes not only cells but also proteins larger than 60 kD from the ultrafiltrate. Smaller proteins are variably filtered at the glomerulus and endocytosed in the proximal tubule, so that the protein concentration of the urine is normally quite low. Kidney disease reflects a failure in the quantity or quality of the glomerular ultrafiltrate.

The normal glomerular filtration rate (GFR) may decline in hours or a few days in acute kidney injury or over months and years in chronic kidney disease. An acute decline in glomerular filtration is the necessary and sufficient condition for the diagnosis of acute kidney injury, but abnormal urinary findings can assist with elucidating of the etiology of the injury. Proteinuria, ranging from microscopic to the nephrotic range (Chapter 123), and urinary findings, from a few cells per microscopic high-power field to gross hematuria or pyuria, may be the only evidence of the earliest stages of chronic kidney disease. As chronic kidney disease advances, the decline in the GFR progresses until dialysis or transplantation (Chapter 133) is required to forestall or treat the syndrome of uremia.

Serum creatinine is, to a first approximation, neither secreted nor reabsorbed, so the amount appearing in the urine per unit time is a measure of the amount that was filtered at the glomerulus during that period. As a result, the rate of creatinine clearance is, at first approximation, equivalent to the GFR. A decrement in the GFR diminishes creatinine clearance but has no immediate effect on creatinine production by muscle; as a result, the serum creatinine concentration rises. The change in serum creatinine over time indicates the tempo of the renal disease and can distinguish acute injury from chronic kidney disease. Advanced chronic kidney disease (Chapter 132) is commonly associated with anemia, renal osteodystrophy, and a small kidney size on ultrasonography, although kidney size may be normal or increased with amyloidosis or diabetes mellitus. Hyperphosphatemia, which develops within 1 or 2 weeks after acute kidney injury, is less useful as a discriminator of acute versus chronic renal injury.

The serum creatinine level is elevated in both acute and chronic kidney disease, but an actively rising serum creatinine level confirms an acute or acute-on-chronic insult to kidney function. As a blood filtration organ, the kidney is susceptible to an acute compromise of renal arterial perfusion (Chapter 127), such as prerenal kidney injury, or blockage in urine outflow, such as urinary obstruction owing to benign prostatic hypertrophy (Chapter 131). The intrarenal causes of acute kidney injury (Chapter 122) include acute tubular necrosis, acute interstitial nephritis, acute glomerulonephritis, and acute vasculitis and vascular disease. Dysmorphic red blood cells in the urine or clumps of cells in the form of the renal tubules, so-called tubular casts, suggest the site of the lesion and narrow the range of potential etiologies.

Most of the diagnoses of renal disease can be made with a careful history and physical examination supplemented by review of basic laboratory tests, especially the urinary sediment. The specificity of the diagnosis can be improved by the use of serologic analysis, imaging, and, occasionally, invasive procedures such as angiography and renal biopsy.

History

The history reviews potential factors that contribute to the development of renal disease and identifies the systemic features of diseases that may affect the kidney. These factors include the following:

- Medication use
- Family history of renal disease
- The time of onset of symptoms of renal dysfunction
- Changes in bladder function, including nocturia, polyuria, and hesitancy
- Fatigue and weakness
- Dyspnea on exertion, a manifestation of fluid overload or acidosis
- Systemic features of vasculitis

A systemic vasculitis may present in a variety of ways, with skin manifestations including petechial rash, purpura, digital gangrene, and splinter hemorrhages. Otitis, sinusitis, epistaxis, hemoptysis, and nasal septal ulcers are common manifestations of Wegener's granulomatosis (Chapter 278). Pulmonary hemorrhage can be a catastrophic manifestation of Goodpasture's syndrome (Chapter 123) or anti–glomerular basement membrane (anti-GBM) disease. Abdominal distention may be seen in nephrotic syndrome with ascites, as well as in autosomal polycystic kidney disease (Chapter 129). Abdominal pain and tenderness and gastrointestinal hemorrhage may be observed in Henoch-Schönlein purpura and classic polyarteritis nodosa (Chapter 278). Lower extremity edema is common in cirrhosis (Chapter 156), heart failure (Chapter 58), and nephrotic syndrome (Chapter 123). Neurologic symptoms may be a manifestation of vasculitis, such as microscopic polyangiitis (Chapter 278) and cryoglobulinemia (Chapter 193).

Physical Examination

The vital signs are crucial. A patient with a "normal blood pressure" may be relatively hypotensive in the setting of renovascular disease. Orthostatic hypotension may explain the acute decompensation of kidney function in a patient with chronic kidney disease (Chapter 132). Pulsus paradoxus may reflect cardiac tamponade (Chapter 77).

The eyes may exhibit conjunctivitis, episcleritis, or uveitis. In the abdomen, ascites may be seen in cirrhosis, nephrosis, and heart failure. Hepatomegaly is seen in passive congestion and amyloidosis (Chapter 194). Splenomegaly may be seen in amyloidosis, endocarditis (Chapter 76), and lymphoma (Chapters 191 and 192). Kidney and liver enlargement may be seen in autosomal dominant polycystic kidney disease. Lower extremity edema can be seen in cirrhosis, nephrotic syndrome, and heart failure. Splinter hemorrhages, as well as Osler nodes and Janeway lesions, may represent bacterial endocarditis. Rashes can be seen in many of the vasculitides.

Cardiovascular Signs

Assessment of the jugular venous pressure (Chapter 50) can play a crucial role in the bedside evaluation of volume status. The presence of a pericardial friction rub can be observed in the serositis associated with systemic lupus erythematosus (SLE; Chapter 274) or the pericarditis associated with uremia (Chapter 132). Infiltrative diseases, such as amyloidosis and sarcoidosis (Chapter 95), can lead to restrictive cardiomyopathy with associated heart failure. The presence of a fourth heart sound (S_4) may be a sign of cardiac hypertrophy, and S_3 may be a sign of heart failure. Vascular bruits reflect generalized atherosclerosis, and the presence of an abdominal bruit may be an important clue to the presence of renovascular disease (Chapter 127).

Neurologic Signs

Peripheral neuropathy may be seen in vasculitis with involvement of the nerves as mononeuritis multiplex. Frank cerebrovascular accidents may be seen in SLE and in the antiphospholipid antibody syndrome (Chapter 179).

The signs and symptoms of chronic renal failure are shown in Figure 116-1.

Laboratory Findings

Measurement of Renal Function

Renal function is routinely assessed in clinical practice by the measurement of serum creatinine. Creatine is released as a waste product from myocytes and converted to creatinine in the liver. The normal range of serum creatinine is 0.6 to 1.5 mg/dL, and the value for a given patient is relatively fixed in the absence of a change in renal function. About 90% of the daily production of creatinine is excreted through glomerular filtration and the remainder by tubular secretion. Mild elevations of the plasma creatinine concentration can

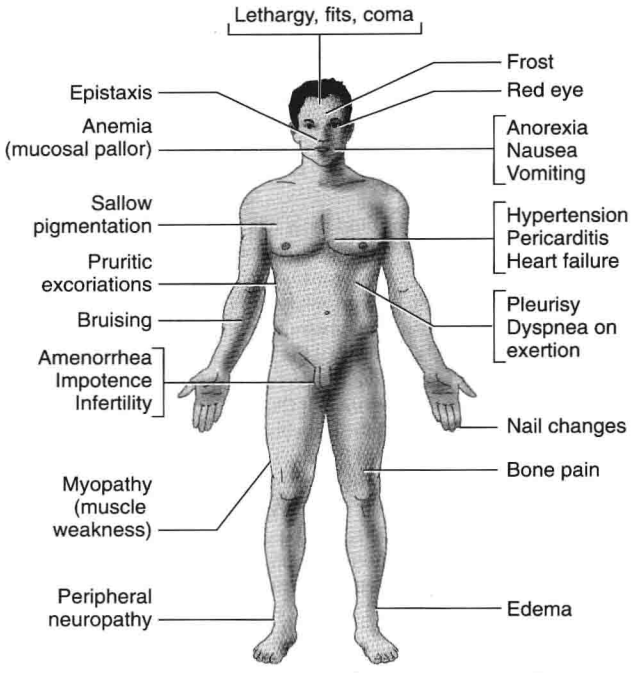

FIGURE 116-1. Common symptoms and signs of chronic renal failure. (Redrawn from Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*, 3rd ed. London: Mosby; 2003.)

occur during treatment with cimetidine or trimethoprim, both of which interfere with the tubular secretion of creatinine, but neither is likely to cause significant elevations of the plasma creatinine level. Ketoacids (Chapter 236) can cause an artifactual increase in the plasma creatinine by interfering with the creatinine assay. The reciprocal relationship between the GFR and the serum creatinine level explains why the serum creatinine concentration will rise but still remain in the normal range despite a substantial loss of renal function. The concentration of blood urea nitrogen (BUN), which is a product of protein catabolism, is about ten-fold higher than the creatinine concentration; because the BUN-to-creatinine ratio commonly rises with arterial underfilling, the BUN typically is used as a marker of effective volume status. The BUN may be inappropriately high in other circumstances, however, such as with gastrointestinal bleeding or the use of steroids or tetracyclines. The BUN may be low in patients who have a poor dietary intake of protein or who have liver disease.

The creatinine clearance can be estimated from the serum creatinine concentration by the Cockcroft-Gault formula:

$$\text{GFR} = \frac{(140 - \text{age}) \times \text{weight [in kg]}}{72 \times \text{serum creatinine}} (\times 0.85 \text{ if female})$$

Creatinine clearance often is calculated using a 24-hour urine collection for measurement of the creatinine concentration. The patient must be instructed to discard the first-morning urine before initiating the collection and to conclude the collection by including the next morning void. The formula for calculating creatinine clearance is as follows:

$$\text{CCr} = (\text{urine Cr} \times \text{V})/(\text{plasma Cr})$$

where *CCr* is creatinine clearance, *urine Cr* is urine creatinine concentration, *V* is urine flow rate, and *plasma Cr* is plasma creatinine. The creatinine clearance overestimates GFR by about 10% owing to tubular secretion of creatinine. This secretion can be modified by the use of cimetidine, which is a competitive inhibitor of tubular creatinine secretion.

Inulin, a 5200-D uncharged polymer of fructose, is an ideal marker for the measurement of GFR because it is not reabsorbed, secreted, synthesized, or metabolized. It is not available for routine clinical assessment, however. Iothalamate clearance is an accurate measurement of GFR and is available as a diagnostic tool in clinical studies. Other agents that are used for the measurement of GFR include technetium-99m diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) and chromium 51-labeled ethylenediaminetetraacetic acid.

Urine Tests

The following aspects of the assessment of the urine are important in the approach to the patient with renal disease.

Twenty-Four-Hour Urine Collection for Protein Excretion

Proteinuria (as albuminuria) of greater than 3.5 g in 24 hours generally indicates glomerular disease (Chapter 123). Lesser quantities do not preclude glomerular disease, and electrophoresis gives valuable insight into the composition of the proteinuria (Chapter 193). Occasionally, overflow proteinuria of a low-molecular-weight protein, such as light chains in Bence Jones proteinuria, can be greater than 3.5 g/day without any of the manifestations or implications of the nephrotic syndrome; a urine protein electrophoresis study is important in making the distinction. Collection must be done by discarding the first morning void and collecting all urine output for the next 24 hours, including the first morning void the next day.

Protein-to-Creatinine Ratio

The 24-hour urine collection for protein excretion is cumbersome and subject to inaccuracies. Instead, a spot urine sample for protein and creatinine can be used to estimate the amount of protein excreted. A protein-to-creatinine ratio of 3 estimates that the 24-hour protein excretion is about 3 g. The ratio may be inaccurate in patients with orthostatic proteinuria.

Urine for Microalbumin

The excretion of abnormal quantities of albumin below the level detectable by the urine dipstick is called *microalbuminuria*. Normal albumin excretion, which is less than 30 mg/day, is best detected by radioimmunoassay or enzyme immunoassay. Microalbuminuria is the earliest clinically detectable stage of diabetic nephropathy (Chapter 126).

Fractional Excretion of Sodium

The excretion of sodium in the setting of oliguria and acute kidney injury (Chapter 122) often gives insight into the appropriateness of tubular function. The fractional excretion of sodium (Fe_{Na}) is calculated as follows:

$$Fe_{Na} = (\text{urine Na}/\text{plasma Na})/(\text{urine Cr}/\text{plasma Cr}) \times 100$$

where *Na* is the sodium concentration (in millimoles per liter [mmol/L]), and *Cr* is the creatinine concentration (in mmol/L). In the setting of oliguria, an Fe_{Na} of less than 1% often denotes prerenal azotemia, whereas an Fe_{Na} of greater than 1% denotes intrinsic renal damage. Although this measurement is generally useful, an Fe_{Na} of less than 1% may be seen without evidence of a prerenal component, including contrast nephropathy, hepatorenal syndrome (Chapter 157), obstructive uropathy (Chapter 125), interstitial nephritis (Chapter 124), glomerulonephritis (Chapter 123), and rhabdomyolysis (Chapter 115). Conversely, a high Fe_{Na} can be seen in cases in which there is a prerenal component, including diuretic use, adrenal insufficiency, cerebral salt wasting, and salt-wasting nephropathy (Chapter 118). The Fe_{Na} must be evaluated in the context of the clinical situation because it can be low or high in a normal patient or in a patient with chronic kidney disease. Ultimately, volume assessment is done best by assessing the patient at the bedside and cannot be deduced from a measurement of electrolytes.

Fractional Excretion of Urea

Urea reabsorption varies with volume status, increasing in the setting of volume depletion. A fractional excretion of urea less than 30% indicates a state of decreased effective circulating volume. The formula for calculation of the fractional excretion of urea is as analogous to that of Fe_{Na}.

Twenty-Four-Hour Urine for Calcium, Uric Acid, Oxalate, and Citrate

These studies are performed in the evaluation of the patient with recurrent kidney stones (Chapter 128). Depending on the laboratory, the calcium measurement may be made on a different collection from the others. These measurements should be conducted with the patient on a normal diet and with normal activity, and they should not be done during a hospitalization. Often these tests need to be repeated before therapeutic decisions are made. The 24-hour urine creatinine excretion should be determined with each measurement to ensure an adequate collection.

Urine Potassium Excretion

Potassium is handled differently than sodium. Potassium is completely reabsorbed and then secreted in a flow-dependent manner. Secretion depends on

adequate distal sodium delivery and reabsorption to provide a sufficient electrochemical gradient for tubular potassium excretion (Chapter 119). The excretion of less than 15 mmol/day of potassium in the face of hyperkalemia suggests an inadequate renal response. The transtubular potassium gradient (TTKG) is an approximation of the gradient of potassium before the effect of antidiuretic hormone on the concentration of potassium in the urine. The formula for the measurement of the TTKG is as follows:

$$\text{TTKG} = (\text{urine K}/\text{plasma K})/(\text{urine Osm}/\text{plasma Osm})$$

where *K* is the potassium concentration and *Osm* is osmolality. A TTKG ratio of less than 4 in the setting of hyperkalemia implies either inadequate distal sodium delivery or inadequate distal potassium excretion system. A TTKG ratio of greater than 10 in the setting of hypokalemia supports the presence of renal potassium wasting, and further elucidation of the exact stimulus for potassium loss is warranted.

Urine Net Charge

Urine net charge measures the ability of the kidney to synthesize ammonia (NH_4^+) and to excrete acid in non–anion gap metabolic acidosis. The difference between the concentration of urine cations (Na^+ and K^+) and that of urine anions (mainly Cl^-) represents the urine net charge.

$$\text{Urine net charge} = (\text{urine } Na^+ + \text{urine } K^+) - (\text{urine } Cl^-)$$

A negative urine net charge indicates NH_4^+ in the urine. This formula does not apply when an unmeasured anion is present in the urine in a patient with an anion gap metabolic acidosis (Chapter 120).

Urinalysis

The analysis of the urine sample involves simple observation and separate measurements using specific tools or commercially available dipsticks.

Appearance and Color

The normal color of the urine is derived from urochromes, which are pigments excreted in the urine. Abnormal color or appearance of the urine may be explained by many conditions (Table 116-1).

TABLE 116-1

APPEARANCE	CAUSE
Milky	Acid urine: urate crystals Alkaline urine: insoluble phosphates Infection: pus Spermatozoa Chyluria
Smoky pink	Hematuria (>0.54 mL blood/L urine)
Foamy	Proteinuria
Blue or green	*Pseudomonas* urinary tract infection Bilirubin Methylene blue
Pink or red	Aniline dyes in sweets Porphyrins (on standing) Blood, hemoglobin, myoglobin Drugs: phenindione, phenolphthalein Anthocyaninuria (beetroot, "beeturia")
Orange	Drugs: anthraquinones (laxatives), rifampicin Urobilinogenuria
Yellow	Mepacrine Conjugated bilirubin Phenacetin Riboflavin
Brown or black	Melanin (on standing) Myoglobin (on standing) Alkaptonuria
Green or black	Phenol Lysol
Brown	Drugs: phenazopyridine, furazolidone, L-dopa, niridazole Hemoglobin and myoglobin (on standing) Bilirubin

From Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*, 3rd ed. London: Mosby; 2003.

Specific Gravity

The specific gravity of the urine generally is related linearly with osmolality. However, it can be raised by the presence of molecules with relatively high molecular weight, such as glucose or contrast dye. A fixed specific gravity of 1.010, so called isosthenuria, is characteristic of chronic kidney disease (Chapter 132).

pH

Urine pH typically is 5 as a result of daily net acid excretion. An alkaline pH often is noted after meals, when an "alkaline tide" to balance gastric acid excretion increases urine pH. A high urine pH also is seen in patients who are on a vegetarian diet. An exceptionally high urine pH is indicative of an infection with a urea-splitting organism, such as *Proteus* species (Chapter 292). An inappropriately high urine pH in the setting of systemic non–anion gap metabolic acidosis may be seen in certain forms of renal tubular acidosis (RTA; Chapter 130). In a proximal RTA, the urine pH is high until the tubular reabsorption threshold for bicarbonate, which is abnormally low, is reached. At this point, the urine pH decreases to 5. In distal RTA, the inability to create a sufficient gradient for hydrogen ions results in a urine pH that is always higher than 5.5; the urine net charge gives complementary and confirmatory information. In type 4 RTA, the urine pH is often 5, and the urine net charge is often positive, thereby confirming the absence of significant amounts of ammonium in the urine; this defect is exacerbated by the accompanying hyperkalemia.

Glucose

Glucose in the urine is detected by an assay using dipsticks impregnated with the enzyme glucose oxidase. Glycosuria is seen in diabetes mellitus (Chapter 236), when pregnancy causes the tubular threshold for glucose reabsorption to change, and in tubular diseases that affect the proximal convoluted tubule and cause tubular glycosuria. Evidence for pan-proximal tubular dysfunction (e.g., glycosuria, aminoaciduria, phosphaturia) indicates that Fanconi's syndrome is present.

Protein

The dipstick for protein is a sensitive assay based on color change induced by the presence of proteins at a given pH. It is most sensitive to the presence of albumin and is much less sensitive to other proteins, such as the light chains of Bence Jones protein (Chapter 193). The presence of 1+ protein correlates with about 30 mg/dL of albuminuria, and 3+ protein correlates with greater than 500 mg/dL of proteinuria. Because the dipstick is not a quantitative measurement, small amounts of proteinuria in an oliguric patient may give the false appearance of high-grade proteinuria.

Heme

The dipstick for heme uses the peroxidase-like activity of hemoglobin and myoglobin molecules to detect the presence of heme pigment. The reaction occurs on exposure to hemoglobin, myoglobin, or intact red blood cells (RBCs). The presence of myoglobin, which is found in patients with rhabdomyolysis (Chapter 115), or free hemoglobin, which is seen in patients with intravascular hemolytic anemias (Chapter 163), is suspected if the heme reaction is intensely positive and there is a paucity of cellular elements in the sediment.

Leukocytes

The dipstick detection of leukocytes depends on the presence of leukocyte esterase. Leukocyte esterase is usually present in infections (Chapter 292) and in inflammatory conditions.

Urine Sediment

Cells

RBCs, white blood cells (WBCs), tubular cells, transitional cells, and squamous epithelial cells may be seen in the urine. Casts are formed in tubules and may contain cells or cellular debris, or may be acellular.

RBCs may originate from intrarenal vessels, glomeruli, tubules, or anywhere in the urogenital tract. Dysmorphic RBCs are cells that have been deformed by transit through the glomerulus and through the medullary interstitium, as opposed to RBCs from the remainder of the genitourinary tract (Figs. 116-2 and 116-3); these cells are often lysed and less refractile than nonglomerular RBCs. Dysmorphic RBCs often fragment with poikilocytosis and with blebs, forming so-called Mickey Mouse RBCs. Phase contrast microscopy aids in the identification of dysmorphic RBCs. The presence of

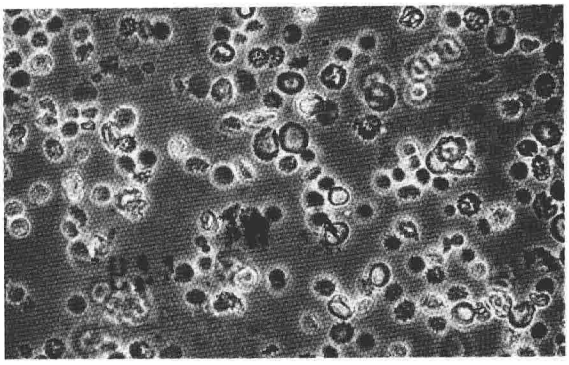

FIGURE 116-2. Dysmorphic erythrocytes. These dysmorphic erythrocytes vary in size, shape, and hemoglobin content and reflect glomerular bleeding. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

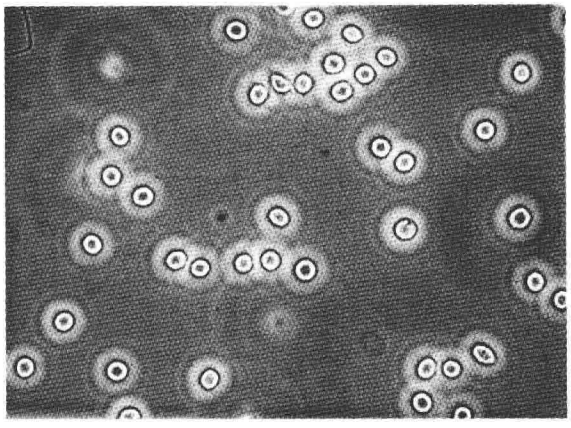

FIGURE 116-3. Isomorphic erythrocytes. These erythrocytes are similar in size, shape, and hemoglobin content. Isomorphic cells reflect nonglomerular bleeding from lesions such as calculi or papillomas or hemorrhage from cysts in polycystic renal disease. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

a majority of dysmorphic RBCs in a urine sediment points to a glomerular origin of the hematuria. The presence of RBC casts is often conclusive evidence for the presence of glomerulonephritis.

WBCs are seen most commonly in urinary tract infections, but they also can be seen in acute interstitial nephritis, with *Legionella* (Chapter 322) and *Leptospira* (Chapter 331) species infections, chronic infections such as tuberculosis (Chapter 332), allergic interstitial nephritis (Chapter 124), atheroembolic diseases (Chapter 127), and granulomatous diseases such as sarcoidosis (Chapter 95) and tubulointerstitial nephritis uveitis syndrome. Mononuclear cells often appear with transplant rejection. Tubular cells, which are seen in many conditions involving tubulointerstitial diseases, also are seen in ischemic and nephrotoxic injury, such as with myeloma kidney (Chapter 193) or cast nephropathy. Eosinophils require special stains, with the Giemsa stain being much less sensitive than the Hansel stain (Chapter 124). Urine eosinophils classically are seen in allergic interstitial nephritis (Chapter 124), but they also are seen in atheroembolic disease (Chapter 127), prostatitis (Chapter 131), and vasculitis.

Other Elements

Bacteria may be seen in the urine sediment. A spun urine sediment may show rods or cocci in chains, but bacteria are identified best by Gram staining of the urine sediment. Budding yeast forms, which are highly refractile, trichomonads, and spermatozoa also may be seen in the urinary sediment.

Casts

Casts, which are formed in tubules, are characterized by the arrangement of the cells in a clearly formed matrix composed of Tamm-Horsfall protein. Because casts are formed in the renal parenchyma, they may give a clue to the origin of accompanying cellular elements.

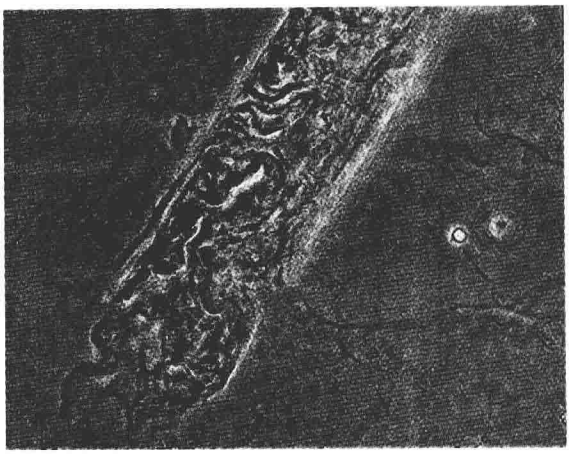

FIGURE 116-4. Hyaline cast of the type seen in small numbers in normal urine. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

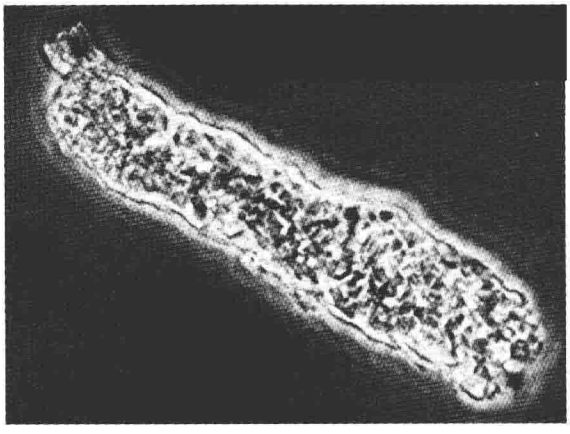

FIGURE 116-5. Number and type of granules and their density in the cast vary in different casts. The presence of erythrocytes in this cast may mean that the granules are derived partly from disrupted erythrocytes. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

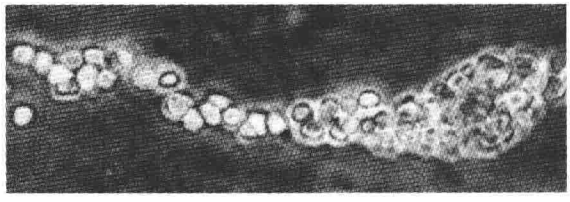

FIGURE 116-6. A cast composed entirely of erythrocytes reflects heavy hematuria and active glomerular disease. Crescentic nephritis is likely to be present if erythrocyte cast density is greater than 100/mL. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

Hyaline casts are composed of Tamm-Horsfall proteins that are formed normally and are seen in increased numbers after exercise (Fig. 116-4). *Granular casts* are degenerated tubular cell casts that are seen in the setting of tubular injury (Fig. 116-5). *Pigmented granular casts* are seen in rhabdomyolysis (Chapter 115) with myoglobinuria or, rarely, hemoglobinuria. *RBC casts* (Fig. 116-6) are rarely seen in allergic interstitial nephritis and diabetic nephropathy, but they are frequently seen in acute glomerulonephritis (Chapter 123). The presence of RBC casts in a patient with microscopic hematuria can narrow the focus of the evaluation to a glomerular lesion. *WBC casts* are seen commonly in pyelonephritis (Chapter 292) and in acute and chronic nonbacterial infections. They also are seen in other conditions in which WBCs are associated with parenchymal renal processes, such as allergic interstitial nephritis (Chapter 124), atheroembolic diseases (Chapter

FIGURE 116-7. Typical hexagonal cystine crystal. A single crystal provides a definitive diagnosis of cystinuria. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

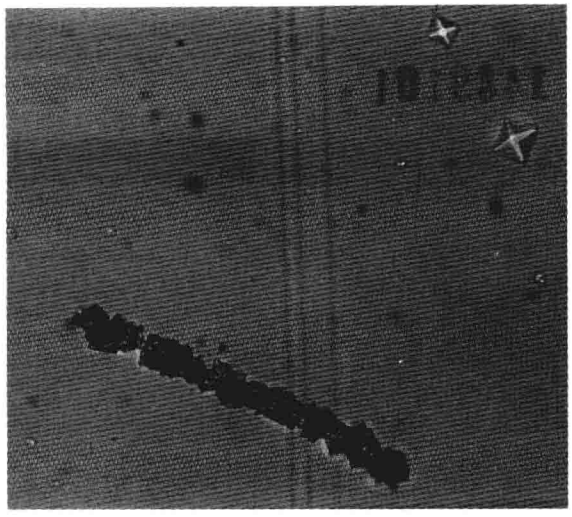

FIGURE 116-8. Oxalate crystals. A pseudocast of calcium oxalate crystals accompanied by crystals of calcium oxalate dehydrate. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

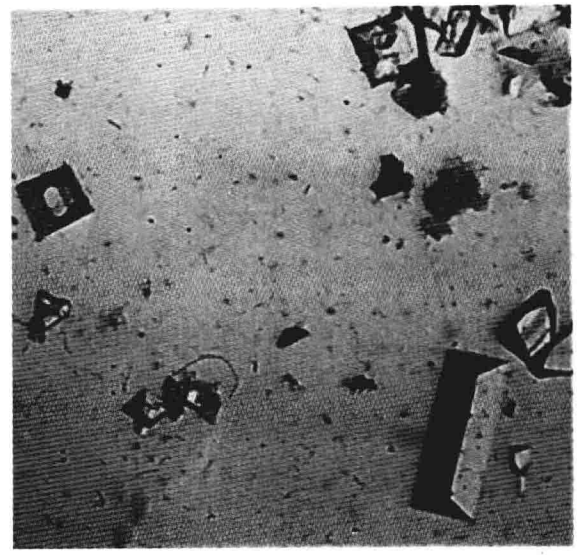

FIGURE 116-9. Coffin-lid crystals of magnesium ammonium phosphate (struvite). (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

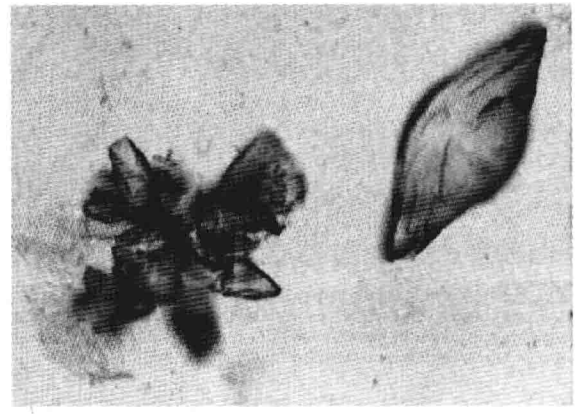

FIGURE 116-10. Urate crystals. Complex crystals suggestive of acute urate nephropathy or urate nephrolithiasis. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

127), and granulomatous diseases such as sarcoidosis (Chapter 95). Rarely, WBC casts can be a dominant feature of many diseases that traditionally are thought of as glomerular diseases, such as SLE (Chapter 274) and Wegener's granulomatosis (Chapter 278). *Tubular cell casts* are seen with any acute tubular injury and are the dominant cellular casts in ischemic acute tubular necrosis (Chapter 122). They also can be seen with nephrotoxic injury, such as with aminoglycosides and cisplatin. Some casts may contain both leukocytes and tubular cells or be difficult to distinguish.

Crystals

Crystals can be a normal finding in the urine or serve as clues to pathophysiologic processes. Certain crystals, such as the hexagonal crystals seen with cystinuria (Chapter 130), are always abnormal (Fig. 116-7). Others, such as the octahedral calcium oxalate crystals (Fig. 116-8), may be a normal finding or may be evidence for ethylene glycol intoxication (Chapter 110). Triple phosphate crystals, which are composed of ammonium magnesium phosphate and are coffin shaped (Fig. 116-9), are seen in urinary tract infections with urea-splitting organisms (Chapter 292). Uric acid crystals, sodium urate crystals (Fig. 116-10), and calcium phosphate amorphous crystals are common and do not have pathologic significance.

Serologies for the Evaluation of Renal Disease

The evaluation of renal dysfunction has to follow a stepwise progression from noninvasive serologic evaluation to a definitive or confirmatory diagnostic evaluation, such as a renal biopsy. Sometimes an expeditious diagnosis is needed, and a biopsy may be done relatively early in the evaluation. Serologic diagnostic markers for certain diseases, such as Wegener's granulomatosis (Chapter 278), can sometimes avoid the need for a diagnostic renal biopsy in patients with renal insufficiency.

Antinuclear Antibody

An antinuclear antibody (ANA) can be useful to evaluate glomerular disease, especially the nephrotic syndrome. A high ANA titer (e.g., 1:320), especially if it is accompanied by a more specific finding such as anti-double-stranded DNA (anti-dsDNA) antibody or anti-Smith antibody, can be highly specific for the diagnosis of SLE renal disease (Chapter 274), which usually requires a renal biopsy. Lower titers (e.g., 1:80 or 1:40) are nonspecific.

Rheumatoid Factor

A rheumatoid factor titer will usually be elevated in patients with rheumatoid arthritis, but vasculitis is a relatively late and rare event. Rheumatoid factor can be detected in cryoglobulinemia (Chapter 193); immunoglobulin M (IgM), which is present in type II and type III cryoglobulinemia, has rheumatoid factor activity. Rheumatoid factor also can be seen as a nonspecific finding in bacterial endocarditis (Chapter 76) and systemic vasculitis (Chapter 278).

Complement

The levels of complement components C3 and C4 and the 50% hemolyzing dose of complement (CH_{50}) usually are measured in the evaluation of suspected rapidly progressive glomerulonephritis (Chapter 123). Complement levels are usually low in active SLE (Chapter 274), poststreptococcal glomerulonephritis (Chapter 123), endocarditis (Chapter 76), membranoproliferative glomerulonephritis, cryoglobulinemia (Chapter 193), shunt nephritis, and glomerulonephritis associated with visceral abscesses. A

particularly depressed C4 compared with C3 should raise the suspicion of cryoglobulinemia.

Serum and Urine Immunoelectrophoresis and Bence Jones Protein

Elevated polyclonal IgA levels are seen in about 50% of cases of IgA nephropathy (Chapter 123) and Henoch-Schönlein purpura (Chapter 123). Polyclonal elevation of IgG may occur in a variety of systemic diseases and is a nonspecific finding. The presence of a monoclonal protein in the serum should raise the suspicion for a monoclonal gammopathy–associated disease (Chapter 193). The differential diagnosis includes monoclonal gammopathy of uncertain significance, myeloma kidney, lymphomas (Chapter 191), amyloidosis (Chapter 194), light chain deposition disease, heavy chain deposition disease, immunotactoid glomerulonephritis, and cryoglobulinemia. The concentration of the monoclonal protein is higher when the diagnosis of multiple myeloma is made, but even small quantities of Bence Jones proteins in the serum can have clinical significance. Because a substantial fraction of multiple myelomas can have no heavy chain excretion and small quantities of light chains may be hard to detect by serum immunoelectrophoresis, a urine immunoelectrophoresis always should be obtained concomitantly to ensure a complete evaluation. A new, more sensitive assay for serum free light chains and an assessment of the ratio of kappa to lambda lights chains increase the sensitivity for detecting monoclonal gammopathies.

A urine test for Bence Jones protein complements the serum immunoelectrophoresis. Patients may have Bence Jones proteinuria even in the absence of an M component in the serum immunoelectrophoresis. Bence Jones proteinuria may be present in myeloma kidney, amyloidosis, light chain deposition disease, lymphoma, or, occasionally, monoclonal gammopathy of uncertain significance. However, many patients with systemic amyloidosis have a normal serum immunoelectrophoresis and no Bence Jones proteinuria (Chapter 193).

Antineutrophil Cytoplasmic Antibody

The antineutrophil cytoplasmic antibody (ANCA) assay has allowed for earlier and more definitive recognition of one of the most common causes of rapidly progressive glomerulonephritis. The ANCA test, when confirmed by enzyme-linked immunosorbent assay (ELISA), is highly sensitive and specific for a group of vasculitides (Chapter 278). The antibodies are present in the serum of the affected patient and cause two different patterns of staining: perinuclear staining (p-ANCA) and cytoplasmic staining (c-ANCA). Both antigens actually have a cytoplasmic distribution, and the former pattern is an artifact of the fixation method. The antigen for p-ANCA is myeloperoxidase, and the antigen for c-ANCA is proteinase-3. p-ANCA is associated with microscopic polyangiitis, idiopathic crescentic glomerulonephritis, or Churg-Strauss syndrome (Chapter 278). The c-ANCA serology result often correlates with the classic disease of Wegener's granulomatosis (Chapter 278). Immunofluorescence is highly sensitive but is not specific, unless used with ELISA and Western blotting. In the appropriate clinical setting, it can avoid the need for renal biopsy. Anti-GBM antibody staining also may occur in the presence of a positive ANCA, the significance of which is unclear. It is speculated that exposure of the Goodpasture antigen, as a result of the glomerular injury, leads to anti-GBM antibody formation as a secondary process.

Anti–Glomerular Basement Membrane Antibody

Anti-GBM antibodies are autoantibodies to the Goodpasture antigen, which resides in a domain of the α chain of type 4 collagen. An early and accurate diagnosis of Goodpasture's syndrome can be made by immunofluorescence and confirmed by Western blot analysis.

Cryoglobulins

Cryoglobulins (Chapter 193) are thermolabile immunoglobulins of single monoclonal type (type I cryoglobulinemia); in type II and type III cryoglobulinemia, the mixture of immunoglobulins includes one with rheumatoid factor activity against IgG. Type I and type II cryoglobulins are more likely to be associated with clinical disease, especially at higher titers. In type II cryoglobulinemia, the monoclonal component has rheumatoid factor activity and is often an IgM κ M component. Type III cryoglobulinemia is often of less clinical significance. Type I cryoglobulinemia is seen with Waldenström's macroglobulinemia and multiple myeloma (Chapter 193); type II, with hepatitis C infection (Chapters 150 and 151), Sjögren's syndrome (Chapter 276), lymphomas (Chapters 191 and 192), and SLE (Chapter 274); and type III, with hepatitis C (Chapters 150 and 151), chronic infections, and inflammatory conditions. When cryoglobulinemia is associated with hepatitis C, the hepatitis C virus (HCV) RNA is concentrated in the cryoprecipitate; the diagnosis can be made by an RNA assay of the cryoprecipitate at 37° C.

Other Serologies

Membranous nephropathy is associated with chronic hepatitis B infection with hepatitis B surface antigenemia (Chapter 151). Classic polyarteritis nodosa (Chapter 278) occasionally is seen with chronic hepatitis B infection, often with surface antigenemia and hepatitis B e-antigenemia.

Hepatitis C serology is associated with a variety of renal entities, including cryoglobulinemia, membranoproliferative glomerulonephritis, and membranous nephropathy. The evaluation may include the antibody test and an assay for HCV RNA. Occasionally, the HCV RNA analysis may have to be conducted on the cryoprecipitate at 37° C.

Human immunodeficiency virus (HIV)-associated nephropathy (Chapter 123) is associated with nephrotic syndrome and acute kidney injury. In the appropriate clinical setting, HIV serology and viral titers are appropriate tests for both clinical syndromes.

Streptococcal infection can be confirmed as the cause of postinfectious glomerulonephritis (Chapter 123) with an anti-DNase or antistreptolysin assay. Acute and convalescent serology assays are used to confirm recent infection.

Erythrocyte Sedimentation Rate

The erythrocyte sedimentation rate (ESR) is a relatively nonspecific test in the evaluation of renal disease. However, a high ESR often points to systemic vasculitis (Chapter 278), multiple myeloma (Chapter 193), or malignancy as the underlying cause. However, the ESR often is elevated in the nephrotic syndrome (Chapter 123), including diabetic nephropathy (Chapter 126).

Noninvasive Imaging

A variety of renal imaging techniques can assist in the evaluation of diseases of the kidney. Of note is that plain films and intravenous pyelography largely have been replaced by renal ultrasonography and computed tomography (CT) for the evaluation of renal size and the detection of stones and masses.

Renal Ultrasonography

Ultrasonography, which is the most commonly used renal imaging study (Fig. 116-11), provides reliable information regarding obstruction, renal size, the presence of masses, and renal echotexture. The study has only 90% sensitivity for the detection of hydronephrosis, however, and is not sufficient to exclude obstruction with certainty. Additionally, its inability to detect stones in the ureters and bladder limits its utility in the evaluation for kidney stones. Doppler imaging permits evaluation of the renal vessels and resistive index.

Computed Tomography

A stone protocol CT scan of the kidneys, ureter, and bladder has become the study of choice for the detection of kidney stones (Chapter 128) because of its ability to detect stones of all kinds, including uric acid stones and nonobstructing stones in the ureters (Fig. 116-12). Masses in the kidney can be evaluated using either contrast CT or a renal ultrasound. CT angiography with iodinated contrast material can assess possible renal artery stenosis

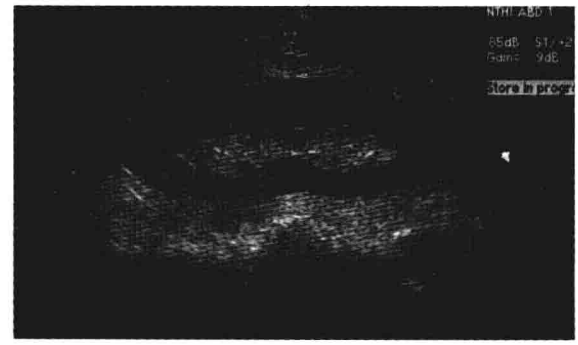

FIGURE 116-11. Normal sagittal renal ultrasound. The cortex is hypoechoic compared with the echogenic fat containing the renal sinus. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

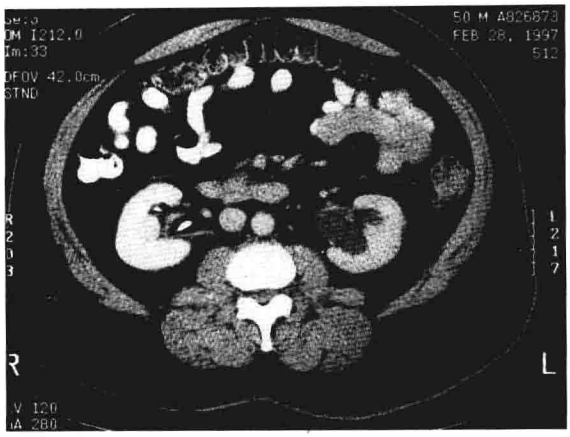

FIGURE 116-12. Delayed excretion in the left kidney secondary to a distal calculus. Contrast-enhanced computed tomography scan shows dilated left renal pelvis. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

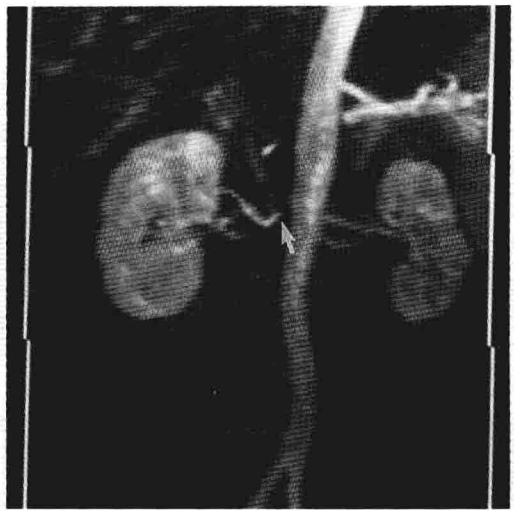

FIGURE 116-13. Magnetic resonance angiography. Coronal three-dimensional image shows right renal artery stenosis *(arrow)*. (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

(Chapter 127) with an accuracy comparable to magnetic resonance (MR) angiography.

Magnetic Resonance Imaging with Magnetic Resonance Angiography

Magnetic resonance imaging (MRI) with MR angiography (Fig. 116-13) is highly sensitive for detecting atherosclerotic renovascular disease (Chapter 127), but it tends to overestimate the degree of stenosis. Its accuracy in detecting fibromuscular dysplasia, however, is less well validated. MRI also can be used to evaluate renal masses. MRI does not require iodinated contrast material, but gadolinium-based contrast agents for vascular studies are associated with the syndrome of nephrogenic systemic fibrosis in patients with renal failure (Chapter 275).

Renography

The uptake by the kidneys of ^{99m}Tc-DTPA, as a marker of GFR, and mercaptoacetyl triglycine, as a marker of renal blood flow, can help evaluate patients with suspected renovascular disease. However, neither is commonly used now that CT angiography and MR angiography are widely available.

Invasive Evaluation

Renal Angiography

Renal arteriography, which is the gold standard in the evaluation of renal artery stenosis (Chapter 127), also is used for the evaluation of arteriovenous malformations, polyarteritis nodosa, and other vascular lesions of the kidneys. This invasive study uses iodinated contrast material and incurs a small risk for atheroembolic disease (Chapter 127). Therapeutic angioplasty and stenting can be done at the time of the angiogram.

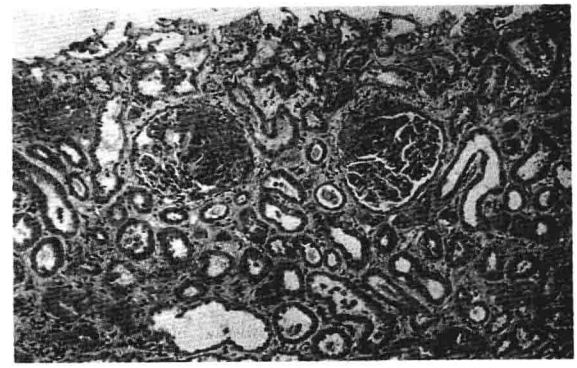

FIGURE 116-14. Systemic lupus erythematosus. This renal biopsy specimen shows proliferative change and crescent formation in both glomeruli (hematoxylin and eosin stain; magnification, 116×). (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

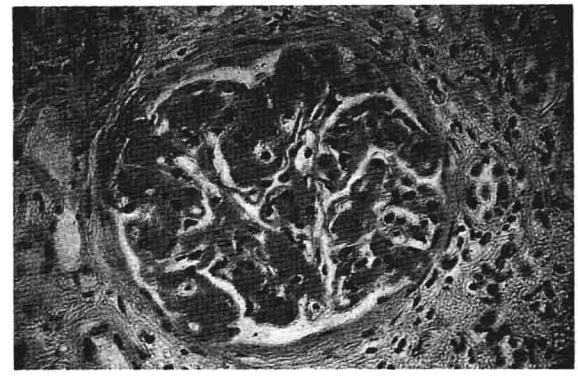

FIGURE 116-15. Renal amyloidosis. The glomerulus shows amyloid deposition, stained by Congo red, in the glomerular capillaries (magnification, 330×). (From Johnson RJ, Feehally J. *Comprehensive Clinical Nephrology*. London: Mosby; 2000.)

Renal Biopsy

Renal biopsy usually is performed percutaneously with real-time ultrasound or CT guidance. The risk for bleeding that requires a transfusion is 1 to 2% in patients without coagulopathy. The transjugular approach can be used in patients in whom the risks for bleeding are high. Current indications for renal biopsy include the following:

1. Rapidly progressive glomerulonephritis. Biopsy is generally indicated for ANCA-related vasculitis unless the case is classic, such as red blood cell casts and renal dysfunction. For patients with cryoglobulinemia and SLE, biopsy is recommended to stratify patients before therapy.
2. SLE with renal involvement to categorize the degree of nephropathy, which cannot be assessed based on clinical criteria (Fig. 116-14). A repeat biopsy is indicated if a change in immunosuppressive therapy is planned and the clinical picture is at all ambiguous (e.g., serum creatinine, urine sediment, and proteinuria are in good control but anti-DNA antibody titers remain high).
3. Nephrotic syndrome without an obvious cause. In childhood nephrotic syndrome, empirical steroid therapy is used routinely because of the high prevalence of steroid-responsive minimal change disease. In adults, the approach generally is to use the biopsy to guide appropriate therapy (Fig. 116-15).
4. Unexplained renal failure of any cause, especially if immunosuppressive therapy is contemplated. Patients with hospital-acquired renal failure rarely require renal biopsy.
5. Unexplained proteinuria below the nephrotic range to exclude nephrosis in evolution. Biopsy is recommended if proteinuria exceeds 1 g per 24 hours or occurs in the setting of a reduced GFR.

6. Renal transplantation with acute and chronic renal failure, in which the biopsy information can be crucial in guiding diagnosis and treatment.

MAJOR RENAL SYNDROMES

Renal disease can be divided logically into major overlapping categories, which are used to characterize the most common renal syndromes.

Acute Kidney Injury

Acute kidney injury (Chapter 122) is a syndrome in which glomerular filtration declines over a period of hours to days. The patient with acute renal failure is approached best by evaluation for prerenal, renal, and postrenal causes. Most cases of acute renal failure in the hospital have hemodynamic or toxic etiologies. The careful and systematic evaluation of the patient should start with a thorough history and physical examination, which should be followed by selected laboratory tests and often an imaging test, such as renal ultrasonography.

Nephritic Syndrome

The acute nephritic syndrome is an uncommon but dramatic presentation of an acute glomerulonephritis (Chapter 123). The hallmark of the acute nephritic syndrome is the presence of dysmorphic RBCs and RBC casts, but their absence does not exclude the syndrome. The acute nephritic syndrome can be caused by any of the rapidly progressive glomerulonephropathies, all of which warrant urgent and usually inpatient evaluation.

Nephrotic Syndrome

The nephrotic syndrome (Chapter 123) is characterized by the presence of proteinuria of greater than 3.5 g/day/1.73 m^2, with accompanying edema, hypertension, and hyperlipidemia. Other consequences include a predisposition to infection and hypercoagulability. In general, the diseases associated with nephrotic syndrome do not cause acute kidney injury, although acute kidney injury may be seen with minimal change disease, HIV-associated nephropathy, and bilateral renal vein thrombosis (Chapter 127). The causes of primary idiopathic nephrotic syndrome, in decreasing order of prevalence, are focal and segmental glomerulosclerosis, membranous nephropathy, minimal change disease, and membranoproliferative glomerulonephritis. Secondary causes of the nephrotic syndrome include diabetic nephropathy (Chapter 126), amyloidosis (Chapter 194), and SLE (Chapter 274) with membranous nephropathy.

Tubulointerstitial Diseases

Tubulointerstitial diseases (Chapter 124) vary in presentation from acute kidney injury to chronic kidney dysfunction that manifests as asymptotic mild renal insufficiency (Table 116-2). The urine sediment often contains small-to-moderate amounts of proteinuria, usually less than 1 g/day, as well as WBCs, RBCs, tubular cells, and WBC casts. RBC casts are rare in acute interstitial nephritis and are more characteristic of glomerular disease.

Vascular Diseases of the Kidney

Vascular diseases of the kidney can be divided into large-vessel obstruction and medium- to small-vessel diseases (Chapter 127). Renovascular disease is a common cause of hypertension, heart failure, and renal insufficiency. About 90% of renal artery stenosis is atherosclerotic in origin, with most of the remaining caused by fibromuscular dysplasia, which is more common in women 20 to 50 years of age. Medium-sized arterial vessel diseases include polyarteritis nodosa, which is seen in patients with hepatitis B, HIV infection, or, rarely, hepatitis C. Symptoms include abdominal pain, hypertension, and mild renal insufficiency, often with a benign sediment; diagnostic findings include microaneurysms at the bifurcation of medium-sized arteries. Other diseases involving small vessels include atheroembolic disease (Chapter 127), which is seen either spontaneously or after arteriography or surgery; this syndrome typically affects the kidneys, gastrointestinal tract, and lower extremities, but it can also involve the central nervous system when the aortic arch is affected.

The thrombotic microangiopathies include hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura (Chapter 174). Thrombocytopenic purpura is associated with an acquired inhibitor to, or the congenital inherited absence of, a protease that cleaves large-molecular-weight von Willebrand multimers. Hemolytic-uremic syndrome is caused by endothelial injury induced by Shiga toxin from *Escherichia coli* O157:H7 infection. The antiphospholipid antibody syndrome (Chapter 179) can cause large vessel thrombosis and stenosis as well as a thrombotic microangiopathy with proteinuria, hypertension, and renal insufficiency. Scleroderma renal crisis, which is a manifestation of systemic sclerosis (Chapter 275), often leads to an inexorable progression to end-stage renal insufficiency if it is untreated.

TABLE 116-2

Ischemic and toxic acute tubular necrosis
Allergic interstitial nephritis
Interstitial nephritis secondary to immune complex–related collagen vascular disease, such as Sjögren's disease or systemic lupus erythematosus
Granulomatous diseases: sarcoidosis, tubulointerstitial nephritis with uveitis
Pigment-related tubular injury: myoglobulinuria, hemoglobinuria
Hypercalcemia with nephrocalcinosis
Tubular obstruction: drugs such as indinavir, uric acid in tumor lysis syndrome
Myeloma kidney or cast nephropathy
Infection-related interstitial nephritis: *Legionella, Leptospira* species
Infiltrative diseases, such as lymphoma

Papillary Necrosis

Acute necrosis of the renal papilla is associated with sickle cell anemia (Chapter 166), analgesic nephropathy (Chapter 124), diabetic nephropathy (Chapter 126), and obstructive pyelonephritis (Chapter 125). In sickle cell disease (Chapter 166), the hypoxic and hypertonic milieu of the inner medulla promotes sickling, and chronic sickling at the vasa recta results in medullary ischemia. Massive and prolonged consumption of analgesics, particularly the combination of aspirin, caffeine, and acetaminophen, is associated with chronic interstitial nephritis and a predisposition to papillary necrosis (Chapter 124); medullary ischemia is thought to be caused by inhibition of synthesis of vasodilatory prostaglandins by aspirin, and direct toxicity is attributed to metabolites of phenacetin. Similarly, medullary perfusion is thought to be compromised in diabetic nephropathy (Chapter 126) and obstructive pyelonephritis (Chapter 125).

The clinical manifestations of papillary necrosis can include flank pain and hematuria. If the papilla is sloughed, obstruction may occur at the renal pelvis or ureter of the affected kidney, with referred pain migrating from the flank to the groin. A sloughed papilla may precipitate frank renal failure if the function of the contralateral kidney is impaired or if obstruction occurs at the level of the bladder or urethra (Chapter 125).

Classically, papillary necrosis is diagnosed on an excretory pyelogram as a calyceal defect after sloughing of a papilla, but CT with contrast is as good for advanced lesions. If the necrotic papilla is retained, however, the defect will be more subtle. Transitional cell carcinoma (Chapter 203) can occur in the setting of papillary necrosis or can mimic its appearance. Obstruction, if present, must be relieved, but treatment otherwise is limited to pain control and hydration.

Chronic Kidney Disease

Chronic kidney disease, which is defined as either kidney damage or a GFR of less than 60 mL/min/1.73 m^2 for longer than 3 months, includes five stages (Table 116-3). Kidney damage is defined as pathologic abnormalities or markers of kidney damage, including abnormalities in the composition of blood or urine or abnormalities on imaging tests. The excretion of 30 to 300 mg of albumin in a 24-hour period defines microalbuminuria. An estimated 12% of the adult U.S. population has abnormal albumin excretion in the urine, and the frequency increases with age. Kidney failure is defined as either a GFR of less than 15 mL/min/1.73 m^2 that is accompanied by signs and symptoms of uremia or a need for initiation of kidney replacement therapy for treatment of complications of decreased GFR. End-stage renal disease includes all cases requiring treatment by dialysis or transplantation regardless of the level of GFR.

Patients with chronic kidney disease warrant referral to a nephrologist. Care of these patients should focus on efforts to slow disease progression, optimize medical management, and make a seamless transition to renal replacement therapy (Chapter 132). The care should include optimal blood pressure control, use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers if indicated, dietary counseling, careful management of calcium and phosphorus levels, control of the parathyroid hormone level, and management of anemia with the use of erythropoietin and iron supplements. Early referral for placement of access for dialysis and initiation of

TABLE 116-3 STAGES OF CHRONIC KIDNEY DISEASE

STAGE	DESCRIPTION	GFR (mL/min/1.73 m²)
1	Kidney damage with normal or ↑GFR	≥90
2	Kidney damage with mild or ↓GFR	60-89
3	Moderate ↓GFR	30-59
4	Severe ↓GFR	15-29
5	Kidney failure	<15 (or dialysis)

*Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m² for ≥3 months. Kidney damage is defined as pathologic abnormalities or presence of markers of damage, including abnormalities in blood or urine tests or image studies.
GFR = glomerular filtration rate.
From http://www.kidney.org/kidneydisease/ckd/knowGFR.cfm. Accessed Jan. 31, 2010.

transplant evaluation (Chapter 133) are important components of the care of patients with chronic kidney disease.

SUGGESTED READINGS

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117 STRUCTURE AND FUNCTION OF THE KIDNEYS

QAIS AL-AWQATI AND JONATHAN BARASCH

The kidney regulates the ionic composition and volume of body fluids, the excretion of nitrogenous waste, the elimination of exogenous molecules (e.g., many drugs), the synthesis of a variety of hormones (e.g., erythropoietin), and the metabolism of low-molecular-weight proteins (e.g., insulin). Befitting such an array of responsibilities, the kidney receives 25% of the cardiac output. The gross anatomy of the kidney is notable for a weight of approximately 150 g and a characteristic bean shape with approximate dimensions of 11 × 6 × 2.5 cm. On bisection, a simple gross structure is evident with an outer cortex and a more central medulla that narrows to multiple papillae at the apices of so-called pyramids (Fig. 117-1).

Understanding the kidney, however, requires an appreciation of the intricate microstructure that underlies its complex functions. The kidney is a composite organ comprising approximately 1 million essentially identical functional units termed *nephrons*. All the functions of the kidney are performed by each individual nephron, and at a first approximation, all nephrons are independent of each other because they have their own innervation and blood supply. The nephron is made up of two functional subunits, the glomerulus and the following tubules and ducts (Fig. 117-2). The glomerulus begins with the branching of the afferent arteriole, an end artery of the corresponding renal artery, to a tuft of capillaries. The glomerular capillaries invaginate an epithelium with the visceral epithelial cells adjacent to the capillary and the parietal epithelial cells outside this tuft. The space between the epithelial layers is the urinary space. The fenestrated glomerular capillary endothelium, the intervening basement membrane, and the foot processes of the visceral epithelium, so-called podocytes, make up the glomerular filtration barrier. The balance of hydrostatic and oncotic pressures drives the extrusion of a protein-free filtrate through this barrier into the urinary space. The urinary space then leads to a series of tubules and ducts: the proximal tubule, the thin limb of the loop of Henle, the thick limb of the loop of Henle,

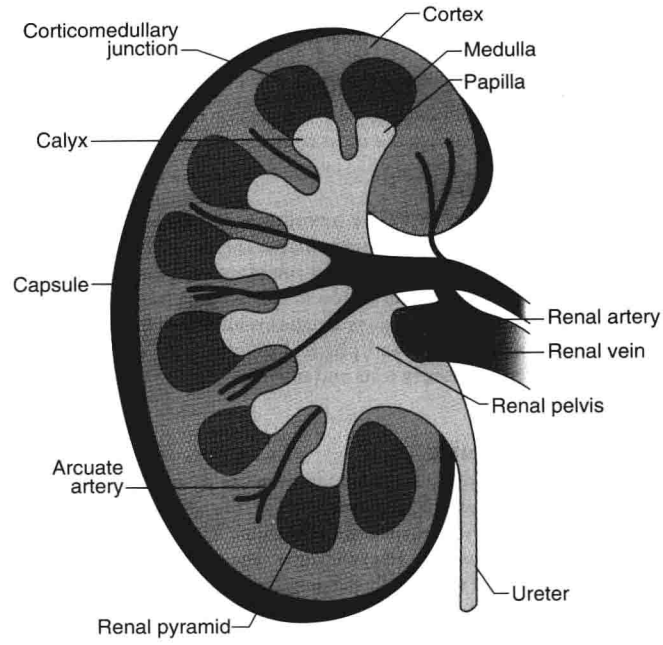

FIGURE 117-1. Sagittal section of the human kidney depicting gross anatomy and organization.

the distal convoluted tubule, the cortical collecting duct, and the medullary collecting duct. The papillary collecting duct empties through the renal papilla into the renal pelvis and then to the ureter. The glomerular capillary bed coalesces to form the efferent arteriole, a vessel that is exquisitely sensitive to angiotensin II, and then to the peri (proximal) tubular capillaries. This system allows efferent arteriole constriction to regulate proximal tubule reabsorption, as described later.

The nephron regulates homeostasis by three actions. First, in the glomerulus, nephrons produce as much as 120 mL/minute of an ultrafiltrate of blood. Second, in different segments of the nephron, the composition of the filtrate is altered by the transfer of nearly 99% of its components (e.g., glucose, NaCl, water) from the lumen to the blood. Third, additional electrolytes (e.g., NH_4^+, K^+, HCO_3^-) are secreted from the blood into the lumen.

To perform these functions, each nephron segment, with the exception of the collecting ducts, is composed of a single epithelial cell type whose luminal or apical surface (facing the urine) and basolateral surface (facing the blood) differentially express various proteins and lipids. For example, the apical membrane often has microvilli or cilia, whereas the basolateral membrane does not. Apical polarized endocytosis and exocytosis are often important in the regulation of the number of transport proteins on the apical surface. In addition, epithelia are connected to one another by tight junctions, which confer a characteristic ionic permeability on the epithelial sheet. Transepithelial transport occurs largely through the cell, but transport through the tight junction (the *paracellular pathway*) can also be important in different segments of the tubule. For instance, Na transport begins with entry at the luminal surface down an electrochemical gradient, whereas its exit at the basolateral surface is uphill and requires adenosine triphosphate (ATP) hydrolysis. The Na^+, K^+-ATPase is located at the basolateral surface of all epithelia, and all "active" energy-consuming transport is coupled directly or indirectly to it with the exception of H^+ transport. Each segment has a distinct composition of channels, carriers, and ATPases, and each segment is regulated by different chemical and physical sensors, so the "final urine" contains the components that must be discarded to maintain constancy of body composition.

THE KIDNEY REGULATES EXTRACELLULAR FLUID VOLUME BY REGULATING ITS SODIUM CONTENT

Filtration of 180 L/day containing 24,000 mEq of Na^+ is followed by the reabsorption of more than 99% of the filtered Na^+. Na^+ reabsorption accounts for more than 90% of oxygen consumed by the kidney. Na^+ reabsorption is regulated by volume receptors, which are located in the carotid artery and

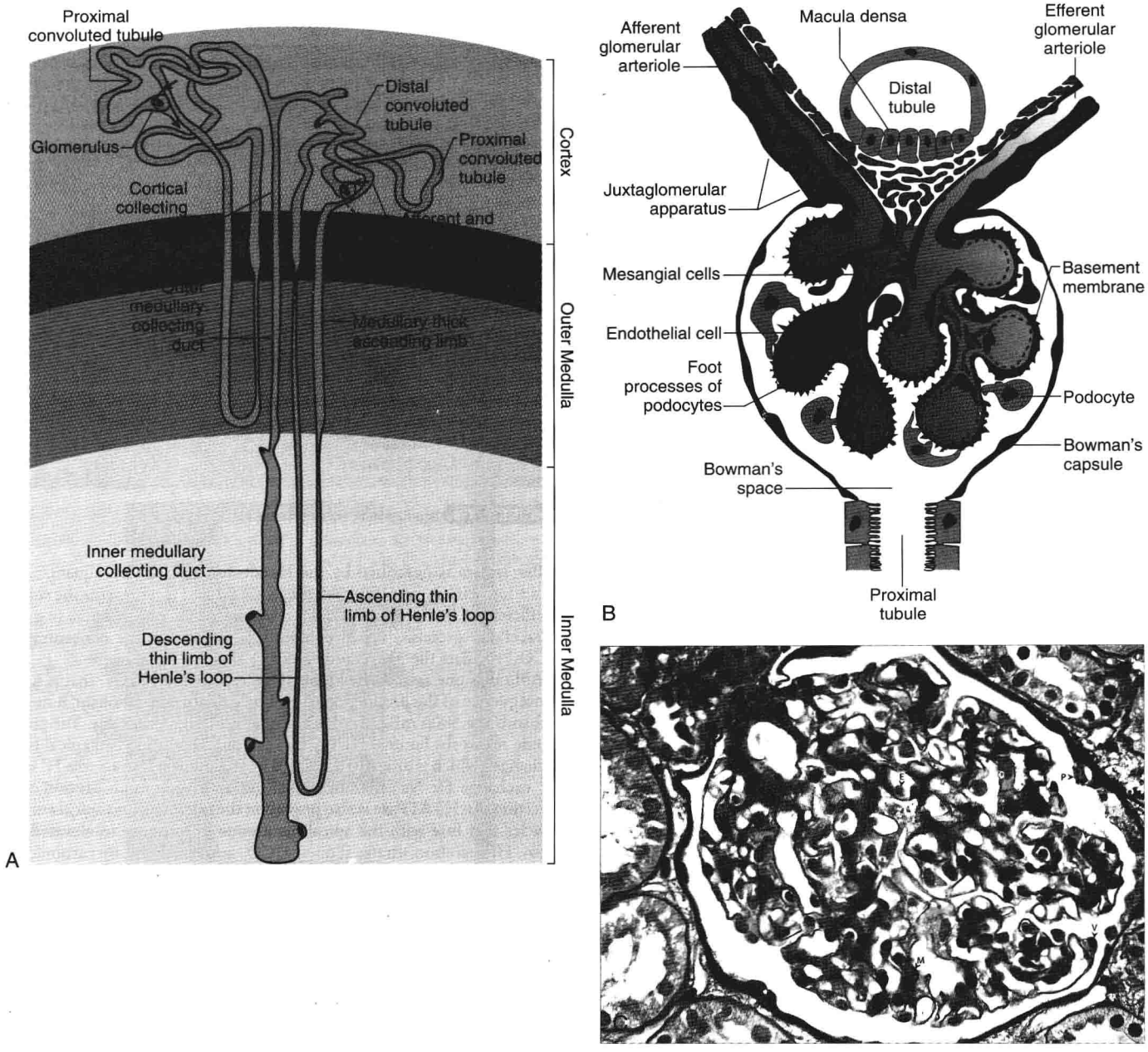

FIGURE 117-2. Structure of the nephron. A, Components of the cortical and juxtaglomerular nephrons. **B,** Anatomy of the glomerulus. **C,** Light micrograph of a human glomerulus. E = endothelial cell; M = mesangial cell; P = parietal epithelial cell; V = visceral epithelial cell. (**C,** Courtesy of Dr. Glen Markowitz.)

increase β-sympathetic output, which in turn release renin, an aspartate protease from the granular cells of the juxtaglomerular apparatus. The renin-releasing cells are close to the afferent arterioles, where renin cleaves angiotensinogen to angiotensin I, which is then converted locally to angiotensin II. Angiotensin II binds to angiotensin receptors and constricts the efferent arteriole, thereby affecting glomerular hemodynamics. The increased hydrostatic pressure within the glomerular capillaries drives the formation of an ultrafiltrate of plasma. As filtration progresses, a protein-rich, oncotically active solution in the capillary opposes the glomerular capillary hydrostatic pressure until a pressure equilibrium is achieved before the efferent arteriole is reached. Consequently, angiotensin II may not change glomerular filtration rate (GFR) markedly, but it can increase proximal reabsorption by reducing the hydrostatic pressure and increasing the oncotic pressure in the peritubular capillaries that surround the proximal tubule in a plexus, thereby favoring reabsorption of water and solutes such as urea.

The glomerular filtrate next enters the tubular portion of the nephron, where Na^+ traverses the cell by entering the apical membrane either through a cotransporter or countertransporter or through an Na^+ channel, depending on the specific mechanisms of different segments. In the apical membrane of the proximal tubule, an Na^+/H^+ (NHE_3) exchanger, an Na-coupled glucose carrier, and an Na^+-coupled amino acid and phosphate cotransporter are present. Subsequently, Na^+ is actively transported by the basolateral Na^+, K^+-ATPase into the paracellular space, thereby resulting in local hypertonicity, which causes osmosis through low-resistance tight junctions of the initial segments of the proximal tubule (Fig. 117-3).

In the thick ascending limb of Henle, Na^+ is absorbed by an NaK-2Cl cotransporter. The driving force for this neutral carrier allows Na^+ and Cl^- to enter the cell, but K^+ is then recycled across the apical membrane, thereby resulting in depolarization of the transepithelial membrane potential. In the distal convoluted tubule, Na^+ is absorbed by a thiazide-sensitive cotransporter, which conducts Na^+ and Cl^- in a strict 1:1 stoichiometry. Na^+ exits as usual by the Na^+, K^+-ATPase, but there is also a basolateral Na/Ca exchanger. In this short segment, the macula densa helps control the GFR by regulating renin release through secretion of adenosine and prostaglandins.

In the principal cells of the collecting duct, aldosterone, derived from the zona glomerulosa of the adrenal cortex, increases reabsorption of the final 50 to 100 mEq/day of Na^+ remaining in the lumen by increasing the number of open Na^+ channels (ENac), by activating expression of α-subunits, and by