Manual of Nephrology

Diagnosis and Therapy

Second Edition

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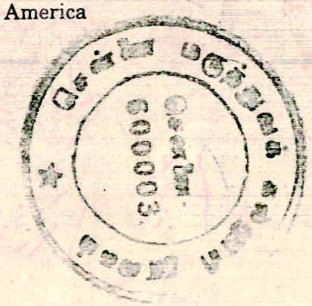

Preface

The first edition of *Manual of Nephrology: Diagnosis and Therapy* was written explicitly for the primary care physician. This updated edition maintains that emphasis.

A practical approach to *diagnosis* and *therapy* constitutes the focal point of the Manual. Our companion text, *Renal and Electrolyte Disorders* (3rd ed.), due for publication by Little, Brown in 1985, emphasizes the importance of an understanding of the pathophysiology of disease. Although there is overlap in the areas discussed in these two texts, the approaches differ considerably. *Manual of Nephrology* avoids the discussion of pathophysiology of disease and instead addresses a number of important clinical problems from a diagnostic, therapeutic, and cost-effective viewpoint.

For example, Dr. Fredric L. Coe presents a practical approach to the diagnostic evaluation and treatment of the patient with renal stones, and Dr. L. Barth Reller discusses urinary tract infections. Dr. Michael J. Dunn deals with the practical and cost-effective diagnosis and treatment of the hypertensive patient. Drs. Robert E. Cronin and Ronald B. Miller discuss the diagnosis and management of the patient with acute or chronic elevation in blood urea nitrogen and/or serum creatinine. Dr. Miller also discusses many practical points that the primary care physician should know concerning modalities for treatment of end-stage renal disease by dialysis or transplantation. This information will allow the physician to participate in a more knowledgeable way with the patient, the family, and the nephrologist in making important decisions about modes of treatment of end-stage renal disease. Diagnostic and therapeutic approaches to various electrolyte and acid-base problems are presented in a systematic manner for (1) the edematous patient (Dr. Mortimer Levy), (2) hypo- and hypernatremia (Dr. Robert W. Schrier), (3) hypo- and hyperkalemia (Dr. Richard L. Tannen), (4) elevation and depression of serum bicarbonate (Dr. Jordan J. Cohen), and (5) hypo- and hypercalcemia and hypo- and hyperphosphatemia (Drs. Zalman S. Agus, Stanley Goldfarb, and Alan Wasserstein).

What constitutes a practical approach to the evaluation of the patient with hematuria and /or proteinuria is discussed by Drs. Antoine M. de Torrenté and Robert J. Anderson. For example, the question of which patients with hematuria should have cystoscopy, renal biopsy, or renal angiogram is examined. How the physician should alter drug therapy in the patient with renal disease is discussed by Dr. William M. Bennett. Drs. Marshall D. Lindheimer and Adrian I. Katz present a practical approach to management of the pregnant patient who has hypertension or renal disease, or both. They also discuss which patients the physician should advise not to become pregnant because of either danger to the mother or the prospect of worsening of renal disease. Lastly, many sophisticated and expensive radiologic procedures besides excretory urography (e.g., ultrasonography, computerized tomography, cyst puncture, renal scan, renal angiography) are available now. Drs. Robert A. Older, Larry M. Crane, Daniel E. Wertman, and Hector Hidalgo present a practical and systematic approach for the use of these procedures in the evaluation of the patient with a renal mass, renal failure, urinary tract obstruction, hematuria, renal transplant, renal and perirenal infection, or renal hypertension. The authors of these chapters were invited by the editor to contribute to the Manual

not because of their sophistication in the science of medicine, although sophisticated scientists they are, but because they are physicians who are able to use their scientific knowledge in a practical way to allow for a cost-effective plan of therapy and treatment that is in the best interests of their patients. In this same spirit I would like once again to dedicate this to Professor Hugh de Wardener, a humane physican, a man of science, and above all, a practical man whose uncanny ability to focus on important issues in many areas, including sodium and water metabolism, bone disease, chronic dialysis, and hypertension, has benefited medical science and his patients for over 35 years.

R.W.S.

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Chapter 14

Manual of Nephrology

Diagnosis and Therapy

Notice

The indications and dosages of all drugs in this book have been recommended in the medical literature and conform to the practices of the general medical community. The medications described do not necessarily have specific approval by the Food and Drug Administration for use in the diseases and dosages for which they are recommended. The package insert for each drug should be consulted for use and dosage as approved by the FDA. Because standards for usage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

1 The Edematous Patient

Mortimer Levy

I. **Types of edema.** *Edema* refers to an excessive collection of fluid within the interstitial space (i.e., within the nonvascular portion of the extracellular fluid volume). Edema itself is not a disease but a symptom of many different disorders that share as a common feature the propensity to induce fluid collection within the interstitial space. Edema may be localized or generalized.

A. **Localized edema.** Localized edema occurs when alterations of the Starling forces are restricted to a given organ or discrete vascular territory. Fluid collects locally because of either an increment in capillary hydrostatic pressure (induced by arteriolar dilatation or, more commonly, venous obstruction) or some obstruction to regional lymphatic flow. Less commonly, there may be some increase in capillary wall permeability, resulting from either trauma or histamine release. Alternatively, a generalized disturbance such as hypoalbuminemia may find clinical expression only as localized ankle edema because of postural considerations. Depending on the magnitude of the local disturbance, the edema may vary in volume from barely detectable amounts to several hundred milliliters of fluid. Although conceptually there may be a period of transient plasma volume contraction and urinary sodium retention in these patients, by the time they are seen by their physicians they are generally free of urinary sodium retention or any alteration of systemic or renal hemodynamics.

Clinical causes of localized edema include:

1. Inflammation
2. Trauma (burns)
3. Venous obstruction (thrombophlebitis)
4. Lymphatic obstruction (postsurgical or metastatic)
5. Angioedema

B. **Generalized edema.** Generalized edema can occur when the potential for fluid to leave the vascular space exists for all vascular beds within the body. Depending on the nature of the underlying disease, postural influences, and magnitude of the underlying disorder, however, fluid may be detected only in a single site, such as the lungs (pulmonary edema) or lower extremities. Patients confined to bed may preferentially collect edema in the presacral area, periorbital area, or fingers.

1. **Clinical causes.** Important conditions associated with generalized edema are as follows:
   a. Low-output cardiac failure
   b. High-output cardiac failure
   c. Kidney disease
      (1) Nephrotic syndrome
      (2) Acute glomerulonephritis
      (3) Acute renal failure
      (4) Chronic renal failure
   d. Cirrhosis of the liver
   e. Idiopathic recurrent edema
   f. Consumption of certain drugs (e.g., estrogens and antihypertensive vasodilators)
   g. Toxemia of pregnancy

2. **Physiologic disturbances.** Conditions associated with generalized edema may be accompanied by a variety of physiologic disturbances:
   a. Urinary sodium retention (i.e., urinary sodium excretion is less than sodium intake when sodium intake is normal.)
   b. Urinary composition (urinary sodium less than 20 mEq/L, urinary osmolality greater than 400 mOsm/kg H_2O, urine-plasma creatinine ratio greater than 35) confirms prerenal failure unless acute or chronic renal failure or diuretic use is present.
   c. Total plasma volume, particularly the venous portion, is usually expanded; decreased plasma volume may, however, occur with nephrotic syndrome.
   d. Inappropriately elevated or normal plasma levels of renin, aldosterone, and antidiuretic hormone are present in spite of sodium and water retention.
   e. Hypokalemia and hyperuricemia may be present.
   f. Hyponatremia may be present even without excess water intake.
   g. Increment in blood urea nitrogen (BUN) is generally greater than increment in serum creatinine (i.e., ratio greater than 10:1)—evidence of prerenal azotemia and renal hypoperfusion.

The volume of plasma transudate that may accumulate as edema, particularly within the peritoneal space as ascites, is often much larger than the circulating plasma volume. Generalized edema would be a self-limiting process were it not for continuing urinary sodium retention, which permits replenishment of the plasma volume. Two physiologic disturbances highlight the progressive accumulation of edema: (a) urinary retention of salt and water, and (b) the dislocation of retained fluid into the interstitial fluid from the intravascular compartment under the dictate of altered Starling forces.

II. Starling forces as determinants of edema formation

A. Starling forces. Extracellular fluid (ECF) represents in normal circumstances about 20 percent of the total body weight. Of the approximately 14 liters found in an average 70-kg man, about 25 percent of the total, or 3.5 to 4.5 liters, circulates within the vascular space as plasma, while the remainder is confined to the nonvascular portion of the extracellular space as interstitial fluid (ISF) and lymph. The volumes of fluid normally found within and without the vascular tree are in equilibrium. Fluid leaves the arteriolar end of capillaries to enter the ISF because capillary hydrostatic pressure exceeds plasma colloid osmotic pressure; fluid reenters the capillary at the venular end because plasma colloid osmotic pressure exceeds capillary hydrostatic pressure at that site. This balance of hydrostatic and colloid osmotic pressures regulating the transcapillary movement of fluid is termed the Starling forces. Interstitial fluid that is not resorbed into capillaries is returned to the vascular compartment by lymphatic drainage. These events are summarized in Figure 1-1.

B. Edema formation. Edema occurs when more fluid leaves the vascular compartment than can be returned there by the lymphatics. Since fluid can leave the circulation only at the level of the capillary bed, it follows that edema can accumulate only when those factors that normally determine the transcapillary partitioning of ECF become deranged. The more important of these factors are:
1. Decreased plasma colloid osmotic pressure
2. Increased capillary hydrostatic pressure
3. Increased permeability of the capillary wall
4. Obstruction of regional lymphatic flow

Although localized edema can occur with local disturbances of capillary hydrostatic pressure, increased permeability, and obstruction to lymph flow, generalized edema can occur only when there is a widespread increment in capillary hydrostatic pressure and/or a marked decrement in plasma colloid osmotic pressure.

III. Clinical signs and symptoms

A. "Pitting" versus "nonpitting" edema. Because of postural influences, edema is usually first detected by the physician in the subcutaneous space of the lower extremities (ankles), but fluid can collect in any organ or tissue in which fluid is leaving the vascular space. The edema is said to be "pitting" if digital pressure causes transient indentation of the skin and "nonpitting" if such indentation does not occur. Pitting reflects the opportunity for ISF to move freely within that space, whereas nonpitting edema usually reflects hindrance to such movement and may be associated with lymphatic obstruction or regional fibrosis of the subcutaneous space, such as might occur with the edema of chronic venous stasis or lymphedema.

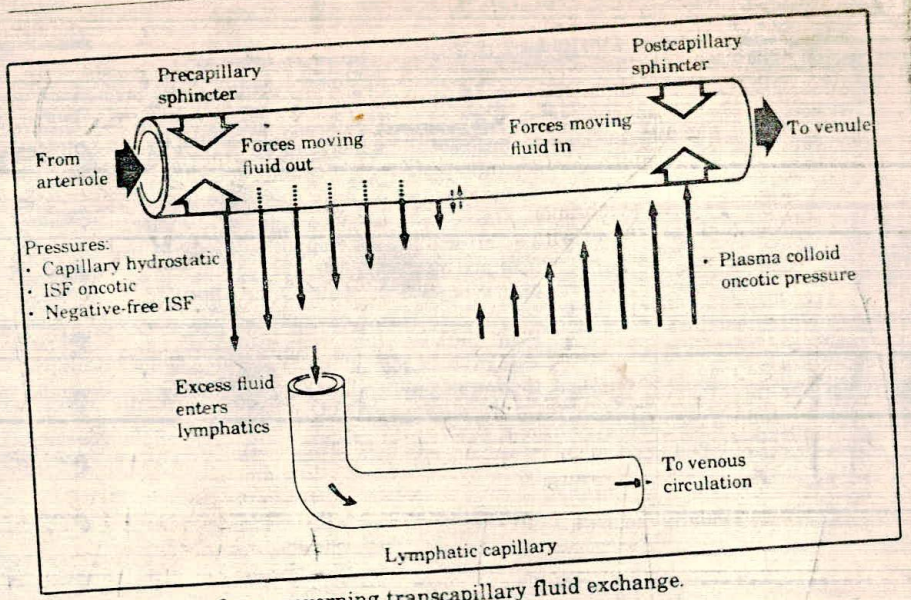

Fig. 1-1. Starling forces governing transcapillary fluid exchange.

B. Incipient edema. Since there may be an additional accumulation of as much as 4 to 5 liters of fluid in the ECF space before the patient or physician observes pitting edema, there is a period of variable duration (depending on dietary intake of salt and the degree of disease present) during which symptoms of incipient edema formation may precede its actual detection. These early symptoms are as follows:
1. Weight gain.
2. Very marked diurnal swings in weight (heaviest in the evenings).
3. Reduction in urinary output.
4. Nocturia.
5. "Shoes get very tight and uncomfortable during the day."
6. "I feel bloated."
7. "Urine looks darker in color."
8. "Swollen eyes on awakening"; "rings are too tight."
9. Cough or dyspnea in horizontal position.
10. Shortness of breath on exertion.

The nature of the signs and symptoms that appear in individual edema states will of course be determined by the pathophysiology of the underlying disease process.

IV. Diagnosis of specific disorders that cause edema

A. Congestive heart failure. In congestive heart failure (CHF), both pulmonary edema and peripheral edema are the major consequence of inability of the ventricles to deal with the venous return. **Dyspnea,** both at rest and on exertion, **orthopnea, paroxysmal nocturnal dyspnea, nocturnal coughing episodes,** and **weight gain** are usually prominent symptoms. **Tachycardia, jugular venous distention, basal pulmonary rales, swollen ankles,** and an **abnormal chest x-ray** usually complete the clinical picture. Heart failure may occur in a clinical setting of hypertension, arteriosclerotic coronary artery disease, rheumatic valvular disease, kidney failure,

arrhythmias, hyperthyroidism, pulmonary embolic episodes, or chronic obstructive lung disease. Evidence for these underlying diseases is generally present.

B. **Nephrotic syndrome.** Nephrotic syndrome refers to a constellation of clinical findings, which includes **heavy proteinuria, hypoalbuminemia, hypercholesterolemia, and edema.** This syndrome may occur secondary to lipoid nephrosis or nil disease, in which the light microscopy of the kidney is normal, or it may be secondary to some form of glomerulopathy (membranous, focal glomerulosclerotic, proliferative, or membranoproliferative). Renal lesions leading to nephrotic syndrome may also appear with a variety of systemic diseases, such as diabetes mellitus, lupus erythematosus, malignancies, or infections, or with a variety of drugs. The various causes of nephrotic syndrome are listed in Table 8-3. The diagnosis is made by demonstrating marked proteinuria (usually in excess of 3.5 gm per day); usually an abnormal sediment, which may contain red and white blood cells, various types of casts, and oval fat bodies; and marked hypoalbuminemia. Edema may be localized to the lower extremities but is often quite diffuse. Nephrotic patients may present with generalized anasarca, which may include both peritoneal and pleural effusions. Periorbital edema, especially on awakening in the morning, and edema of the fingers may be quite common.

Edema accumulates because of the marked decrement in plasma colloid osmotic pressure caused by albumin losses in the urine. If the formation of edema has been particularly rapid, especially if salt intake has been low, patients may present with oliguria, dizziness, and orthostatic hypotension. A renal biopsy may be required to diagnose the cause of the heavy proteinuria, particularly if systemic causes have been excluded.

C. **Acute glomerulonephritis.** Edema may accompany any renal lesion which produces an acute glomerulopathy (i.e., acute glomerulonephritis). Acute glomerulonephritis may occur with malignant hypertension, poststreptococcal renal involvement, an acute collagen vascular disease such as lupus erythematosus, or hypersensitivity vasculitis. The edema is usually mild and restricted to the lower extremities, unless there is a marked reduction in the glomerular filtration rate (GFR). Hypertension and mild-to-modest oliguria may be present. The urinary sediment is characteristically abnormal; proteinuria, many red and white cells, and a large number of granular and red cell casts in their various forms are present.

Serum creatinine and BUN are invariably elevated to some extent, and there may be mild hypoalbuminemia. Serum complement levels may be reduced if the glomerulonephritis is due to the deposition of immune complexes within the kidney (e.g., glomerulonephritis associated with streptococcal infection, lupus nephritis, or bacterial endocarditis). Systemic symptoms such as pleuritis, arthralgias, and cutaneous rashes may be present, depending on the underlying lesion (e.g., vasculitis and collagen vascular diseases). A renal biopsy may be required for diagnostic purposes.

D. **Cirrhosis of the liver.** In cirrhosis of the liver, edema is generally confined to the peritoneal space as ascites because of the portal venous hypertension, and to the lower extremities because of the combined effects of hypoalbuminemia and the increased pressure on the abdominal vena cava exerted by tense ascites. Edema in cirrhosis usually does not occur until the disease is well advanced, and diagnosis is easily made by the history, physical examination, and results of liver function tests.

E. **Idiopathic recurrent edema.** Idiopathic recurrent edema refers to a group of signs and symptoms observed predominantly in obese premenopausal women, but it may occur rarely in males. The syndrome is usually characterized by anxiety, irritability, abdominal bloating, headaches, and recurrent edema, usually most marked in the lower extremities. Renal, hepatic, and cardiac functions are normal. Although the edema may be cyclic, it may also be persistent and may demonstrate a marked diurnal variation (i.e., nonexistent in the morning and marked in the evenings). The diagnosis of this syndrome is one of exclusion.

F. **Drug ingestion.** Edema caused by ingestion of drugs is generally a diagnosis of exclusion which is made by obtaining a history of drug intake. The drugs usually involved are estrogens, oral contraceptives, and antihypertensive vasodilators, especially minoxidil.

G. **Toxemia of pregnancy.** Edema caused by preeclampsia usually occurs in the last trimester of pregnancy in a primiparous patient. Hypertension and proteinuria are always present. The cause of the sodium retention is obscure, and plasma volume is often reduced. Although ankle edema is most common, finger and periorbital edema may also be present. It must be remembered, however, that as many as 75 percent of normal pregnancies may be associated with detectable ankle edema.

V. **Treatment of edema.** Appropriate therapy for edema in clinical practice rests on three basic principles: (a) identification, and when possible, treatment of the underlying cause of urinary sodium retention; (b) manipulation of dietary intake of salt and water; and (c) modification, when possible, of the renal excretion of salt and water. Because manipulation of dietary sodium intake and modification of renal sodium excretion are common modes of therapy for all the edematous states, let us consider them first.

A. **Manipulation of dietary intake of sodium.** Readjustment of salt intake in the diet to provide, if possible, a smaller amount of sodium than is excreted in the urine may be quite helpful in treating edema. This is particularly useful in the sodium retention associated with chronic renal failure, because in this situation daily urinary sodium excretion proceeds at a fairly fixed rate provided urinary output is maintained at a reasonable level. Ingestion of less dietary sodium than is excreted in the urine often leads, within several days, to complete mobilization of the edema. Even when daily urine and sodium excretion is quite modest, restriction of oral intake may allow the patient to achieve "sodium balance" without progressive fluid accumulation.

1. **Indications for restricting sodium intake.** Patients who actively form edema retain a fraction of the daily ingested sodium to replenish the "effective" circulating arterial volume. Measurement of the 24-hour urinary excretion of sodium thus provides a measure of the renal ability to handle an oral sodium load. A proper "balance" study is not required, because by definition such edematous patients are in positive sodium balance, and the daily urinary output represents the best that the kidneys can do with the patient on a given diet. In fact, even a 24-hour urine collection is unnecessary to assess whether or not the patient is retaining sodium; low sodium concentrations in an aliquot of urine (e.g., less than 10 to 15 mEq/L), especially when coupled with an elevated urine-plasma creatinine ratio (greater than 35), suggest very strongly that the patient is in positive sodium balance.

2. **Guidelines for dietary planning**

   a. In planning dietary restriction of salt, it is helpful to recall that a 1-gm salt (NaCl) diet contains 17 mEq of Na^+, whereas a 1-gm Na^+ diet contains about 43 mEq of Na^+. Restricting sodium to less than 20 mEq per day is probably not worthwhile, because such diets are quite unpalatable, and patient compliance is low. The average sodium intake in North America is about 80 to 200 mEq per day. By restricting use of the saltshaker at mealtime, this level of intake can be reduced to 70 to 125 mEq per day; it can be additionally reduced to 50 to 70 mEq per day by the avoidance of salt in the cooking and preparation of foods.

   b. When a patient is on a diet of severe salt restriction, to avoid hyponatremia free-fluid intake should be restricted to about 1200 to 1500 ml per day, particularly if the patient is taking a diuretic agent as well.

   c. For those patients who cannot tolerate a low salt diet, a variety of salt substitutes is available. These contain largely potassium chloride and therefore should not be prescribed in the presence of marked renal failure, in which urine output is markedly reduced, or when captopril or a potassium-sparing diuretic is being administered (e.g., spironolactone, amiloride, triamterene).

B. **Modification of salt excretion: diuretics**

1. **Indications for using diuretics.** Edematous patients who cannot be managed successfully with dietary therapy alone should be placed on diuretic therapy. So potent and effective are these drugs in producing renal salt wasting that many patients may be treated with just these agents while dietary management

or consideration of the underlying disease is ignored. Nevertheless, the use of diuretics should not replace an intelligent and reasonable therapeutic program but should be looked on as an addendum to a program that already has taken into consideration treatment of the underlying lesion and dietary control of salt.

2. **Action of diuretics.** Diuretics exert their effect by partially inhibiting the renal tubular resorption of sodium and chloride. The resulting natriuresis osmotically obligates water within the tubular lumen so that large amounts of near-isotonic urine may be excreted. An increase in the fractional excretion of salt and water means that less of the glomerular filtrate will be reabsorbed into the peritubular capillary circulation, and thus less glomerular filtrate will be returned to the circulating plasma volume. As the plasma volume contracts, subtle changes in capillary hydrostatic pressure and plasma colloid osmotic pressure cause ISF (edema) to move into the vascular compartment. Thus, a "diuretic response" is translated into a "mobilization response," mediated by some degree of underfilling of the arterial circulation. When the degree of diuresis exceeds the replenishment of the vascular space, volume contraction ensues, renal perfusion declines, and the diuresis usually terminates. If the volume contraction is of sufficient magnitude, orthostatic hypotension, dizziness, and prerenal failure may occur.
3. **Complications of diuretics.** The complications most frequently encountered with diuretics are as follows:
   a. Contraction of the vascular volume (from overzealous diuresis)
   b. Orthostatic hypotension
   c. Hypokalemia
   d. Hyperkalemia (spironolactone, triamterene, and amiloride)
   e. Hyperuricemia
   f. Hypercalcemia (thiazides)
   g. Hypercholesterolemia
   h. Hyponatremia
   i. Metabolic alkalosis
   j. Skin rash
   k. Gastrointestinal upset
   l. Hyperglycemia
   m. Pancreatitis (thiazides)
   n. Acute interstitial nephritis (thiazides, furosemide, and triamterene)
4. **Major diuretic agents.** Some of the major features of diuretics commonly in use today are summarized in Table 1-1. In addition to the diuretics listed in the table, several drug combinations have become increasingly popular in the last several years among family physicians, largely because they diminish the need to be concerned about body K^+ stores and serum K^+ concentration. Dyazide is a triamterene-hydrochlorothiazide preparation, and Moduretic is a hydrochlorothiazide-amiloride preparation. Although useful, both triamterene and amiloride carry their own complications (Table 1-1); if not used cautiously, or if the patient is insufficiently monitored, dangerous hyperkalemia may occur, particularly if the patient becomes acidotic.
5. **Principles of diuretic management**
   a. Except in emergencies, such as acute pulmonary edema, it is rarely necessary to initiate a vigorous diuresis. It is much safer for the patient, particularly the elderly, to be subjected to a gentle diuresis, perhaps no more than 0.5 to 1.0 kg of weight loss per day, to allow sufficient time for vascular replenishment from depots of edema in the interstitial space or serous cavities.
   b. When the desired effects have been achieved with diuresis (i.e., "dry weight,"), one should consider stopping the diuretic, reducing the dose, or even administering it on an alternate-day schedule to reduce the risks of volume contraction, hyponatremia, and hypokalemia.
   c. In most circumstances diuresis should be started with a thiazide drug; the more potent loop-active agents (e.g., furosemide, ethacrynic acid) should

Table 1-1. Features of Commonly Used Diuretics

Generic Name	Brand Name	Tablet Size	Usual Daily Dosage	Comments
Acetazolamide	Diamox	250 mg	250 mg q.i.d.	Should not be used routinely for edema; PO or IV form useful as adjunct to therapy in refractory edema
Hydrochlorothiazide	Hydrodiuril	50 mg	25–200 mg q.d.	PO dose starts acting within 2 hr; should be diuretic first used in most cases; may cause hypokalemia; ineffective with GFR <25 ml/min
Chlorthalidone	Hygroton	50, 100 mg	50–100 mg q.d. (frequently used on alternating-day regimen)	Long-acting (>24 hr); ineffective with GFR <25 ml/min
Furosemide	Lasix	20, 40, 80 mg	20–120 mg q.d. or b.i.d.	Rapid onset 30 min; short-acting 4–6 hr; loop active, very potent; should be used for emergencies; effective with GFR <25 ml/min
Ethacrynic acid	Edecrin	25, 50 mg	50–100 mg q.d.	Longer acting than furosemide; probably more side effects than furosemide at higher doses; effective with GFR <25 ml/min
Spironolactone	Aldactone	25 mg	25–100 mg q.i.d.	Gradual onset; takes 2–3 days for effects; potassium-sparing; contraindicated because of danger of hyperkalemia when GFR <25 ml/min
Triamterene	Dyrenium	100 mg	100–300 mg b.i.d.	Long-acting; potassium-sparing; contraindicated in patients with diabetes, and patients with GFR <25 ml/min; cases of triamterene stones and drug induced interstitial nephritis being reported with increasing frequency
Metolazone	Zaroxolyn	1 mg	1–10 mg q.d.	Effective with GFR <25 ml/min; long-acting; may cause hypokalemia
Amiloride	Midamor	5 mg	5–20 mg q.d.	Potassium-sparing; experience limited with this agent; may cause dangerous hyperkalemia; has additive natriuretic and antihypertensive effect to thiazides; begins acting within 2 hr; effect may last for 24 hr; contraindicated with GFR <25 ml/min
Triamterene-hydrochlorothiazide mixture	Dyazide	Triamterene 50 mg; thiazide 25 mg	1 tablet b.i.d.	Commonly used when K^+-sparing is desired or to avoid prescribing K^+ supplements; should not be used with other K^+-sparing agents or with K^+ supplements; incidence of hyperkalemia increases (12%) in patients over age 60

GFR = glomerular filtration rate.

be reserved for situations in which the patient is resistant to the thiazide diuretic, or a more vigorous diuresis is required.

d. The diuretics acting on the more distal parts of the nephron (e.g., spironolactone, amiloride, triamterene) are weak and also potassium-sparing, an effect that may cause hyperkalemia in the presence of renal failure, acidosis or a diet very high in potassium. These diuretics, therefore, should never be used in the presence of renal failure or with potassium supplements.

C. Treatment of the specific underlying disorder

1. Congestive heart failure (CHF)

a. Cardiac glycosides. Because CHF generally occurs when the heart fails as a pump, the major thrust of therapy in this clinical circumstance is to improve the efficiency of ventricular performance. This is usually accomplished with a cardiac glycoside preparation, most commonly, digoxin.

(1) Action of digoxin. Although a thorough discussion of digoxin is beyond the scope of this chapter, it should be emphasized that the drug is extremely effective in reversing low-output cardiac failure as well as in controlling the ventricular rate in atrial fibrillation and a variety of supraventricular tachyarrhythmias. Its marked inotropic effect on the ventricular myocardium is particularly efficacious in the heart failure associated with coronary artery disease, hypertension, or valvular disease. It is less effective in states of high-output heart failure (e.g., thyrotoxicosis and severe anemia), in cor pulmonale, and in conditions in which there is a disturbance in renal function limiting the ability of the kidneys to increase the fractional excretion of salt and water in response to an improved cardiac output (e.g., uremia or an acute glomerulopathy). Digoxin is also rather ineffective when there is pericardial tamponade or constrictive pericarditis, and it is generally contraindicated in hypertrophic obstructive cardiomyopathy because of the danger of worsening the subaortic stenosis.

(2) Administration and dosage of digoxin. In prescribing digoxin, one should recall that there must be either a reduction in dosage or an increment in dosage interval when renal failure is present. Although theoretically one can administer a standard loading dose, in practice it is probably much safer to administer either a reduced loading dose (e.g., 30 to 50 percent of the usual dose over a period of 24 to 36 hours) or the maintenance dosage without a loading dose, when there is no requirement for rapid digitalization. Additional drug therapy in the azotemic patient is discussed in Chapter 11. In elderly patients, the serum creatinine may not accurately reflect the GFR because of loss of muscle tissue. A serum creatinine of 1.2 mg per deciliter may in fact be associated with a GFR of less than 60 ml per minute. Such considerations should be kept in mind when the potentially lethal cardiac glycosides are prescribed for geriatric patients with CHF, and if there is any doubt, creatinine clearance should be measured and suitable formulas employed for calculating the required dose (see Chap. 11). In practice, because of the serious potential problems associated with glycosides, many physicians prefer to initiate therapy with dietary salt restriction and a diuretic, and avoid using digoxin unless it is absolutely necessary (e.g., for atrial fibrillation).

b. Control of predisposing factors. In addition to cardiac glycosides, control of factors predisposing to CHF should be instituted. These conditions include hypertension, thyrotoxicosis, anemia, hypoxia, and polycythemia. Dietary restriction of salt, reduction in physical activity, avoidance of extremes of heat, moderation in sexual activity, sedation, and use of diuretics usually complete the therapeutic program, although all these maneuvers are not required for every patient. Extreme salt restriction and/or abuse of diuretics may actually be harmful to the patient in CHF. The failing heart maintains a reasonable cardiac output, in part because of plasma volume expansion (caused by renal sodium retention) and increased venous return, which

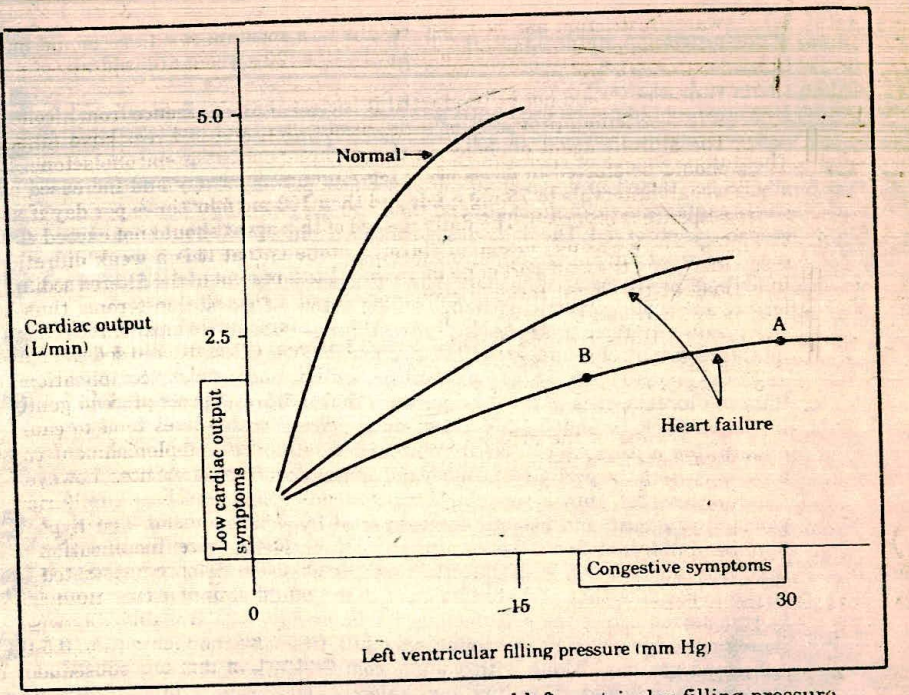

Fig. 1-2. Relationship between cardiac output and left ventricular filling pressure under normal circumstances (*upper curve*) and low-output congestive heart failure (*lower curve*). Reduction of the afterload (e.g., nitroprusside) or improved contractility may shift the lower curve to the middle curve. Diuretic-induced preload reduction or other causes of volume depletion may decrease cardiac output, e.g., shift from point *A* to *B* on the lower curve. (From R. W. Schrier [Ed.], *Renal and Electrolyte Disorders* [2nd ed.]. Boston: Little, Brown, 1980.)

improve myocardial performance. Reduction of the ventricular preload by excessive contraction of the plasma volume (excessive dietary restriction and/or diuretic abuse), in the presence of a failing heart, reduces cardiac output even more and may aggravate existing prerenal failure (Fig. 1-2).

2. Cirrhosis of the liver

a. Abstinence from alcohol and sodium restriction. Treating the underlying cause of established alcoholic cirrhosis of the liver is extremely difficult. Nevertheless, abstinence from alcohol and consumption of a nutritious diet may improve hepatic function and retard the rate of cirrhotic progression. Such improvement may allow the resolution of existent edema and ascites or at least permit other therapy to become more efficacious. In patients with decompensated cirrhosis who actively retain urinary sodium, dietary restriction of sodium is indicated according to the guidelines discussed earlier.

b. Use of diuretics. Most cirrhotic patients with ascites require diuretics at some stage in their disease. Nonetheless, there is no urgency to treat small amounts of ascites in well-nourished patients abstaining from alcohol, and even large amounts of ascites probably never should be removed by paracentesis. There is rarely any urgency in removing ascites unless it is associated with marked pain and discomfort, malnutrition, or circulatory or respiratory embarrassment. Conservative therapy always should be attempted first. Sodium restriction (20 to 50 mEq per day), with only modest

water restriction and bed rest, results in a spontaneous diuresis and mobilization of ascites in approximately 10 to 20 percent of hospitalized patients with ascites.

Diuretics should not be used until it is clear that abstinence from alcohol, salt restriction, provision of a nutritious diet, and bed rest have failed. The diuretic agent of choice in the cirrhotic patient is spironolactone. It should be started in doses of 50 mg four times per day and increased at weekly intervals to 75 mg q.i.d. and then 100 mg four times per day if no response is observed. The daily dosage of this agent should not exceed 400 mg. The great advantage of spironolactone is that it is a weak diuretic, inhibiting the transport of no more than 1 to 2 percent of the filtered sodium load at the distal cationic exchange site of action of aldosterone; thus a slow, gentle diuresis proceeds. In contrast, furosemide or a thiazide may inhibit transport of as much as 10 to 15 percent of the filtered sodium load and thus initiate a more vigorous diuresis, with attendant complications.

c. **Rate of diuresis.** It is of great importance that a diuresis proceed gently in the cirrhotic patient with ascites, since diuretic losses tend to cause underfilling of the arterial circulation, and vascular replenishment can occur only from the peripheral edema and ascites depots. Ascites, however, must be resorbed into a vascular compartment (splanchnic capillaries) where hydrostatic and osmotic forces (portal hypertension and hypoalbuminemia) do not favor the resorption of fluid. Hence, mobilization of fluid may not keep up with diuretic losses. It has been demonstrated in cirrhotic patients that probably no more than 900 ml of ascitic fluid can be transferred across the peritoneum in a single day. It is probably wise, therefore, to keep weight loss induced by diuretics at no more than 0.5 to 1.0 pound per day. Along with volume contraction and the subsequent tendency to induce renal failure, hypokalemia and hyponatremia are frequent complications associated with the overenthusiastic use of diuretics. Hypokalemia has been suggested as a cause of hepatic encephalopathy. Spironolactone may cause hyperkalemia and worsen any tendency for hyperchloremic renal tubular acidosis. Spironolactone may also be associated with painful gynecomastia. Thiazides or furosemide should not be added to spironolactone unless it has been clearly demonstrated that spironolactone alone is not effective.

d. **Plasma volume expansion.** Such maneuvers as infusion of iso-oncotic or hyperoncotic albumin, reinfusion of ascites, and infusion of saline solution generally are not helpful and may actually induce variceal hemorrhage by increasing plasma volume and portal venous pressure transiently.

e. **Portacaval shunts.** Side-to-side portacaval fistulas may be attempted to alleviate marked portal venous hypertension. End-to-side fistulas are associated with unacceptable mortality and should not be contemplated. The former operation carries as much as 40 percent operative mortality and should be reserved only for young patients with cirrhosis who have given up alcohol and whose liver function is reasonably intact. Thus, patients with cirrhosis who have had previous episodes of encephalopathy and who have ascites, jaundice, hypoalbuminemia, and vitamin K-resistant prolonged prothrombin times are not good candidates.

f. **LeVeen shunt.** As many as 95 percent of patients treated with conservative techniques (including diuretics) exhibit complete or partial discharge of the ascites. For those who do not (i.e., "intractable" patients), one may attempt insertion of a LeVeen shunt.

(1) **Technique.** A LeVeen shunt is a Silastic, pressure-sensitive valve that is implanted beneath the abdominal muscles under local anesthesia. One end of the tubing rides within the peritoneal space while the other is tunneled subcutaneously and inserted into a jugular vein. The valve permits flow of fluid from the peritoneum to the jugular vein only as long as a 3- to 4-cm water-pressure difference exists across the valve. The valve functions as an exogenous thoracic duct, conducting fluid continuously from the peritoneal space to the jugular vein. Not only can ascites be completely mobilized in this way, it can also be prevented from reforming. Most patients treated with a LeVeen shunt show a marked diuresis, particularly if diuretics are concomitantly administered. Glomerular filtration rate may improve, and hyperaldosteronism may decline.

(2) **Indications and complications of LeVeen shunt.** LeVeen shunts are not trouble-free, however, and as their use spreads, more and more problems are being observed. The indications for placement of a LeVeen shunt are largely the presence of intractable ascites for which conservative therapy has failed, or the appearance and progression of prerenal failure not responding to volume replacement or other conservative means. Complications observed with a LeVeen shunt include:

(a) Disseminated intravascular coagulation
(b) Continuous leak of ascites
(c) Thrombosis of jugular vein
(d) Infection of shunt and peritonitis
(e) Fever
(f) Variceal hemorrhage
(g) Pulmonary edema
(h) Clotting of shunt

A LeVeen shunt should not be inserted if the patient is unreliable in following medical instructions, if the ascites is infected, if the patient is in congestive heart failure, it there is marked encephalopathy, or if there have been episodes of recent variceal hemorrhage. A thorough discussion concerning the use of LeVeen shunts in cirrhotic patients has recently been published (see reference at end of this chapter).

3. **Nephrotic syndrome**

a. **Specific treatment of systemic disease.** Like cirrhosis of the liver, nephrotic syndrome is very difficult to treat in a way more specific than altering dietary intake of salt and administering diuretic agents. Administering protein solutions intravenously is not helpful because the protein appears in the urine quite rapidly, and any beneficial effect is quite transient. The nephrotic syndrome does, however, have many underlying causes. Some, such as Hodgkin's disease, carcinoma, constrictive pericarditis, drug allergy, and infections (e.g., subacute bacterial endocarditis and secondary syphilis), may be successfully treated with specific therapy, and on resolution of the causal lesion, the protein-losing nephropathy generally disappears. Most instances of nephrotic syndrome, however, are associated with lesions that are not amenable to specific therapy, such as diabetic nephropathy, lipoid (nil or minimal-change disease) nephrosis, membranous nephropathy, and collagen-vascular diseases.

b. **Treatment of nil disease.** In some clinical situations, it is virtually impossible to reverse the nephrotic lesion once it has developed. This is true, for example, in diabetes mellitus, in which renal protein losses generally cannot be reversed by controlling blood sugar concentrations. In other circumstances, a favorable response may be obtained with the use of steroids alone or combined with such immunosuppressive agents as azathioprine or cyclophosphamide. An example of the latter situation is minimal-change nephropathy (lipoid nephrosis) which comprises about 10 to 15 percent of adult cases of nephrotic syndrome and 70% of cases in children. It is characterized by the conventional findings of nephrotic syndrome, but renal function is generally normal and a kidney biopsy reveals normal findings by light microscopy. Immunofluorescence is negative, and electron microscopy reveals fusion of epithelial foot processes. The treatment for this disease is a course of prednisone. The starting dosage is usually 60 to 80 mg per day, and when a response is observed (i.e., a decrease in proteinuria or an increase in serum albumin), the patient may be converted to an alternate-day regimen. Therapy is usually continued until a remission is

obtained, although the dosage may be progressively decreased when it is clear that the patient is showing a beneficial response. A response is generally obtained in greater than 80 percent of adults. Even in patients who are responding, frequent relapses may occur. If there is doubt about the adequacy of steroids, a dosage of prednisone of at least 1 mg/kg/day should be provided. Responders will generally be proteinuria-free within 8 weeks, but decreasing amounts of steroids should be given for a total of 3 months. If a patient is not responding to steroids or is exhibiting frequent relapses and complications from the steroids, cyclophosphamide (2 mg/kg/day) may be given orally for a 2-month period as an adjunct to or substitute for the steroids. Azathioprine is generally not helpful in this disorder, but chlorambucil may be as effective as cyclophosphamide. One should be aware of the toxic side effects of steroids (e.g., hypertension, thromboembolic phenomena, increased predisposition to infection, osteoporosis, aseptic necrosis, cataracts) and of alkylating agents (e.g., bone marrow suppression, increased predisposition to infection, liver disease, hemorrhagic cystitis, sterility) before commencing therapy. Since each alkylating agent has different complications, however, the physician should become familiar with the complications or specific side effects of an agent before using it.

c. **Treatment of membranous nephropathy and lupus nephritis.** Idiopathic membranous glomerulopathy is a common cause of nephrotic syndrome in adults. It generally occurs in patients over the age of 40 and accounts for at least 50 percent of the adult cases of idiopathic nephrotic syndrome in North America. The onset of this disease is insidious, its course may be indolent and prolonged, and there may be spontaneous remission in as many as 20 percent of cases. Whether steroids are useful in the treatment of this disease is still controversial. Nevertheless, because of the poor prognosis if membranous nephropathy is permitted to continue unabated, many nephrologists advocate a trial of therapy for patients whose renal function is not severely depressed. If a course of therapy is undertaken, it should be vigorous (e.g., 60 to 80 mg of prednisone per day or 125 mg on alternate days) for as long as 2 months, with total duration of therapy (at reduced doses of 60 to 80 mg on alternate days) lasting for 6 to 12 months, before the physician concludes that there has been no response. Alkylating agents are not generally indicated for idiopathic membranous nephropathy. When the nephrotic syndrome is due to collagen vascular disease (e.g., lupus erythematosus), the primary disease should be fully treated with prednisone and/or azathioprine in an attempt to obtain a remission.

4. **Acute glomerulonephritis.** Edema may occur with any acute glomerulonephritis. Although diuretics and salt restriction are extremely useful in these circumstances, permanent relief from urinary sodium retention will come only as the acute glomerulopathy resolves (e.g., poststreptococcal glomerulonephritis) or is appropriately treated (e.g., malignant hypertension with antihypertensive agents or acute collagen vascular disease with steroids).
5. **Idiopathic edema.** Women troubled with this syndrome may be very difficult to treat. Rarely, men may also be afflicted with this disorder. Since the cause of the sodium retention has not been clearly recognized, it is difficult to recommend specific therapy.
   a. **Supportive therapy.** Some women profit from caloric restriction and weight loss, others from avoidance of excess heat, whereas in others regular exercise, particularly swimming, may prove quite helpful. Almost all women profit from avoidance of the orthostatic position, combined with the wearing of elastic support hose.
   b. **Drug therapy.** Some women have obtained relief with the use of sympathomimetic amines that constrict precapillary resistances. Dextroamphetamine, 10 to 25 mg per day, has been quite helpful in some women in reducing the daily swings in body weight and fluid collection. Since this drug causes insomnia and excitement in some patients, it is probably best used in combination with a barbiturate. The decision to use this drug should not be taken lightly, however, and the patient must be carefully monitored. Recent evidence suggests that dopamine agonists may be quite helpful in producing a natriuretic effect in women with idiopathic recurrent edema, but it is not yet clear whether this drug is suitable for long-term therapy. The majority of these patients are treated with dietary salt restriction and diuretics. Although in many cases this therapeutic regimen may keep the patient edema-free, there are potential complications with the long-term use of diuretics in this syndrome. The patient may come to exhibit a marked "dependence" on these drugs and use them as cure-alls for many different types of complaints. Indeed, many women with recurrent edema are anxious and often irritable. Abuse of thiazide diuretics or furosemide may lead to chronic hypokalemia, which in itself may be a salt-retaining influence. It has also been postulated that in sensitive people volume contraction induced by diuretics may provoke persistent secondary hyperaldosteronism and excess tubular retention of sodium such that edema may actually be produced and perpetuated. Other complications of chronic diuretic abuse include hyperlipidemia, hyperuricemia, and profound metabolic alkalosis.

VI. **Refractory edema.** Often, strict control of dietary salt intake and use of diuretic agents are not sufficient to control edema, presumably because the salt-retaining signal to the renal tubule is simply too potent, due to the underlying disease. Alternatively, the alteration in Starling forces tending to force fluid out of the vascular space may be so marked that virtually complete urinary sodium retention is required to replenish the vascular space. In patients whose edema is refractory to conventional therapy, the following guidelines may be helpful:

A. **Bed rest,** with some elevation of the lower extremities, may be beneficial in patients with refractory edema. There tends to be a transfer of blood to the central circulation with bed rest, resulting in an augmented cardiac output and improved renal perfusion. Bed rest may also lead to a decrease in circulating levels of antidiuretic hormone and aldosterone. Bed rest often converts an edematous patient who is refractory to diuretics to one who is more responsive to diuretics, which may permit a reduction in dosage.

B. **Compression stockings** for the lower extremities may aid in forcing the interstitial fluid of edema back into the vascular space, thereby improving central blood volume and renal perfusion.

C. **In diuretic therapy** it may be necessary to make changes as follows:
   1. Administer medication intravenously rather than orally to avoid failure of intestinal absorption because of gastrointestinal edema.
   2. Change the diuretic; patients may respond to ethacrynic acid when they have stopped responding to furosemide.
   3. Use combinations of diuretics that act at different sites within the nephron (e.g., acetazolamide, followed by large doses of furosemide, thiazides, and/or spironolactone). The combination of furosemide and metolazone administered together has been proposed as an effective alternative in furosemide-resistant patients.
   4. Attempt to improve renal perfusion by infusing preglomerular vasodilators such as dopamine.
   5. Occasionally, only marginal adrenal function is present, particularly in elderly patients who have been chronically ill and who have recently suffered from additional acute stresses. In these circumstances, intravenous injections of soluble glucocorticoid may permit a heightened response to a given dosage of diuretic, perhaps by increasing glomerular filtration rate.

D. **In specific edematous states,** it may be necessary to resort to unusual procedures. Thus, pregnant women with toxemia may be confined to the lateral recumbent position in bed, a posture that improves renal hemodynamics. As already discussed, patients with cirrhosis of the liver may be subjected to Le Veen shunting, whereas patients with nephrotic syndrome may be given simultaneous infusions of hyperoncotic albumin and diuretics.

E. Patients with CHF may be treated with a pharmacotherapeutic protocol that includes such vasodilators as nitroprusside or hydralazine in an attempt to reduce the afterload, ameliorate ventricular pumping, and reduce venous pressure. This approach may improve renal perfusion (despite a reduction in blood pressure), and a more potent diuretic response may be obtained. Because peripheral resistance is in part angiotensin-dependent in CHF, captopril, a new, potent vasodilator that inhibits angiotensin generation, has been particularly helpful in some patients with advanced CHF and refractory edema. It produces marked afterload reduction and assists in the mobilization of fluid. Because of its potency and potentially hazardous complications, the physician should become thoroughly familiar with this agent before contemplating its use.

Suggested Reading

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2 The Patient With Hyponatremia or Hypernatremia

Robert W. Schrier

Hyponatremia

Hyponatremia, defined as a plasma sodium concentration of less than 135 mEq per liter, is a frequent occurrence in the hospitalized patient. It has been suggested that approximately 15 to 25 percent of patients in hospitals have a low plasma sodium concentration at some time during their stay. Hyponatremia in the ambulatory outpatient is a much less frequent occurrence and is usually associated with a chronic disease state.

I. Clinical settings. Many clinical disorders may be associated with hyponatremia. In fact, a low plasma sodium concentration may be a finding that leads to the diagnosis of a specific disease state. For example, hyponatremia is associated with severe and overt cardiac failure or liver disease. A low plasma sodium concentration also may be present in the patient with undiagnosed Addison's disease, hypopituitarism, or hypothyroidism, or it may be a harbinger of excessive diuretic use even before symptoms of volume depletion become apparent. Hyponatremia may also present as a complication of other drug use (e.g., antineoplastic agents, including vincristine and cyclophosphamide), or it may be an early feature of oat cell carcinoma of the lung. It is clear, therefore, that even in the asymptomatic patient the presence of hyponatremia cannot be ignored; rather, a diagnostic approach that leads to the specific cause of the hyponatremia must be used.

II. Signs and Symptoms

A. Age of patient and rate of development of hyponatremia. The level of hyponatremia that may cause signs and symptoms varies with the rate of decline in the plasma sodium concentration and the age of the patient. In general, the younger patient appears to tolerate a specific level of hyponatremia better than does the older patient. However, the acute (few hours) development of hyponatremia in a previously asymptomatic young patient may cause severe central nervous system (CNS) signs and symptoms, such as depressed sensorium, seizures, and even death, when the plasma sodium concentration has reached a level only between 125 and 130 mEq per liter. This is because the capacity of brain cells to extrude osmotically active particles, thus relieving the brain swelling that accompanies hyponatremia, requires a longer time to be invoked. On the other hand, this protective mechanism against brain swelling is very effective with the chronic development of hyponatremia over days or weeks, so that an elderly person may present without signs or symptoms even with a plasma sodium concentration below 110 mEq per liter.

B. Gastrointestinal and CNS dysfunction. Gastrointestinal symptoms, including anorexia and nausea, may occur early with hyponatremia; however, the more severe later signs and symptoms relate to the CNS. This is because the cell swelling that occurs with hyponatremia is least well tolerated within the rigid encasement of the skull. Severe hyponatremia of rapid onset may lead to brain edema and herniation and thus requires rapid treatment. Cheyne-Stokes respiration may be a hallmark of severe hyponatremia; in addition to exposure, uremia, and hypothyroidism, hyponatremia also should be considered in the differential diagnosis of the hypothermic patient.

In summary, **symptoms** that may be associated with hyponatremia include:

1. Lethargy, apathy
2. Disorientation
3. Muscle cramps
4. Anorexia, nausea
5. Agitation

Signs that may be associated with hyponatremia include:

1. Abnormal sensorium
2. Depressed deep tendon reflexes
3. Cheyne-Stokes respiration
4. Hypothermia
5. Pathologic reflexes
6. Pseudobulbar palsy
7. Seizures

III. Diagnosis

A. Pseudohyponatremia. It is important to ascertain that the low plasma sodium concentration is not a consequence of drawing the sample from a vein into which a hypotonic solution is being infused. Pseudohyponatremia does not require a diagnostic search, since the sodium concentration in plasma water is normal. Patients with lipid or protein disorders may have a large percentage of their plasma occupied by these solids, in contrast to the 8 percent of solids that occupy normal plasma. Thus, measurement of sodium concentration in the total plasma will be low. However, removal by ultracentrifugation of lipids from the plasma of a patient with nephrotic syndrome or pancreatitis or of proteins from the plasma of a patient with Waldenström's macroglobulinemia reveals a normal sodium concentration in plasma water. Because ultracentrifugation may not be readily available, a more practical means of documenting the diagnosis of pseudohyponatremia is to measure the plasma osmolality. All other hyponatremic states are accompanied by hypoosmolality, but with pseudohyponatremia plasma osmolality is normal. With very high plasma lipid concentrations, the level of pseudohyponatremia may be below 120 mEq per liter, and yet the plasma water sodium concentration will be between 145 and 150 mEq per liter.

B. Hyponatremia and increased ECF osmolality. Another cause of hyponatremia is the presence of an increased number of osmotically active particles in the extracellular fluid (ECF) compartment that do not readily penetrate into cells (e.g., mannitol administration or hyperglycemia in the untreated diabetic patient). With hyperglycemia it can be calculated that for each 100 mg per deciliter rise in blood sugar a 1.6 mEq per liter fall in plasma sodium concentration will occur as ECF water moves out of cells. For example, as blood sugar rises from 200 to 1200 mg per deciliter in an untreated diabetic patient, the plasma sodium concentration would be expected to fall from 140 to 124 mEq per liter (1.6 mEq/L × 10 = 16 mEq) without a change in total body water and electrolytes. Conversely, treatment with insulin and lowering of the blood sugar in this diabetic patient from 1200 to 200 mg per deciliter would result in comparable osmotic water movement from the ECF into cells and a return of plasma sodium concentration to 140 mEq per liter without any change in total body water or electrolytes.

C. Assessment of ECF volume status and classification of hyponatremia. In the absence of pseudohyponatremia or with an excess of osmotically active solute in the ECF, the most important initial step in the diagnosis of hyponatremia is an assessment of the ECF volume status. The hyponatremic patient can then be classified in one of three categories: (a) hyponatremia in the presence of an excess of total body sodium, (b) hyponatremia in the presence of a deficit of total body sodium, and (c) hyponatremia with a near normal total body sodium. Sodium is the primary cation in the ECF compartment and, with its accompanying anions, dictates ECF osmolality and fluid volume. Thus, ECF volume provides the best index of total body exchangeable sodium. A careful physical examination focused on the evaluation of ECF volume status therefore allows for the classification of the hyponatremic patient into one of the above categories. For example, the edematous patient is classified as having hyponatremia with an excess of total body sodium. The volume-depleted patient with flat neck veins, decreased skin turgor, dry mucous membranes, and orthostatic hypotension and tachycardia is classified as having hyponatremia with a deficit of total body sodium. Lastly, the patient without either edema or evidence of ECF volume depletion is classified as having hyponatremia with near normal total body sodium.

D. Edematous hyponatremic patient. This classification of the hyponatremic patient (Fig. 2-1) narrows the diagnostic focus and diminishes the diagnostic possibilities. The hyponatremic edematous patient must have either cardiac failure, cirrhosis, nephrotic syndrome, or renal failure. When hyponatremia is secondary to cardiac and hepatic disease, the disease is advanced and readily evident on clinical examination. In the absence of the use of diuretics the urinary sodium concentration in the hyponatremic edematous patient should be quite low (less than 10 mEq per liter) because of avid tubular sodium resorption. The exception is in the presence of acute or chronic renal failure, in which, because of tubular dysfunction, the urinary sodium concentration is higher (greater than 20 mEq/L).

E. Hypovolemic hyponatremic patient. The diagnostic possibilities in the hypovolemic hyponatremic patient are entirely different. Again, a spot urinary sodium concentration is of value. If the volume-depleted hyponatremic patient has a low (less than 10 mEq/L) sodium concentration, the kidney is functioning normally by conserving sodium in response to ECF volume depletion. On the other hand, if the urinary sodium concentration is greater than 20 mEq per liter in a hypovolemic hyponatremic patient, the kidney is not responding appropriately to the ECF volume depletion, and renal losses of sodium and water must be considered as the likely cause of the hyponatremia.

1. **Gastrointestinal or "third space" losses—urinary sodium less than 10 mEq per liter.** In a hypovolemic hyponatremic patient with urinary sodium concentration less than 10 mEq per liter, a gastrointestinal source of sodium and water losses must be sought. This may be readily apparent if the patient presents with a history of vomiting and/or diarrhea. In the absence of an obvious history of gastrointestinal fluid losses, several other diagnostic possibilities must be considered. Substantial ECF losses may occur into the abdominal cavity with peritonitis or pancreatitis and into the bowel lumen with ileus or membranous colitis. The surreptitious cathartic abuser may present with evidence of ECF volume depletion and no history of gastrointestinal losses. A clue to this diagnosis may be the presence of hypokalemic metabolic acidosis and phenolphthalein in the urine. Loss of haustra on barium enema and melanosis coli are other clues to cathartic abuse. Burns or muscle damage may also lead to a state of hypovolemia and hyponatremia secondary to substantial fluid and electrolyte losses from skin or into muscle.
2. **Renal losses—urinary sodium greater than 20 mEq per liter.** In a hypovolemic hyponatremic patient with a urinary sodium level greater than 20 mEq per liter, several different diagnostic possibilities must be considered.
   a. **Diuretic use.** Foremost among these diagnoses is excessive use of diuretics. In fact, a fall in plasma sodium concentration in a patient receiving diuretics may be the first clue to the need to readjust the dosage of the diuretic. There are some patients with diuretic abuse in whom ECF volume depletion is not readily apparent from clinical examination. As important clue, however, to the diagnosis of diuretic-induced hyponatremia is that virtually all of these patients have an associated hypokalemic alkalosis. Cessation of use of the diuretic is the best means of confirming the diagnosis of diuretic-induced hyponatremia. It must be remembered, however, that restoration of ECF volume and potassium balance are also necessary to correct the hyponatremia.
   b. **Surreptitious diuretic abuse.** Surreptitious diuretic abuse is becoming very common, particularly among premenopausal women who use diuretics for weight loss or other cosmetic reasons (e.g., thick ankles or calves, "puffy" face, swelling of ankles.) These patients may be difficult to distinguish from patients with surreptitious vomiting, because both may present with evidence of ECF volume depletion and hypokalemic metabolic alkalosis.

Fig. 2-1. Diagnostic approach to the hyponatremic patient.

The presence or absence of the hyponatremia depends on the patient's water intake. The pivotal diagnostic test to distinguish between the hypovolemic hyponatremic patient with metabolic alkalosis who is a diuretic abuser versus the patient who is surreptitious vomiter is the urinary chloride concentration. The surreptitious vomiter will have a low (less than 10 mEq/L) concentration and the surreptitious diuretic abuser a high (greater than 20 mEq/L) urinary chloride concentration.

c. **Salt-losing nephritis.** Patients with medullary cystic disease, chronic interstitial nephritis, polycystic disease, analgesic nephropathy, partial urinary tract obstruction, and, rarely, chronic glomerulonephritis may present with hypovolemic hyponatremia secondary to salt-losing nephritis. These patients generally have moderately advanced renal impairment with serum creatinine levels greater than 3 to 4 mg per deciliter. This diagnosis should virtually never be considered in patients with renal disease that is not associated with a rise in serum creatinine. Patients with salt-losing nephritis may need supplemental sodium chloride intake to avoid ECF volume depletion or may be very susceptible to ECF volume depletion in association with either decreased intake or extrarenal (e.g., gastrointestinal) sodium and water losses. Because these patients may be pigmented, secondary to uremic dermatitis, and exhibit hyponatremia and volume depletion, their disease was initially described as mimicking Addison's disease.

d. **Addison's disease.** The patient with Addison's disease generally has associated hyperkalemia, and the prerenal azotemia generally does not increase serum creatinine to levels greater than 3.0 mg per deciliter. ECF volume repletion in these patients may correct both the hyponatremia and the hyperkalemia. Moreover, the plasma cortisol during periods of stress may fall within the normal range. Thus if adrenal insufficiency is suspected, a 2-hour cosyntropin (Cortrosyn) stimulation test should be performed. In addition to a urinary sodium concentration greater than 20 mEq per liter, a urinary potassium concentration of less than 20 mEq per liter may be another clue to mineralocorticoid deficiency. If fluid intake has been restricted, the patient with Addison's disease may not present with hyponatremia, and hyperkalemia may not be present if the ECF volume depletion is not severe. Thus, a high index of suspicion is necessary to make the diagnosis of adrenal insufficiency. These patients may present with nonspecific symptoms such as weight loss, anorexia, abdominal pain, nausea, vomiting, diarrhea, or fever.

e. **Osmotic diuresis or anion excretion.** Another major diagnostic consideration in the hypovolemic hyponatremic patient with a urinary sodium concentration greater than 20 mEq per liter is whether an osmotic diuresis is obligating urinary sodium excretion.

(1) **Glucose, urea, or mannitol diuresis.** The uncontrolled diabetic patient may have substantial glucosuria, causing water and electrolyte losses and thus ECF volume depletion. The urea diuresis after relief of urinary tract obstruction is another example of an osmotic diuresis that can cause ECF volume depletion. A chronic mannitol infusion without electrolyte replacement can produce a similar situation.

(2) **Bicarbonaturia.** Increased anion excretion also can obligate renal water and electrolyte losses. The most frequently encountered example of this is metabolic alkalosis with bicarbonaturia. The bicarbonate anion in the urine is accompanied by cations, including sodium and potassium, which maintain electrical neutrality. Bicarbonaturia may accompany the early development of metabolic alkalosis with postoperative nasogastric suction or vomiting. Proximal renal tubular acidosis (e.g., Fanconi's syndrome) is another condition in which bicarbonaturia causes renal electrolyte loss. In the absence of a urinary tract infection with urease-producing organisms, a urinary pH greater than 6.1 indicates the presence of bicarbonate in the urine.

(3) **Ketonuria.** Ketoacids are other anions that can obligate renal electrolyte losses in spite of ECF volume depletion; this may contribute to urinary electrolyte losses in diabetic or alcoholic ketoacidosis and starvation.

f. **Euvolemic hyponatremic patient.** There are a limited number of diagnostic possibilities with hyponatremic patients who exhibit neither edema nor ECF volume depletion (i.e., euvolemic hyponatremic patients). Two endocrine disorders must be considered—hypothyroidism and secondary adrenal insufficiency associated with pituitary or hypothalamic disease.

(1) **Hypothyroidism.** The occurrence of hyponatremia with hypothyroidism generally suggests severe disease, including myxedema coma. In some patients, particularly the elderly, the diagnosis may not be readily apparent. Thus, thyroid function must be assessed in the euvolemic hyponatremic patient.

(2) **Glucocorticoid deficiency.** An intact renin-angiotensin-aldosterone system avoids ECF volume depletion with secondary adrenal insufficiency, but it is clear that glucocorticoid deficiency alone can impair water excretion and cause hyponatremia. Although skull films and computed axial tomography (CT scan) should always be obtained in the euvolemic hyponatremic patient when the cause of the hyponatremia is not obvious, normal skull films or CT scans do not exclude secondary adrenal insufficiency. A low plasma cortisol level associated with a low adrenocorticotropic hormone (ACTH) level supports the diagnosis of secondary adrenal insufficiency. In this setting, both secondary adrenal insufficiency and secondary hypothyroidism may contribute to the hyponatremia accompanying pituitary insufficiency.

(3) **Emotional stress, pain, and drugs.** In the absence of endocrine disorders, drug effects and emotional or physical stress must be considered in the euvolemic hyponatremic patient before invoking the diagnosis of the syndrome of inappropriate antidiuretic hormone (SIADH) secretion. Acute pain or severe emotional stress (e.g., decompensated psychosis associated with continued water ingestion) may lead to acute and severe hyponatremia. Drugs that either stimulate the release of antidiuretic hormone (ADH) or enhance its action include:

(a) Nicotine
(b) Chlorpropamide
(c) Tolbutamide
(d) Clofibrate
(e) Cyclophosphamide
(f) Morphine
(g) Barbiturates
(h) Vincristine
(i) Carbamazepine (Tegretol)
(j) Acetaminophen
(k) Indomethacin
(l) Isoproterenol

Thus, determining whether the patient is receiving such drugs is an important diagnostic step with the euvolemic hyponatremic patient.

(4) **SIADH.** After exclusion of the diagnoses given above in the euvolemic hyponatremic patient, the diagnosis of SIADH may be considered. In general, the causes of SIADH include:

(a) Carcinomas
  (i) Lung
  (ii) Duodenum
  (iii) Pancreas
(b) Pulmonary disorders
  (i) Viral pneumonia
  (ii) Bacterial pneumonia
  (iii) Pulmonary abscess
  (iv) Tuberculosis
  (v) Aspergillosis
(c) Central nervous system disorders
  (i) Encephalitis, viral or bacterial
  (ii) Meningitis, viral, bacterial, or tubercular
  (iii) Acute psychosis
  (iv) Stroke (cerebral thrombosis or hemorrhage)
  (v) Acute intermittent porphyria
  (vi) Brain tumor
  (vii) Brain abscess
  (viii) Subdural or subarachnoid hematoma or hemorrhage
  (ix) Guillain-Barré syndrome
  (x) Head trauma

(5) **Evaluation of urinary sodium concentration.** The urinary sodium concentration in SIADH as well as in other conditions leading to euvolemic hyponatremia is generally greater than 20 mEq per liter. However, if the patient with SIADH is on a sodium-restricted diet or is volume depleted, the urinary sodium concentration may be less than 10 mEq per liter. Refeeding with a normal salt intake or expansion of ECF volume with saline will increase urinary sodium concentration to greater than 20 mEq per liter, but the hyponatremia will persist in the patient with SIADH or another euvolemic cause of hyponatremia.

V. **Therapy.** The therapy of hyponatremia depends on several factors, including (a) the cause of the hyponatremia, (b) the degree of the hyponatremia, and (c) the severity of signs and symptoms relating to the hyponatremia. Hyponatremia relating to mineralocorticoid, glucocorticoid, and/or thyroid hormone deficiency is of course best treated by hormone replacement.

A. **Specific treatment of cause of hyponatremia.** Drug-induced hyponatremia or hyponatremia related to physical or emotional stress is best managed by removal of the drug or stress. Treatment of edematous disorders (e.g., cardiac glycosides with cardiac failure or corticosteroids with nephrotic syndrome secondary to nil disease, or lipoid nephrosis) may also suppress nonosmotic vasopressin release and improve the renal capacity to excrete water, thus correcting the hyponatremia. Correction of ECF volume depletion, whether secondary to gastrointestinal or third space losses, diuretic abuse, Addison's disease, or salt-losing nephritis, also may correct the hyponatremia. In an occasional patient with diuretic-induced hyponatremia, cessation of the drug and restoration of ECF volume is inadequate to correct the hyponatremia if total body potassium stores are not repleted. Treatment of the uncontrolled diabetic patient with profound hyperglycemia, ketonuria, and glucosuria will also diminish renal losses of fluid and electrolytes, thereby alleviating the precipitating cause of the hyponatremia.

B. **Restriction of water intake.** If none of these specific treatments is possible, adequate restriction of water intake will increase plasma sodium concentration independent of the cause of the hyponatremia. Adequate fluid restriction is restriction to an amount less than urine output and estimated insensible losses. For example, if a hyponatremic patient has a daily urine output of 500 ml and estimated daily insensible losses of 500 ml, daily water restriction to 1000 ml should be expected to prevent additional lowering of the plasma sodium concentration; more severe fluid restriction to less than 1000 ml per day is necessary to increase plasma sodium concentration.

C. **Demeclochlortetracycline administration.** In a patient with chronic SIADH who will not voluntarily restrict water intake to a degree sufficient to avoid symptomatic hyponatremia, the administration of demeclochlortetracycline (600 to 1200 mg per day) may be used to create a state of drug-induced nephrogenic diabetes insipidus, thereby allowing more liberal fluid intake without associated hyponatremia. It must be remembered, however, that demeclochlortetracycline is metabolized largely by the liver, and patients with liver disease may develop azotemia associated with high plasma drug concentrations and nephrotoxicity. This tetra-

cycline may also cause a natriuresis, with subsequent ECF volume depletion. Lithium has also been used to cause a vasopressin-resistant nephrogenic diabetes insipidus in patients with chronic SIADH and symptomatic hyponatremia, but this drug is less consistently effective and has more side effects than demeclochlortetracycline. Specific antagonists to arginine vasopressin have now been developed and should be available for clinical use in the near future.

D. Treatment of acute symptomatic hyponatremia with furosemide and hypertonic saline. For the asymptomatic patient who has no reversible cause of hyponatremia and a plasma sodium concentration of not less than 130 mEq per liter, only careful monitoring may be appropriate. On the other hand, if the plasma sodium concentration decreases to 125 mEq per liter or less, cell swelling is no doubt occurring, and appropriate water restriction to maintain plasma sodium concentration at a level greater than 130 mEq per liter is indicated. As already emphasized, however, the rate of decrease in plasma sodium concentration is an important determinant of associated signs and symptoms.

1. **Indications for treatment.** In a patient with acute hyponatremia and CNS symptoms, including stupor, coma, or seizures, rapid treatment to decrease the brain swelling is indicated. The best approach is to increase ECF osmolality by administering hypertonic (3%) saline at a rate equal to furosemide-induced renal losses of sodium, potassium, and chloride. The difference in the hourly rate of urine flow and hypertonic saline infusion will equal the net negative fluid balance. For example, if a furosemide-induced (1 mg intravenously) diuresis of 1 liter per hour occurs and the urinary electrolyte losses are replaced by 150 ml of 3% saline, then 850 ml of net negative water balance has been achieved. This approach avoids dangerous overexpansion of ECF and corrects the primary cause of the hyponatremia—excessive total body water. When available vasopressin antagonists will be very useful in the treatment of acute symptomatic hyponatremia.
2. **Calculation of desired negative water balance.** The following example illustrates the method of correcting the plasma sodium concentration from 115 to 130 mEq per liter in a stuporous, hyponatremic 70-kg man:

   Total body water (TBW) = body weight × 60% or $70 \times 0.6 = 42\text{L}$

   Then,

   $$\frac{\text{Actual plasma concentration}}{\text{Desired plasma concentration}} \times \text{TBW} \quad \text{or} \quad \frac{115\ \text{mEq/L}}{130\ \text{mEq/L}} \times 42\ \text{L} = 36.5\ \text{L}$$

   Therefore, 5.5 liters (42.0 L–36.5L) negative water balance will be needed to raise plasma sodium concentration to 130 mEq per liter.
   Therefore, an approximate net negative fluid balance of 900 ml per hour in this patient should raise the plasma sodium concentration to 130 mEq per liter in 6 hours. Nevertheless, careful monitoring of the patient during these rapid changes in fluid balance is important.

Hypernatremia

Hypernatremia, defined as a plasma sodium concentration greater than 150 mEq per liter, is less frequent than hyponatremia. This is probably not due to a more frequent occurrence of disorders of renal dilution than of renal concentration. If there is an inability to dilute the urine, however, water intake of 1 to 2 liters per day may cause hyponatremia. This amount of fluid intake may be ingested as routine behavior in spite of a hypo-osmolar stimulus to suppress thirst, thus perhaps explaining the frequency of hyponatremia. On the other hand, renal concentrating defects that cause renal water losses generally do not cause hypernatremia unless a disturbance in thirst is present or the patient cannot drink or obtain adequate fluid to drink. The very young, the very old, and the very sick are, therefore, the populations that develop hypernatremia most frequently. In the absence of an inability to drink (e.g., coma, nausea, and vomiting) or to obtain water (e.g., infants or severely ill adults), the thirst mechanism is very effective in preventing hypernatremia. Patients with complete central diabetes insipidus may have renal water losses in excess of 10 liters per day. Even so, these patients rarely present with hypernatremia since thirst stimulation leads to increased water intake with only a 1 to 2 percent rise in plasma osmolality, thus avoiding frank hypernatremia.

I. Clinical settings. Renal concentrating defects can occur either secondary to inadequate vasopressin release (central diabetes insipidus) or as an impaired renal response to vasopressin (nephrogenic diabetes insipidus).

A. Central diabetes insipidus. Approximately 50 percent of instances of central diabetes insipidus have no detectable underlying cause and thus are classified as idiopathic. Trauma, surgical procedures in the area of the pituitary or hypothalamus, and neoplasms, either primary or secondary (e.g., metastatic breast cancer) constitute the majority of the remaining causes of central diabetes insipidus. In addition, encephalitis, sarcoidosis, or eosinophilic granuloma may cause central diabetes insipidus.

B. Nephrogenic diabetes insipidus. Nephrogenic diabetes insipidus can be secondary to a variety of conditions (Table 2-1).

Table 2-1. Acquired Causes of Nephrogenic Diabetes Insipidus

Chronic renal disease
Polycystic disease
Medullary cystic disease
Pyelonephritis
Ureteral obstruction
Far-advanced renal failure
Analgesic nephropathy
Electrolyte disorders
Hypokalemia
Hypercalcemia
Drugs
Lithium
Demeclocycline
Acetohexamide
Tolazamide
Glyburide
Propoxyphene
Amphotericin
Methoxyflurane
Vinblastine
Colchicine
Sickle cell disease
Dietary abnormalities
Excessive water intake
Decreased sodium chloride intake
Decreased protein intake
Miscellaneous
Multiple myeloma
Amyloidosis
Sjögren's disease
Sarcoidosis

From T. Berl and R. W. Schrier, *Disorders of Serum Sodium Concentration.* Irvine, Calif.: McGaw Laboratories, Division of American Hospital Corporation, 1979.

1. **Secondary to renal diseases.** Medullary or interstitial renal diseases are particularly likely to be accompanied by vasopressin-resistant renal concentrating defects; the most frequent of these diseases are medullary cystic disease, chronic interstitial nephritis (e.g., analgesic nephropathy), polycystic disease, and partial bilateral urinary tract obstruction. Far-advanced renal disease of any cause is uniformly associated with a renal concentrating defect. However, because of the very low glomerular filtration rate, the renal water loss (i.e., polyuria) is modest (2 to 4 L per day).
2. **Secondary to hypercalcemia and hypokalemia.** Hypercalcemia secondary to any cause, including primary hyperparathyroidism, vitamin D intoxication, milk alkali syndrome, hyperthyroidism, and tumor, may cause nephrogenic diabetes insipidus. Similarly, hypokalemia secondary to any cause, including primary aldosteronism, diarrhea, or chronic diuretic use, may cause nephrogenic diabetes insipidus.
3. **Drugs, dietary abnormalities, and other causes.** Various drugs impair the end-organ response to ADH and thus cause a renal concentrating defect (Table 2-1). Excess water intake as well as dietary sodium and/or protein restriction also has been shown to impair urinary concentration. Other unique causes of nephrogenic diabetes insipidus include multiple myeloma, amyloidosis, Sjögren's disease, and sarcoidosis.

C. Insensible losses or osmotic diuresis. Excessive insensible losses without adequate intake will cause hypernatremia since these losses are always hypotonic in nature. Also, renal losses are generally hypotonic during an osmotic diuresis such as occurs with glucose, urea, or mannitol and thus may lead to hypernatremia. However, hypernatremia will occur secondary to hypotonic losses only if (a) the thirst mechanism is impaired, (b) fluid is not available, or (c) the patient is unable to obtain and/or drink fluid. Thus, since hypotonic fluid losses are most frequently associated with an intact thirst mechanism, availability of fluid, and ability to drink, hypernatremia is not a frequent occurrence.

D. Administration of hypertonic salts. A rare cause of hypernatremia is the administration of hypertonic salt substances. Thus, hypernatremia may occur during cardiopulmonary resuscitation and administration of large amounts of sodium bicarbonate or during inadvertent intravascular infusions of hypertonic saline in therapeutic abortions. Sea water drowning or hemodialysis with a mistakenly high sodium concentration dialysate are other causes of hypernatremia. The use of sodium chloride tablets without adequate water intake in a hot, humid environment may occasionally lead to profound hypernatremia in some people. The modest elevation of plasma sodium concentration in patients with Cushing's syndrome or primary hyperaldosteronism may provide a clue to the diagnosis but is of no clinical consequence. When hypernatremia occurs in any of the above clinical settings, severe signs and symptoms may be associated.

II. Signs and symptoms. Polyuria and polydipsia may be prominent symptoms of the patient who subsequently develops hypernatremia in association with inadequate water intake.

A. CNS dysfunction. Neurologic abnormalities constitute the most prominent manifestations of hypernatremic states. These neurologic manifestations appear to be due primarily to cellular dehydration and shrinkage of brain cells that is associated with tearing of cerebral vessels. Capillary and venous congestion, subcortical and subarachnoid bleeding, and venous sinus thrombosis all have been described with hypernatremia.

B. Prognosis of acute versus chronic hypernatremia. The signs and symptoms of hypernatremia are more severe with acute than with chronic hypernatremia. Indeed, 75 percent mortality has been reported in association with acute hypernatremia in adults with acute elevations of plasma sodium concentration above 160 mEq per liter. These adults, however, frequently have severe primary diseases associated with their hypernatremia, and these primary diseases may largely account for the high mortality. A 45 percent mortality has been reported in children with acute hypernatremia, and as many as two-thirds of the surviving children may have neurologic sequelae.

C. Idiogenic osmoles with chronic hypernatremia. The more benign course of chronic hypernatremia appears to be related to cellular mechanisms that protect against severe brain dehydration. The brain, however, requires some period of time, perhaps days, to adapt. With chronic hypernatremia brain cells generate idiogenic osmoles, some of which appear to be amino acids; these idiogenic osmoles are osmotically active and restore brain water to near control levels in spite of persistent hypernatremia. The presence of these idiogenic anions with chronic hypernatremia, although protective against brain dehydration and shrinkage, may predispose to brain edema if the hypernatremia is corrected too rapidly.

D. Correlation of CNS dysfunction with degree of hyperosmolality. The earliest manifestations of hypernatremia are restlessness, increased irritability, and lethargy. These symptoms may be followed by muscular twitching, hyperflexia, tremulousness, and ataxia. The level of hyperosmolality at which these signs and symptoms occur depends not only on the rapidity of the change in the plasma sodium concentration but also on the age of the patient; the very young and the very old exhibit the most severe manifestations. In general, however, these signs and symptoms may occur progressively with plasma osmolality in the range of 325 to 375 mOsm per kilogram of water. At plasma osmolalities above this level tonic muscular spasticity, focal and grand mal seizures, and death may occur. The elderly patient with dementia or severe cerebrovascular disease may demonstrate these life-threatening signs and symptoms at a lower level of plasma hyperosmolality.

Because of the potential severe consequences of hypernatremia, it is important to make a specific diagnosis of the cause and institute appropriate therapy.

III. Diagnosis. As with hyponatremia, a diagnostic approach (Fig. 2-2) that classifies patients on the basis of total body sodium or ECF volume status may be used. Such an approach allows the clinician to focus on the most likely diagnosis in each category.

A. Hypovolemic hypernatremic patient. The hypernatremic patient may have evidence of ECF volume depletion that has occurred secondary to either renal or extrarenal losses.

1. **Extrarenal losses.** If the losses have been from an extrarenal site (e.g., diarrhea), then sodium and water conservation by the kidney should be readily apparent. In such patients the urine sodium concentration is less than 10 mEq per liter and the urine is hypertonic.
2. **Renal losses.** In contrast, hypotonic electrolyte losses may occur in the urine during an osmotic diuresis. In these patients evidence of renal sodium and water conservation is of course not present because the urine is the source of the losses. Thus, the urine is not hypertonic, and urine sodium concentration is generally greater than 20 mEq per liter. In the hyperglycemic diabetic patient with good renal function and profound glucosuria, hypernatremia may be a presenting feature because hypotonic renal losses may obscure any effect of hyperglycemia to shift water osmotically from cells to ECF.

B. Hypervolemic hypernatremic patient. Patients with hypernatremia also may have evidence of ECF volume expansion. Generally, these are patients who have received excessive amounts of hypertonic sodium chloride or sodium bicarbonate. In such an acute setting the incidence of ECF volume expansion is most likely to be associated with pulmonary congestion and/or elevated neck veins rather than peripheral edema. This variety of hypervolemic hypernatremia is rather infrequent.

C. Euvolemic hypernatremic patient. More frequent are hypernatremic patients who exhibit evidence of neither ECF volume depletion nor expansion. These are patients who have suffered primarily from water losses without electrolyte losses. Because of free permeability of membranes to water, water losses are only one-third from the ECF compartment and two-thirds from within cells. This is the main reason that hypernatremia rather than ECF volume depletion primarily occurs with water losses.

1. **Insensible water losses.** Ill patients who do not receive replacement of insensible losses will become hypernatremic. The acclimatized patient also has primarily water loss without electrolyte loss with prolonged sweating and may

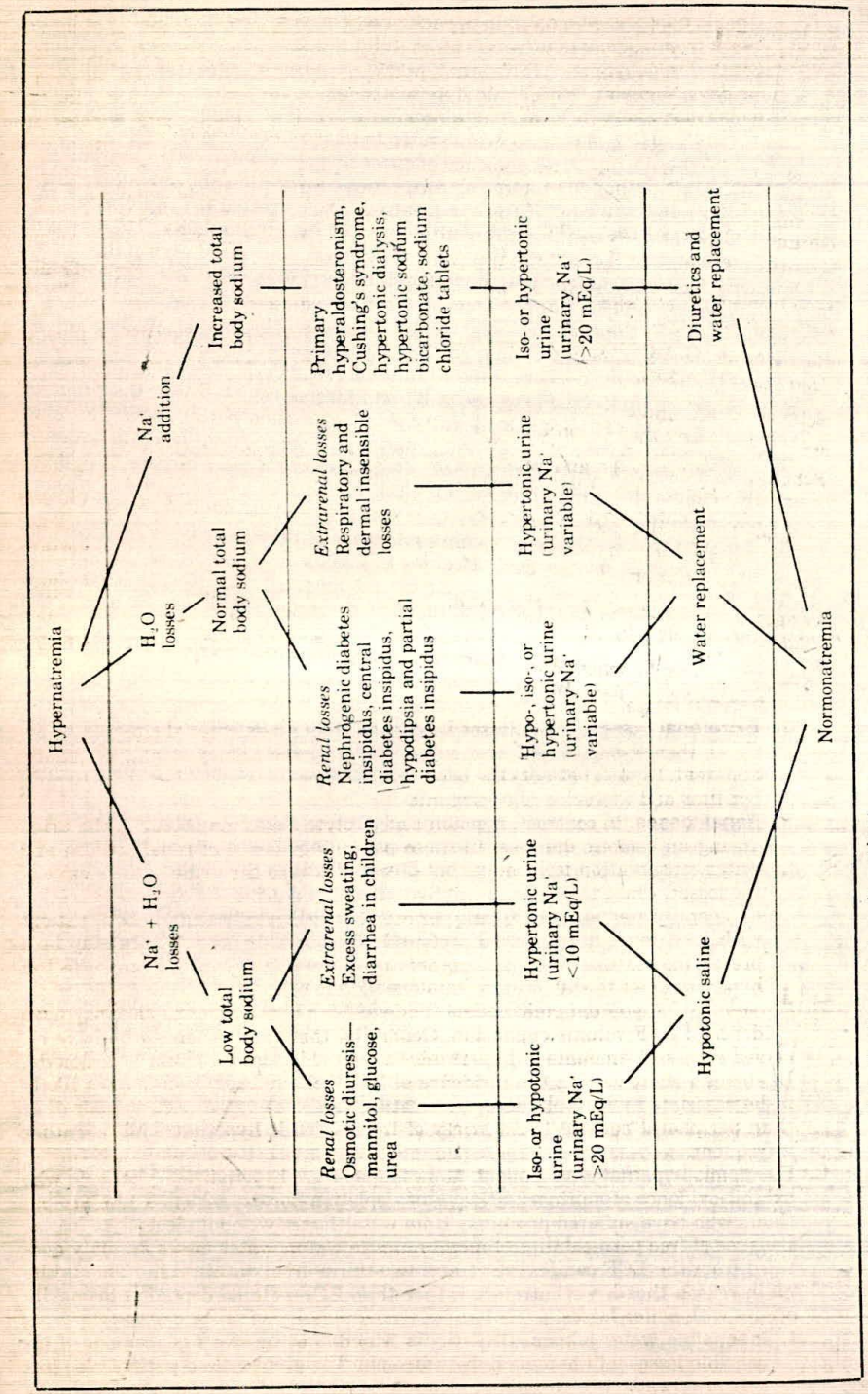

Fig. 2-2. Diagnostic approach to the hypernatremic patient.

become hypernatremic. This is rare, however, since stimulation of thirst and water intake are generally adequate to avoid hypernatremia. With these extrarenal water losses the urine becomes concentrated, and the urine sodium concentration reflects sodium intake.

2. **Partial central diabetes insipidus.** Patients with partial central diabetes insipidus, particularly with hypothalamic lesions associated with hypodipsia, may present with hypernatremia and hypertonic urine.
3. **Hypernatremia, hypodipsia, and hypertonic urine.** Patients with virtual absence of osmotic vasopressin release may maintain normal nonosmotic vasopressin release (e.g., secondary to volume depletion) and present with hypernatremia, hypodipsia, and maximally concentrated urine. These patients generally have hypothalamic brain lesions. Their disorder has in the past been termed essential hypernatremia or a reset osmostat.
4. **Complete central diabetes insipidus.** In patients with complete central diabetes insipidus the urine is hypotonic in spite of plasma hyperosmolality, which normally stimulates vasopressin release and concentrates the urine.
5. **Responses to fluid deprivation and exogenous ADH.** In Table 2-2 are shown the responses to fluid deprivation (3 to 5 percent loss of body weight) followed by exogenous vasopressin administration in patients with partial and complete diabetes insipidus compared to normal subjects. Patients with compulsive water drinking may present with polyuria and a blunted response to the fluid deprivation test; on cessation of fluid intake, hypernatremia does not develop in these patients and their renal concentration defect is primarily due to a resistance of the kidney to vasopressin. However, since patients with central or nephrogenic diabetes insipidus may present with polyuria and polydipsia in the absence of hypernatremia, awareness of the diagnosis of compulsive (psychogenic) water drinking is quite important. Menopausal women with previous psychiatric problems are particularly prone to compulsive water drinking. Lastly, the patient with nephrogenic diabetes insipidus may occasionally have vasopressin-resistant hypotonic urine (e.g., hypercalcemic or hypokalemic nephropathy); thus, the temporary absence of fluid intake because of an intercurrent illness can be associated with hypernatremia. In all hypernatremic patients who have primarily water losses, the urine sodium concentration merely reflects sodium intake.

IV. **Therapy.** The treatment of hypernatremia depends on two important factors—ECF volume status and rate of development of the hypernatremia.

A. **Correction of ECF volume depletion.** If the hypernatremia is associated with ECF volume depletion, the primary therapeutic goal is to administer isotonic saline until restoration of ECF volume is achieved, as assessed by normal neck veins and absence of orthostatic hypotension and tachycardia. Hypotonic (0.45%) sodium chloride or 5% glucose can then be used to correct plasma osmolality.

B. **Correction of ECF volume expansion.** In contrast, if hypernatremia is associated with ECF volume expansion, diuretics can be used to treat the hypernatremia. The loop diuretic furosemide appears to be particularly useful in the generation of hypotonic urine and thus is particularly effective in this setting. In the presence of renal failure the patient with hypernatremia and fluid overload may need to be dialyzed to treat the hypernatremia.

C. **Water replacement—method of calculation.** Lastly, the patient with euvolemic hypernatremia may be treated primarily with water replacement either orally or parenterally with 5% glucose in water. The method of calculation of the necessary water replacement for a 75-kg man with a plasma sodium of 154 mEq per liter is as follows:

$$\text{Total body water (TBW)} = \text{body weight} \times 60\% \text{ or } \text{TBW} = 75 \times 0.6 = 45 \text{ L}$$

Then,

$$\frac{\text{Actual plasma sodium}}{\text{Desired plasma sodium}} \times \text{TBW} \quad \text{or} \quad \frac{154 \text{ mEq/L}}{140 \text{ mEq/L}} \times 45 \text{ L} = 49.5 \text{ L}$$

Table 2-2. Responses to Fluid Deprivation and Exogenous Vasopressin

	Number of Cases	Mean Uosm with Dehydration	Uosm after Vasopressin	% Change (in Uosm)
Normal subjects	9	1067 ± 68.7	978 ± 79.4	−8.9 ± 3.0
Complete central diabetes insipidus	18	168 ± 13	445 ± 52	180 ± 41.4
Partial central diabetes insipidus	12	437 ± 33.6	548.6 ± 28.2	28.5 ± 4.7
Compulsive water drinking	7	738.2 ± 52.9	779.8 ± 73.1	5 ± 2.2

Data from M. Miller, T. Dalakos, A. M. Moses, et al., Recognition of partial defects in antidiuretic hormone secretion. *Ann. Intern. Med.* 73:721, 1970.

Therefore, 4.5 liters (49.5 L - 45.0 L) positive water balance would correct the plasma sodium concentration.

D. Rate of correction. The recommended rate of correction of the hypernatremia depends on the rate of development of the hypernatremia and the associated symptoms. More neurologic signs and symptoms are associated with acute hypernatremia; therefore, this biochemical abnormality should be corrected rapidly over a few hours.

Idiogenic osmoles appear to accumulate in brain cells during periods of chronic hypernatremia, a mechanism that protects against brain shrinkage. Thus, rapid correction of chronic hypernatremia can create an osmotic gradient between the ECF and intracellular compartments with osmotic water movement into cells and brain edema. In general, therefore, chronic hypernatremia is best corrected gradually at a rate not to exceed 2 mOsm per hour. Total correction time should be 48 hours or longer.

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3 The Patient With Hypokalemia or Hyperkalemia

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Potassium, the major intracellular cation, influences several enzymatic processes. Far more important, however, is the fact that membrane polarization is critically dependent on the relation between extracellular and intracellular potassium concentrations (Ke/Ki). The major clinical manifestations of hypo- and hyperkalemia, caused by alterations of membrane phenomena in excitable tissues, are abnormalities in neuromuscular function and cardiac conduction.

I. **Body potassium stores and factors affecting transcellular distribution.** Total body potassium content in a normal person averages 50 mEq per kilogram and ranges from 31 to 57 mEq per kilogram (Fig. 3-1). Only 1.5 to 2.0 percent of potassium is within the extracellular fluid (ECF) space; the remainder is located in intracellular fluid (ICF), largely in muscle. The normal serum potassium concentration ranges from 3.8 to 5.0 mEq per liter, and intracellular potassium concentration is estimated to be 150 mEq per liter.

In view of the marked disparity between the potassium content of the intra- and extracellular spaces, factors controlling the transcellular distribution of potassium are critical for maintaining normal serum levels (Fig. 3-2).

A. **pH.** Acidosis promotes potassium exit from cells and increases the Ke/Ki ratio; alkalosis acts in the opposite fashion and tends to decrease serum potassium concentration. Alterations in bicarbonate concentration without changes in plasma pH can also modify transcellular potassium movement. In addition, mineral and nonmineral acids may affect potassium in somewhat different fashions. A rough guideline is that each 0.1 unit change in pH results in a reciprocal 0.6 mEq per liter change in serum potassium with hyperchloremic acidosis, but the same change in pH causes an average 0.4 mEq per liter or less change in potassium with other acid-base disturbances.

B. **Insulin.** Insulin promotes potassium entry into cells, which is, at least in part, independent of its action on glucose uptake. Because potassium can stimulate insulin release, this action may represent a regulatory mechanism.

C. **Aldosterone.** The major effect of aldosterone is modification of urinary potassium excretion. Although it has been suggested that it may also promote cellular potassium uptake, this issue remains unresolved at present.

D. **Beta-adrenergic agents.** Beta-adrenergic agents, specifically those with B_2-agonist properties, promote cellular potassium uptake by a direct effect on the sodium-potassium pump. Whether potassium can, in turn, stimulate epinephrine release has not been resolved definitely.

E. **Total body potassium.** It is apparent that alterations in one or several of the above factors can modify the serum potassium concentration independent of any change in total body potassium content. In the absence of changes in these factors, serum potassium concentration parallels changes in cellular potassium stores; depletion results in hypokalemia, and surfeit, in hyperkalemia.

Firm guidelines do not exist to estimate the magnitude of depletion from the measured serum potassium level. A rough rule of thumb is that each 1 mEq per liter decrement in serum potassium concentration corresponds to a loss of approximately 200 to 300 mEq per liter of body potassium stores. Reliable data correlating hyperkalemia with the magnitude of potassium retention are not available, but an increase in potassium of 1 mEq per liter above normal probably

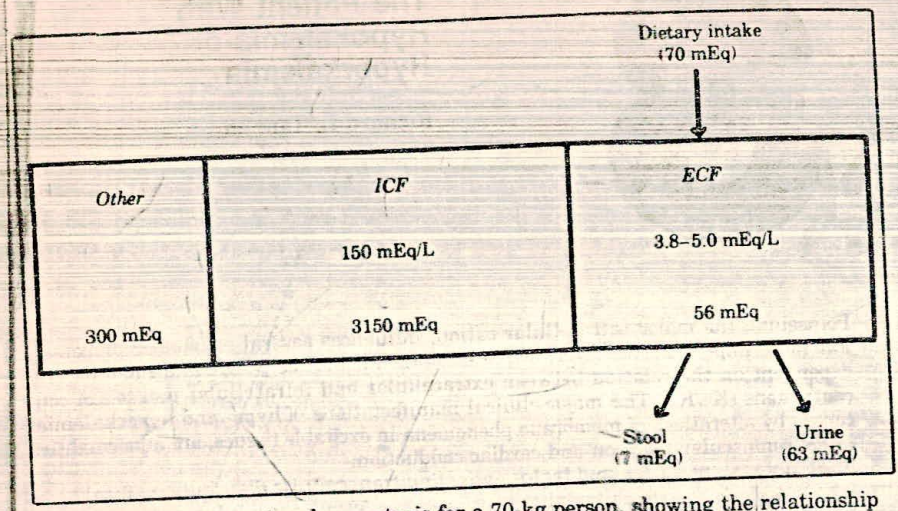

Fig. 3-1. Normal potassium homeostasis for a 70-kg person, showing the relationship between potassium intake, output, and distribution in body compartments.

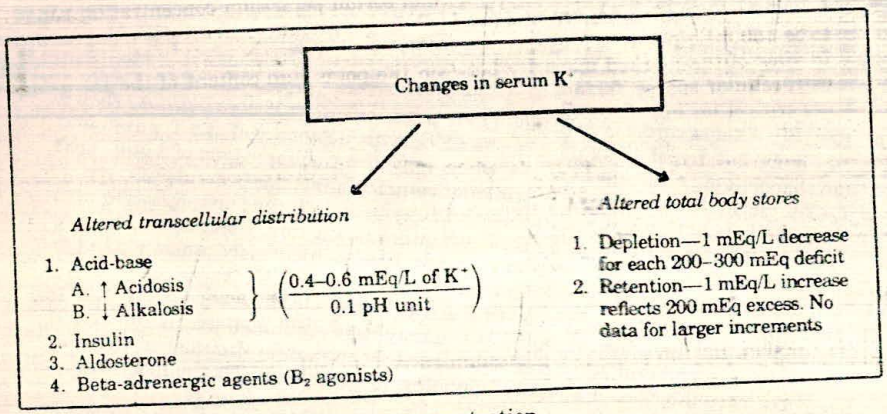

Fig. 3-2. Changes in serum potassium concentration.

reflects at least a 200 mEq per liter excess of body potassium stores. The amount of retention corresponding to higher serum potassium concentrations is not known.

II. **Maintenance of potassium balance—renal regulation of potassium.** Regulation of body potassium stores is relegated to the kidney. As shown in Figure 3-1, 90 percent or more of ingested potassium is excreted in the urine, with the remainder lost in stool. When renal function is substantially impaired, stool losses may account for a greater proportion of potassium excretion; stool excretion averages 34 percent in patients with severe renal failure (i.e., creatinine clearance below 5 ml per minute). A detailed review of renal regulation of potassium is provided in the publication by Wright and Giebisch. In general, potassium is freely filtered and 90 percent is then reabsorbed in the proximal portions of the nephron. The potassium excreted in the urine is largely the result of secretion in the distal convoluted tubule and collecting duct. The factors that influence potassium handling by the distal nephron and, consequently, determine the urinary excretion rate include the following;

A. **Sodium.** Acute changes in sodium excretion result in parallel changes in potassium excretion. A natriuresis promotes potassium excretion by increasing fluid delivery to the distal nephron and perhaps by increasing sodium reabsorption at distal nephron sites. A decrease in sodium excretion diminishes potassium excretion. When a diet high or low in sodium content is ingested for several days, sodium balance is achieved without major changes in total body potassium. Thus, adjustments maintain potassium balance despite variations in sodium intake. In fact, an acute potassium load is excreted more readily on a low than on a high sodium diet, in apparent contrast to the influence of acute changes in sodium excretion on potassium. This probably results from the higher aldosterone level with sodium deprivation.

B. **Mineralocorticoids.** Mineralocorticoids promote sodium retention and potassium excretion, although the two effects may be the result of separate mechanisms. Furthermore, a high potassium concentration stimulates aldosterone secretion, whereas a low potassium concentration is inhibitory. This results from a direct effect of potassium on the adrenal glands rather than an indirect, renin-mediated mechanism, because a high potassium level suppresses and a low potassium level stimulates renin secretion. This interrelation between potassium and aldosterone appears to present an important feedback control mechanism for the regulation of potassium excretion.

C. **Anion excretion.** Excretion of poorly reabsorbable anions such as sulfate promotes kaliuresis. An increase in the negative transtubular voltage across the epithelium of the distal nephron (by providing a more favorable electrochemical gradient for potassium movement into the tubular lumen) and an increase in tubular flow rate both may increase potassium secretion. In addition, recent studies indicate that a decreased chloride concentration in distal tubular fluid directly promotes net potassium secretion by this segment of the nephron.

D. **Acid-base**

1. **Systemic pH.** Changes in systemic pH appear to alter the potassium content of the renal tubular cell in a manner analogous to the effect on other tissues (i.e., acidosis decreases and alkalosis increases intracellular potassium). There is evidence indicating that acute acidosis decreases potassium secretion via this mechanism, whereas alkalosis acts in the opposite fashion. However, this effect is transitory and overridden by other factors when the acid-base abnormality is sustained. Chronic metabolic acidosis is usually accompanied by mild potassium depletion; chronic respiratory acidosis and alkalosis, by little change in total body potassium; and chronic metabolic alkalosis, by severe potassium depletion.
2. **Ammonia metabolism.** A relation between potassium and renal ammonia metabolism has been elucidated. Potassium depletion stimulates renal ammonia production, whereas a high potassium intake is inhibitory. Enhanced ammonia production and excretion in the urine decrease potassium excretion, possibly by favoring hydrogen ion and thereby diminishing potassium secretion. This may be an additional feedback mechanism for control of potassium excretion, but its quantitative importance has not been clearly defined.

E. **Dietary potassium.** Finally, the renal capacity to excrete or retain potassium is influenced by the daily potassium intake. The kidney possesses substantial flexibility in potassium handling, with the capacity to excrete up to 10 mEq/kg/day (700 mEq for a 70-kg man/day) or less than 10 mEq per day. Several days are required for maximal adaptation to either extreme.
Ingestion of a high potassium diet increases aldosterone and the enzyme Na-K-ATPase, which promotes potassium entry into renal tubular cells. This adapted kidney has an enhanced capacity to excrete potassium, and the adapted person has an increased ability to survive an otherwise lethal potassium load. With ingestion of a low potassium diet, urinary potassium excretion diminishes to less than 10 mEq per day within a week. The early potassium-conserving response appears to depend, at least in part, on a decrease in plasma aldosterone concentration; after several days, however, the mechanism is independent of the hormone and involves an intrinsic adaptive response by the kidneys. The precise cellular mechanism responsible for low K^+ adaptation is undefined.
Considering the multitude of factors influencing renal potassium excretion, it is

not surprising that a variety of pathologic events can modify renal potassium handling. Furthermore, when potassium homeostasis is altered by extrarenal phenomena, appropriate and effective modification of renal potassium excretion transpires.

Hypokalemia

I. **Clinical setting.** Hypokalemia occurs as a result of (a) factors that influence the transcellular distribution of potassium, (b) total body potassium depletion, or (c) a combination of these phenomena. The most common cause of hypokalemia secondary to altered transcellular distribution is alkalosis, either respiratory or metabolic, but it also occurs with exogenous glucose or insulin administration. True potassium deficits result from gastrointestinal or renal losses and, rarely, sweat losses. Hypokalemia should be anticipated with loss of either upper or lower gastrointestinal tract secretions; the common renal causes are diuretic therapy or states of excess mineralocorticoid secretion. Potassium depletion is frequently seen in association with metabolic alkalosis, since common mechanisms underlie the development of both disorders.

II. **Signs and symptoms.** The important manifestations of hypokalemia are given in Table 3-1. The major symptoms result from aberrations in membrane polarization that affect function of both neural and muscular tissue.

Table 3-1. Clinical manifestations of hypokalemia

Cardiac
Predisposition to digitalis intoxication
Abnormal ECG
Atrial and ventricular ectopic beats
Cardiac necrosis (rare)
Hemodynamic
Decrease in blood pressure
Decreased pressor response to angiotensin II
Neuromuscular
GI: constipation, ileus
Striated muscle: weakness, paralysis
Life-threatening respiratory paralysis
Rhabdomyolysis
Kidney
Decrease in GFR and renal blood flow
Polyuria and polydipsia
Concentrating defect
Stimulates thirst
Increased renal NH_3 production
Predisposition to hepatic coma
Sodium retention
Hyponatremia (with concomitant diuretic therapy)
Chloride wasting
Metabolic alkalosis
Endocrine
Decrease in aldosterone
Increase in renin
Increase in prostaglandins (possible)
Decrease in insulin
Carbohydrate intolerance

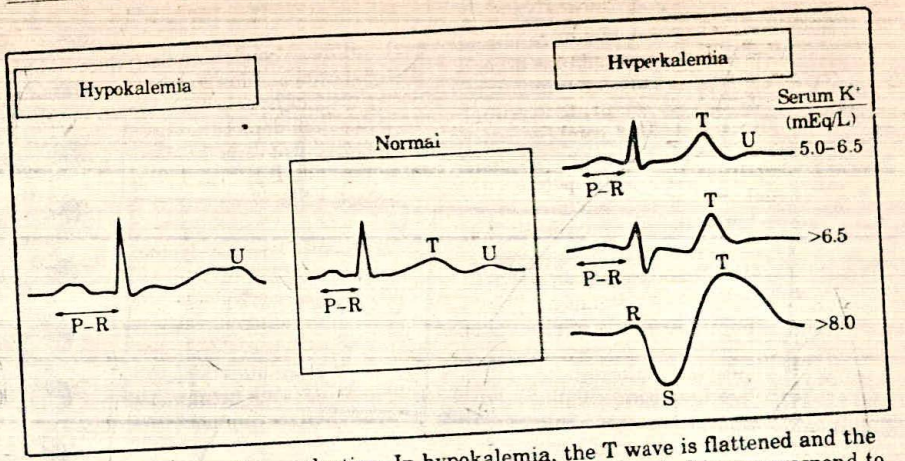

Fig. 3-3. Altered cardiac conduction. In hypokalemia, the T wave is flattened and the U wave is prominent. In hyperkalemia, the ECG changes do not always correspond to the serum potassium values given, but the progression from minor to severe changes correlates to some degree with the potassium level. With potassium concentration less than 6.5 mEq per liter, the early ECG abnormality is peaking or tenting of the T waves. The next change, shown with a level of potassium concentration greater than 6.5, includes flattening of the P wave, prolongation of the PR interval, and widening of the QRS complex, with development of a deep S wave. With severe hyperkalemia (>8.0 mEq per liter), a sine wave pattern develops and ventricular fibrillation or cardiac arrest is imminent.

A. **Cardiac.** Altered cardiac conduction is the most important abnormality. As shown in Figure 3-3, hypokalemia alters the ECG, with flattening of the T waves and development of prominent U waves, which may give the impression of a prolonged Q–T interval. It predisposes to atrial and ventricular ectopic beats. Most critical, however, hypokalemia increases the sensitivity to digitalis and predisposes toward the life-threatening arrhythmias of digitalis intoxication. For this reason, potassium balance must be carefully monitored and meticulously controlled in patients receiving digitalis preparations.

B. **Hemodynamics.** Potassium depletion can decrease blood pressure in both normotensive and hypertensive animals and may have similar effects in humans. A decrease in peripheral resistance, accounted for in part by diminished vascular sensitivity to the pressor effects of angiotensin II, accounts for the modification in systemic hemodynamics.

C. **Neuromuscular.** In individuals with normal cardiovascular status symptoms of potassium depletion are usually not apparent until the deficit exceeds 5 percent of total body potassium stores (200 mEq in a 70-kg person) and the serum potassium is less than 3.0 mEq per liter. Gastrointestinal (GI) tract dysfunction with hypokalemia can be manifested in constipation or frank ileus. Striated muscle abnormalities can vary from mild weakness to overt paralysis, with life-threatening respiratory paralysis. The latter usually requires a serum potassium concentration of less than 2.0 mEq per liter. Potassium depletion also predisposes toward rhabdomyolysis, myoglobinuria, and even acute renal failure.

D. **Renal.** Although renal function is altered by potassium depletion, the manifestations usually do not have a strong impact on the overall well-being of the patient. Severe hypokalemia can result in a functional decline in both renal blood flow and glomerular filtration rate, which is usually reversible with potassium repletion. However, severe and prolonged potassium depletion can result in chronic interstitial nephritis with permanent impairment of GFR and, infrequently, in

the development of severe chronic renal failure. Myoglobinuria-induced acute renal failure represents the other serious renal complication induced by potassium depletion. The most commonly recognized defect of hypokalemia is an inability to concentrate the urine maximally, but potassium depletion also directly stimulates thirst. This combination results in polydipsia and polyuria, which can sometimes provide a clue to underlying potassium depletion but seldom is of a magnitude to require specific clinical attention.

Renal ammonia production is stimulated by potassium depletion. This may explain why hypokalemia can provoke hepatic coma in patients with cirrhosis. Increased ammonium excretion also accounts for a higher than normal urine pH. Potassium depletion promotes sodium retention and may predispose toward edema formation under certain circumstances. Although potassium depletion has been incriminated as a cause of hyponatremia in association with diuretic use, the clinical importance of this effect has not been clearly defined. Severe potassium depletion appears to result in renal chloride wasting. This abnormality may account for the development of metabolic alkalosis with severe depletion (serum potassium less than 2.0 mEq/L).

E. Endocrine. The levels of several hormones are modified by potassium depletion. Aldosterone is depressed, but this is probably a physiologic control mechanism. Hypokalemia also elevates plasma renin activity (PRA). Stimulation of the vascular receptor secondary to renal vasoconstriction and an effect on the macula densa both may account for the increase in hypokalemia-induced PRA. When the potassium deficit is severe, pancreatic insulin release is inhibited; this probably accounts for the abnormal carbohydrate tolerance of potassium-depleted patients. This phenomenon may complicate management of the diabetic patient and occasionally may contribute to a false diagnosis of diabetes mellitus.

III. Differential diagnosis. By employing a systematic approach to the patient in whom hypokalemia is identified, it should be possible to identify the cause in the majority of instances. The important clues are derived from the clinical setting and certain key laboratory parameters, including plasma acid-base values and urinary potassium and chloride measurements. In some instances an assessment of the renin-angiotensin-aldosterone system is indicated. The presence or absence of hypertension may be helpful in the differential diagnosis.

A. Pseudohypokalemia. Potassium concentration can be lowered spuriously if a blood specimen with a high WBC count ($> 10^5$/ml) is stored at room temperature. The fall in plasma or serum potassium, which is caused by uptake by the leukocytes, can be prevented by prompt separation of plasma or serum.

B. Hypokalemia secondary to redistribution. The first question is whether a low serum potassium concentration reflects an alteration in distribution or results from a true potassium deficit. The causes of altered transcellular distribution are as follows:

1. **Alkalosis.** Alkalosis is identified by measurement of plasma pH (either arterial or venous) and determination of either total CO_2 or PCO_2. The rough guideline—a 0.1 unit increase in pH results in a 0.4 mEq per liter or less decrease in serum potassium—gives some indication of whether the hypokalemia results solely from altered transcellular distribution. Chronic respiratory alkalosis does not result in potassium depletion, but metabolic alkalosis is usually associated with a substantial potassium deficit.
2. **Insulin excess.** Insulin administration can decrease serum potassium concentration. More commonly, an acute glucose load promotes insulin release and hypokalemia.
3. **Beta-adrenergic agonists.** Systemic administration of drugs with B_2-agonist properties (e.g., epinephrine, salbutamol, terbutaline) can decrease the serum potassium concentration.
4. **Hypokalemic periodic paralysis.** Hypokalemic periodic paralysis is a rare hereditary disorder with autosomal dominant transmission. It is characterized by recurrent attacks of flaccid paralysis affecting the trunks and limbs, which last for 6 to 24 hours. Attacks are accompanied by hypokalemia caused by redistribution of potassium into cells.

5. **Barium poisoning.** Barium poisoning, caused by ingestion of acid-soluble barium salts, can produce flaccid paralysis and hypokalemia, which appear to result from potassium redistribution into cells. Associated vomiting and diarrhea differentiate it from periodic paralysis.
6. **Toluene intoxication.** Toluene intoxication commonly causes severe hypokalemia, often associated with severe muscular manifestations. In part the hypokalemia may result from redistribution of potassium into cells, although renal potassium wasting secondary to acquired renal tubular acidosis may also play a role.

Altered transcellular distribution clearly can coexist with a change in total body potassium. This should be anticipated in patients with metabolic alkalosis. Conversely, with severe acidosis the serum potassium may be normal in the presence of a potassium deficit. This can be confirmed by monitoring serum potassium as the acidosis is corrected. Diabetic ketoacidosis is a classic example of this phenomenon.

C. Potassium depletion. Hypokalemia unaccounted for by redistribution reflects a true potassium deficit. The cause should be defined not only to guide therapy, but also because it may provide a diagnostic clue to some other clinically important disorder.

A flow diagram for the diagnostic approach to hypokalemia is shown in Figure 3-4. The first step is to determine whether the potassium loss has a renal or extrarenal cause.

1. **Extrarenal potassium loss.** If the primary source of potassium loss is extrarenal and the deficit has persisted for several days, evidence of effective renal potassium conservation should be present. Urinary potassium excretion should be less than 20 mEq per day. The potassium concentration of a spot urine can be misleading because of the associated polyuria; however, a fractional potassium excretion (FEK) of less than 6 percent or a potassium (mEq/L)-creatinine (grams) ratio of less than 20 may be useful for a more rapid but less precise assessment of urinary potassium handling.

   The most common causes of extrarenal potassium depletion are losses from the lower gastrointestinal tract, which also result in metabolic acidosis because of bicarbonate loss. Overt diarrhea does not present a difficult diagnostic problem, nor does copious drainage from a fistula or villous adenoma. Chronic laxative abuse can pose problems of diagnosis because the patient may not admit to use of these agents. Patients with villous adenoma and laxative abuse may also present with a normal acid-base picture or with metabolic alkalosis. Other extrarenal causes are less common. Inadequate potassium intake in the absence of concomitant gastrointestinal problems is an unusual cause of hypokalemia, but it can be seen with anorexia nervosa or in the elderly patient on a tea and toast diet. Potassium depletion from severe perspiration produces an unusual clinical picture, with normal serum potassium levels and high rates of urinary potassium excretion despite substantial cellular potassium depletion. The explanation for these findings is unclear.
2. **Renal causes of potassium depletion.** In the hypokalemic patient a renal cause of potassium wasting should be anticipated if the urinary potassium exceeds 20 mEq per day. As shown in Figure 3-4, the differential diagnosis can be approached by initially segregating the causes according to the acid-base status of the patient.
   a. **With metabolic acidosis.** Renal potassium wasting with an accompanying acidosis can be seen in diabetic ketoacidosis, with either the proximal or distal forms of renal tubular acidosis (RTA), or as a result of therapy with carbonic anhydrase inhibitors (e.g., acetazolamide), which produce a clinical picture similar to RTA. Distal RTA is associated with a hyperchloremic acidosis, inability to acidify the urine, and renal stones or nephrocalcinosis distributed in a medullary pattern. Although uncommon, its initial presentation may be severe potassium depletion with paralysis. Proximal RTA has a similar electrolyte pattern, but the urine can be acidified and nephrocalcinosis does not occur. It is usually accompanied by other mani-

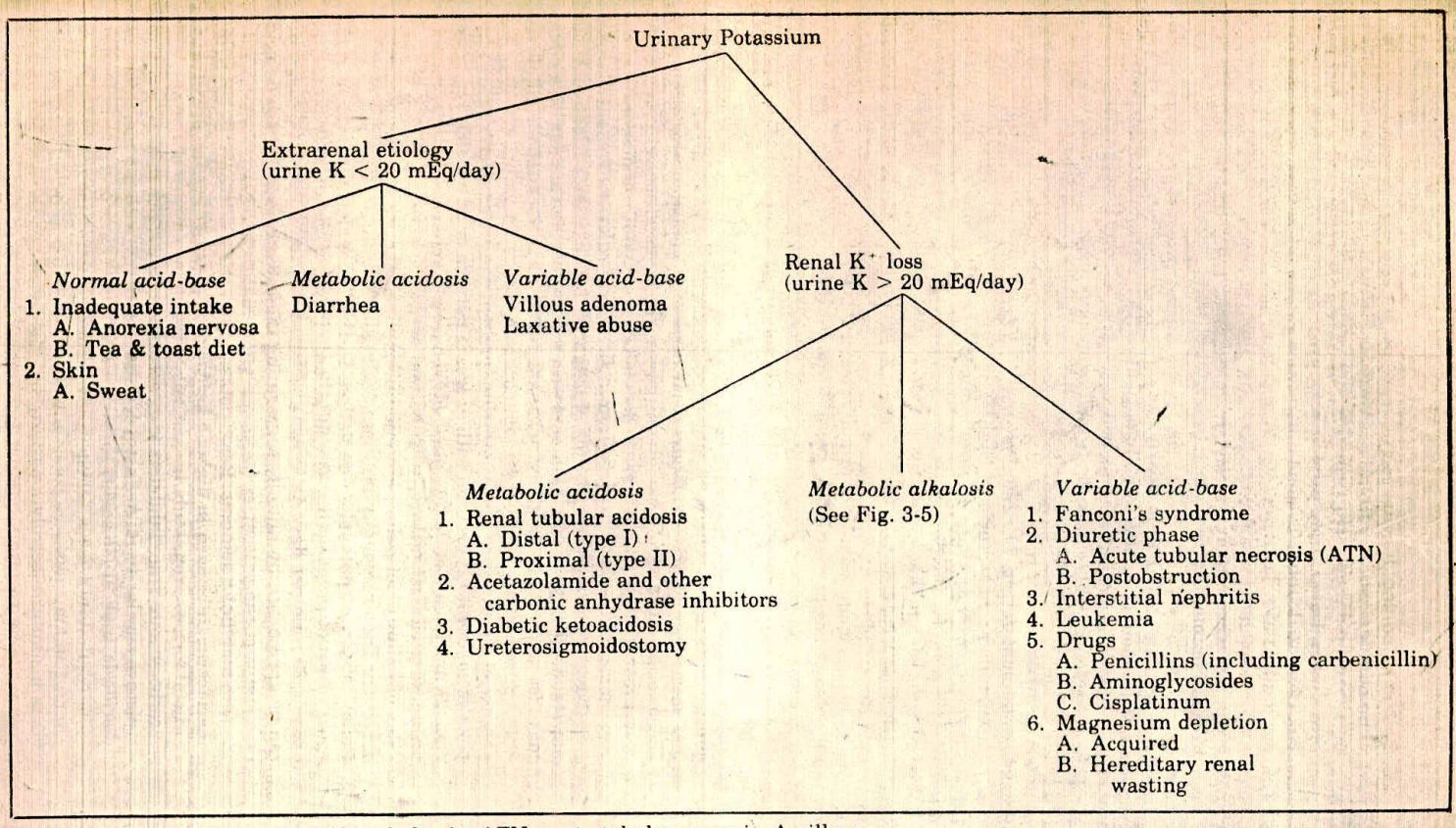

Fig. 3-4. Differential diagnosis of hypokalemia. ATN: acute tubular necrosis. A villous adenoma also may cause metabolic alkalosis secondary to substantial chloride losses.

festations of proximal tubular dysfunction (hypouricemia, hypophosphatemia, glycosuria, and/or aminoaciduria).

Ureterosigmoidostomy can result in potassium loss, due to secretion of potassium into the urine by the portion of the gastrointestinal tract acting as a urinary reservoir.

b. With metabolic alkalosis. Renal potassium wasting presents most commonly in association with metabolic alkalosis (Fig. 3-5). Categorization of the metabolic alkalosis into the syndromes with and without chloride depletion is useful for diagnostic purposes. If the kidney is avidly conserving chloride, the metabolic alkalosis and potassium depletion are of the chloride depletion variety. In this instance, the daily excretion of chloride is less than 10 mEq, and a spot urine concentration less than 10 mEq per liter.

(1) Alkalosis with renal chloride retention (chloride depletion). The most common causes of chloride depletion are diuretic therapy and the loss of upper gastrointestinal fluids from vomiting or nasogastric suction. With vomiting or nasogastric suction, potassium depletion is not due to losses in the gastric fluid itself, which contains potassium at a concentration between 5 and 10 mEq per liter, but rather results from renal potassium wasting. Although diuretics result in a kaliuresis, the potassium depletion accompanying their prolonged use is often sustained because of chloride depletion. Renal chloride conservation will not be apparent if diuretics have not been discontinued before evaluation. A more subtle cause of chloride depletion and hypokalemic alkalosis is posthypercapneic alkalosis. The pathophysiology is hypercapneic-induced chloruresis, with subsequent correction of the CO_2 retention but not the chloride depletion. An uncommon cause of chloride depletion is congenital chloride-wasting diarrhea.

(2) Alkalosis without renal chloride retention

(a) Nonmineralocorticoid causes. Metabolic alkalosis without renal chloride conservation is due to excessive mineralocorticoids, with three notable exceptions. The first and most common exception is the continued administration of diuretic agents. A second possibility is Bartter's syndrome. It has been speculated that this rare abnormality, characterized by normotension, hyperreninemic hyperaldosteronism, urinary hyperexcretion of prostaglandin E and prostacyclins, hyporesponsivity to pressor agents, and hypokalemic alkalosis, may result from a defect in chloride reabsorption in the loop of Henle. Not surprisingly, surreptitious diuretic administration can mimic this picture, and a serum or urinary drug screen for diuretics may be diagnostic in this setting.

Finally, renal chloride wasting can occur secondary to severe potassium depletion. This is observed with a serum potassium concentration less than 2.0 mEq per liter and deficits that approach 1000 mEq. With potassium depletion of this severity, the presence of chloride in the urine does not necessarily indicate a mineralocorticoid-induced cause for the hypokalemic alkalosis.

(b) Mineralocorticoid excess. All the abnormalities in this category are associated with hypertension; thus, the absence of hypertension tends to eliminate this group of disorders. In view of the frequency of essential hypertension, however, the presence of a high blood pressure is consistent with, but not strong evidence for, these abnormalities.

To differentiate disorders with excess mineralocorticoid secretion, measurement of plasma renin (PRA) and aldosterone concentrations (or urinary aldosterone) are helpful. These parameters must be interpreted in relation to sodium homeostasis. The patient should be placed on a defined sodium intake or, alternatively, urinary sodium should be measured as a reflection of sodium intake. Studies on both a high and low sodium diet may be necessary. The relations

Fig. 3-5. Differential diagnosis of hypokalemia secondary to renal causes. ↑ BP: high blood pressure.

among these parameters in normal persons are given in Table 3-2, but since hypokalemia depresses aldosterone and stimulates renin, it distorts these relations to some degree.

(i) **High aldosterone.** An elevated aldosterone is most reliable when the patient is on a high sodium diet, which should suppress aldosterone secretion.

(ii) **Low renin–high aldosterone.** The combination of a low renin and high aldosterone is diagnostic of primary hyperaldosteronism. A low sodium diet or the response to acute furosemide administration is useful to confirm the suppression of PRA. Additional studies are necessary to differentiate between an adrenal adenoma and hyperplasia (see Chap. 8).

(iii) **High renin–high aldosterone.** A high renin associated with a high aldosterone indicates that the primary abnormality is oversecretion of renin with secondary hyperaldosteronism. This occurs with renovascular hypertension, malignant hypertension, and renin-secreting tumors.

(iv) **Low or normal aldosterone.** The combination of a low aldosterone and low renin suggests the presence of excess mineralocorticoid other than aldosterone. Elevated levels of desoxycorticosterone (DOC) or corticosterone, which can result from hereditary adrenal enzyme deficiencies of 11-β and 17-α-hydroxylase, produce this picture. Similarly, excessive ingestion of licorice, which contains glycyrrhizic acid, a compound with mineralocorticoid activity, presents in this fashion. Several families with low aldosterone levels have been described in which excess mineralocorticoid cannot be identified (Liddle's syndrome), and an abnormality in renal tubular function has been postulated.
Cushing's syndrome and ectopic adrenocorticotropic hormone (ACTH) production can also cause hypokalemic alkalosis. Aldosterone and PRA may be low or normal with these entities.

(v) **Variable acid-base status.** Several disorders listed in Figure 3-4 can result in renal potassium wasting with either alkalosis or a normal acid-base status. Sodium salts of penicillin or carbenicillin may result in renal potassium loss, presumably because of the natriuresis and high anion excretion rates. The aminoglycosides and the tumoricidal drug *cis*-platinum can cause both renal potassium wasting and renal magnesium wasting. The mechanism of potassium depletion associated

Table 3-2. Relation Between Sodium Intake, Plasma Renin, and Aldosterone Concentration

Dietary Salt (grams)	Urine Sodium (mEq/day)	PRA (ng/ml/hr)	Aldosterone	
			Plasma (ng/100 ml)	Urine (μg/day
< 2.0	< 50	> 5.0	> 20.0	> 20.0
> 9.0	> 150	< 5.0	< 20.0	< 20.0

PRA = plasma renin activity.
Note: These data refer to noontime determinations in the upright position. The norma values may vary among laboratories, so each institution should define its own guideline Changes in potassium homeostasis alter PRA and aldosterone in opposite fashions and wi distort this relationship. Data must be interpreted with this in mind.

with magnesium depletion is undefined, but serum and urine magnesium should be measured when the cause of hypokalemia is unclear.

IV. Therapy

A. Established potassium deficiency. Treatment of established potassium deficiency requires a decision regarding (a) the type of potassium salt, (b) the route of replacement, and (c) the quantity and speed of drug administration.

1. **Type of potassium salt.** The patient with metabolic alkalosis who is chloride as well as potassium depleted requires potassium chloride for effective correction of the potassium deficit. With the combination of metabolic acidosis and a potassium deficit, potassium with bicarbonate or metabolic precursors of bicarbonate (gluconate, acetate, citrate) is preferable. The diabetic in ketoacidosis is usually phosphate depleted as well as potassium depleted, so potassium phosphate is the most rational therapy. When the cause of the potassium depletion is unclear, potassium chloride is the best choice because it effectively corrects all forms of potassium depletion.
   With primary hyperaldosteronism, sodium restriction concomitant with potassium supplementation is needed to correct the potassium deficit. Alternatively, the aldosterone antagonist, spironolactone, can be used to correct the hypokalemia. As a general rule, the concomitant administration of potassium supplements and potassium-sparing diuretics should be avoided, because of the risk of hyperkalemia.
2. **Route of replacement.** Oral replacement is generally desirable. The exceptions are severe, symptomatic potassium depletion that requires more rapid correction or the inability of the patient to tolerate oral medication.
3. **Quantity and speed.** The guidelines cited earlier (sec. **I.E.**) can provide an estimate of the amount of potassium depletion; however, adequate replacement is determined by monitoring the serum potassium value during therapy.
   In the patient without paralysis, digitalis intoxication, or hepatic coma, it is preferable to replace potassium at a slow rate. Oral potassium or, if necessary, intravenous administration in dosages of 80 to 120 mEq per day is usually satisfactory, and with very minimal depletion even 40 mEq per day may suffice. When intravenous therapy is employed in a nonurgent setting, the potassium concentration of intravenous fluids should not exceed 40 mEq per liter, and the rate of administration should not exceed 10 mEq per hour.
   If urgent treatment is required (digitalis intoxication, paralysis), potassium can be administered more rapidly but should not exceed 40 mEq per hour. In this circumstance ECG monitoring in an intensive care unit is advisable. Potassium concentrations greater than 40 mEq per liter should be administered into a large vein to avoid phlebitis, but central (intracardiac) administration should be avoided because of the danger of cardiac arrhythmias.

B. Potassium replacement with diuretic therapy. In the majority of patients receiving thiazides or loop diuretics for antihypertensive therapy, severe potassium depletion does not develop. Although, prophylaxis is therefore not warranted, the serum potassium should be monitored. If the serum potassium decreases to less than 3.0 mEq per liter, or if the patient develops symptoms attributable to potassium depletion, replacement therapy is advisable. Patients receiving cardiac glycosides or with cardiovascular disease may require potassium supplements with a plasma potassium between 3.0 and 3.5 mEq per liter.
Patients receiving diuretics for edema may be more prone to potassium depletion, and potassium supplementation seems advisable. It is indicated for patients who are susceptible to hepatic coma.
Liquid potassium chloride preparations are probably the therapy of choice, but wax matrix potassium chloride (slow-K) is a suitable substitute if the liquid form is not tolerated. The salt substitutes that contain potassium chloride are the least expensive option for potassium replacement. An alternative is the use of the potassium-sparing diuretics, spironolactone, triamterene, or amiloride. These diuretics are the preferred therapy in the patient with fluid retention secondary to hepatic disease.

C. Complications

1. **Potassium salts**
   a. **Hyperkalemia.** Hyperkalemia is the most important complication. The risk is greatest in patients with abnormal renal function, diabetics, the elderly, and patients receiving potassium-sparing diuretics.
   b. **Ulcers.** Ulcers involving mainly the small bowel were reported frequently with enteric-coated potassium chloride. Gastrointestinal ulceration is also a potential risk with liquid or wax matrix preparations in the presence of decreased gastrointestinal tract motility.
   c. **Phlebitis.** Phlebitis can result at sites of intravenous potassium infusion.
2. **Potassium-sparing diuretics**
   a. **Hyperkalemia.** Potassium-sparing diuretics should not be given to patients with severe impairment of renal function (creatinine greater than 3.0 mg/dl, BUN mg/dl greater than 45, creatinine clearance less than 30 ml per minute), and it is inadvisable to give them concurrently with potassium supplements.
   b. **Gynecomastia.** Gynecomastia occurs with spironolactone.
   c. **Gastrointestinal side effects.** Gastrointestinal side effects may occur with triamterene.

Hyperkalemia

I. **Clinical setting.** Hyperkalemia should be considered a potential complication in any setting with oliguria or serious compromise of renal function, especially with large endogenous or exogenous potassium loads. Other predisposing factors are mineralocorticoid deficiency, insulin deficiency, and acidosis.

II. **Signs and symptoms.** The most important clinical manifestation of hyperkalemia is its effect on cardiac conduction, with potential cardiac arrest. The sequence of ECG changes due to a high potassium, which correlate to some extent with the degree of hyperkalemia, are given in Figure 3-3.
Neuromuscular symptoms include tingling, paresthesias, weakness, and even flaccid paralysis, but cardiotoxicity usually precedes these manifestations.
A high plasma potassium concentration can elevate aldosterone, insulin, and glucagon levels and suppress plasma renin levels. There are no clinical manifestations of these hormonal aberrations, but some may be important feedback defense mechanisms.

III. **Differential diagnosis.** When hyperkalemia is identified, it is important to differentiate between a spurious laboratory determination (pseudohyperkalemia), a redistribution phenomenon, and an increase in total body potassium (Fig. 3-6). Because the clinical manifestations of hyperkalemia relate to the Ke/Ki ratio, the latter two causes both require therapeutic intervention.

A. Pseudohyperkalemia. Pseudohyperkalemia most commonly results from a hemolyzed specimen. With severe degrees of thrombocytosis ($> 10^6$/ml) or leukocytosis ($> 10^5$/ml), potassium released from the platelets during clotting or from the white blood cells during storage in the cold can elevate the serum potassium determination. Under these circumstances the ECG is normal. The potassium will be normal if a heparinized specimen is obtained with thrombocytosis and if the plasma is promptly separated from the cells with severe leukocytosis.

B. Redistribution. Acidosis tends to elevate the serum potassium concentration. The largest increase occurs with hyperchloremic metabolic acidosis, a smaller rise with respiratory acidosis, and little, if any, change with organic acid–induced metabolic acidosis. Insulin deficiency also predisposes toward a high serum potassium level. Hyperkalemia may result in the diabetic patient from a glucose load, which promotes both water and potassium movement from the ICF to the ECF by virtue of its osmotic properties. Although beta-adrenergic inhibition can increase serum potassium, life-threatening hyperkalemia has not been described as a result of beta-adrenergic blocking drugs. Cationic amino acids promote potassium loss from cells, and severe hyperkalemia can accompany arginine hy-

Fig. 3-6. Differential diagnosis of hyperkalemia. PG: prostaglandin.

drochloride infusions. Succinylcholine, which can cause potassium exit from cells by altering membrane permeability, poses a danger to a hyperkalemic patient undergoing anesthesia, particularly patients with renal impairment. Massive digitalis overdose can cause hyperkalemia by interfering with the Na-K-ATPase pump. Finally, hyperkalemic periodic paralysis, a rare autosomal dominant inherited disorder, is manifested in intermittent attacks of tonic paralysis of about 1 hour duration, accompanied by an acute increase in serum potassium.

C. Increase in total body potassium

1. **Renal failure.** Oliguria of any cause predisposes toward potassium retention and hyperkalemia. Hyperkalemia is usually not seen with chronic renal failure until the glomerular filtration rate (GFR) is less than 5 ml per minute, at which point oliguria may also be present.

   In the presence of a large endogenous or exogenous potassium load, hyperkalemia occurs more quickly, is more severe, and can occur with less severe impairment of renal function. Hemolysis, tissue necrosis of any type, and generalized catabolic states all lead to an increase in the endogenous potassium load, predisposing toward hyperkalemia. Obviously, either oral or intravenous potassium administration poses a similar risk.

   Although the vast majority of hyperkalemic patients have severe renal failure, there are several other mechanisms that result in potassium retention.

2. **Mineralocorticoid deficiency.** These patients often present with a hyperchloremic acidosis as well as hyperkalemia.

   a. **Addison's disease.** The diagnosis can be confirmed by measuring basal serum cortisol levels and the response to ACTH.

   b. **Hypoaldosteronism.** Hypoaldosteronism has been recognized with increasing frequency in patients with chronic renal disease. It is usually associated with low renin levels and is thought to result from a defect in renin secretion, hence the term *hyporeninemic hypoaldosteronism*. This symptom complex has been found most frequently in patients with diabetic renal disease or interstitial nephritis, but it is not confined to these pathologic entities. The diagnosis is suspected in the presence of low renin and aldosterone levels in relation to sodium intake, especially during ingestion of a low sodium diet. Care should be taken when placing these patients on a low sodium diet or when administering glucose in diabetic patients, because the hyperkalemia may worsen. Normalization of potassium by administration of the exogenous mineralocorticoid, 9α-fluorohydrocortisone (Florinef), is confirmatory. Hyperkalemia, because of its action in suppressing renal ammonia production, may account, in part, for the associated acidosis.

   c. **Drugs.** Indomethacin, or other nonsteroidal drugs that inhibit renal prostaglandin production, may cause a reversible form of hyporeninemic hypoaldosteronism. The pathophysiology relates presumably to interference with the prostaglandin-mediated control of renin release. Captopril, an inhibitor of angiotensin-converting enzyme, can result in hyperkalemia secondary to hypoaldosteronism induced by low angiotensin II levels. In this case PRA levels are high. Hyperkalemia has infrequently been ascribed to heparin, which can directly inhibit aldosterone biosynthesis by the adrenal gland.

3. **Primary renal tubular dysfunction.** Patients with renal transplants, lupus erythematosus, amyloidosis, multiple myeloma, sickle cell disease, and obstructive uropathy have been reported with hyperkalemia that appears to be secondary to an intrinsic renal tubular defect in potassium secretion. These patients have a normal renin-aldosterone axis, and the hyperkalemia is unresponsive to exogenous mineralocorticoid administration.

   Infants with pseudohypoaldosteronism have high renin and aldosterone levels and present with hyperkalemia and salt wasting unresponsive to mineralocorticoids. In addition, older children and adults with hypertension, hyperkalemic acidosis, and low renin and aldosterone levels have been described who are unresponsive to exogenous aldosterone. It has been speculated that

this condition may represent the converse of Bartter's syndrome, with enhanced sodium chloride reabsorption at some site proximal to the aldosterone exchange site, and these cases have been called pseudohypoaldosteronism, type II.

4. **Drug-induced hyperkalemia**
   a. **Spironolactone.** Spironolactone causes hyperkalemia by antagonizing the effects of aldosterone.
   b. **Triamterene** and **amiloride**. Both of these drugs inhibit potassium secretion by an aldosterone-independent mechanism.

IV. **Therapy.** Treatment of hyperkalemia is dictated by the level of serum potassium and by the findings on ECG. Every hyperkalemic patient should have an immediate ECG. If the ECG findings reflect any changes attributable to hyperkalemia other than peaked T waves, or if the serum potassium exceeds 6.5 mEq per liter, aggressive and prompt therapy should be instituted.

A. **Acute hyperkalemia.** This condition includes acute measures to counteract the effect of potassium on membranes and to shift it into cells, as well as definitive procedures to remove potassium from the body. The uses of calcium gluconate, sodium bicarbonate, and glucose plus insulin are detailed in Table 3-3. These substances act quickly and provide time for definitive therapy (i.e., the removal of excess potassium from the body). This removal of potassium can usually be accomplished successfully with the use of the cation exchange resin, sodium polystyrene sulfouate (Kayexalate). Kayexalate can be given either orally or as a retention enema.
   1. **P.O.** Forty grams of Kayexalate plus 20 ml (70%) sorbitol. Each gram removes approximately 1 mEq of potassium. Repeat every 2 to 4 hours as required until serum potassium is in the normal range.
   2. **Enema.** Fifty to one hundred grams of Kayexalate in 200 ml water, by retention enema. Insert via Foley catheter and inflate balloon to ensure retention for 30 to 45 minutes. Each gram removes approximately 0.5 mEq of potassium. Repeat every 2 to 4 hours as required.
   3. **Dialysis.** Dialysis is rarely required to manage hyperkalemia, since cation exchange resins work so effectively. On occasion, however, such as after colonic surgery or when the rate of endogenous potassium release is massive (crush injuries), dialysis may be required.
      a. **Hemodialysis.** Hemodialysis can remove as much as 25 to 30 mEq of potassium per hour.
      b. **Peritoneal.** This technique is significantly less efficient, with the capacity to remove only 10 to 15 mEq of potassium per hour.

B. **Chronic hyperkalemia.** Chronic and more modest elevations of serum potassium can be managed in several ways, depending on the underlying pathogenesis.

Table 3-3. Treatment of Acute Hyperkalemia

Mechanism	Treatment	Onset of action
Antagonize membrane effects	Calcium gluconate (10–30 ml of 10% solution)	Few minutes
Redistribute	$NaHCO_3$ (44–132 mEq)	15–30 minutes
	Glucose (50 gm) + regular insulin (10 U)	15–30 minutes
Remove	Cation exchange resin: sodium polystyrene suflonate (Kayexalate)	
	Enema (50–100 gm)	60 minutes
	Oral (40 gm)	120 minutes
	Dialysis	
	Hemodialysis	Few minutes after start
	Peritoneal	Few minutes after start

1. **Kayexalate.** Kayexalate is effective in any setting and need not be given with sorbitol, which patients find unpleasant. An effective, less potent cathartic such as bisacodyl (Dulcolax) tablets can also be used.
2. **Mineralocorticoids.** Mineralocorticoid deficiency can be treated with exogenous mineralocorticoids. A high salt diet and Florinef are indicated in Addison's disease. With hyporeninemic hypoaldosteronism, mineralocorticoids usually decrease hyperkalemia, but sodium retention and hypertension may be undesirable side effects.
3. **Diuretics.** Diuretics such as furosemide may reduce hyperkalemia in hyporeninemic patients. There is a suggestion that thiazides may be effective in certain patients with renal tubular disorders, but this observation is not firmly established.
4. **Intake reduction.** Reduction in dietary potassium intake is always appropriate.

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4

The Patient With Abnormal Plasma Bicarbonate, Arterial PCO_2, or pH

Jordan J. Cohen

Disturbances of acid-base equilibrium are extremely common in clinical practice, especially among hospitalized patients. Their presence may be suspected on the basis of bedside appraisal, but, in the final analysis, accurate diagnosis and appropriate management require reliable laboratory data.

The carbonic acid–bicarbonate buffer system is the keystone to the understanding and classification of acid-base disturbances. The following equations are used to describe the equilibrium state of this buffer system in blood:

$$[H^+]\,(nEq/L) = 24\,\frac{PaCO_2}{[HCO_3^-]} \qquad \text{Henderson equation}$$

$$pH = 6.1 + \log\frac{[HCO_3^-]}{0.3 \times PaCO_2} \qquad \text{Henderson-Hasselbalch equation}$$

These are equivalent mathematical expressions differing only in the units chosen to express blood acidity—nanoequivalents per liter of hydrogen ion in one and pH in the other (Table 4-1). In each case, carbonic acid concentration is expressed as the partial pressure of carbon dioxide ($PaCO_2$) in mm Hg, and plasma bicarbonate concentration is expressed directly in mEq per liter. In normal people, arterial carbon dioxide tension and plasma bicarbonate concentration average approximately 40 mm Hg and 24 mEq per liter, respectively. Consequently, normal arterial hydrogen ion is approximately 40 nEq per liter, (pH 7.4). It is apparent from either equation that acidity is determined by the ratio of these two physiologic variables. Thus, analysis of acid-base disturbances requires identification of the pathophysiologic events responsible for altering the $PaCO_2$ and/or plasma bicarbonate concentration.

I. **Practical considerations.** Certain practical aspects of blood sampling, specimen handling, and analytic methodology must be strictly adhered to in order to ensure accurate appraisal of acid-base equilibrium in the clinical setting. Data obtained from the arterial blood are preferred. The most accessible sites for direct arterial puncture are the brachial, radial, and femoral vessels. When frequent assessment of acid-base equilibrium is required, it may be preferable to place an inlying arterial catheter rather than risk multiple arterial punctures. Venous blood drawn without stasis and free-flowing capillary blood obtained by finger stick (especially in infants and young children) may be used, if necessary.

Blood samples for PCO_2 and pH measurements must be prevented from clotting. Heparin is far superior to any other anticoagulant for this purpose because the small quantity required has a negligible effect on acid-base composition. Care must be taken to avoid even brief exposure of the blood sample to air, to avoid loss of carbon dioxide. Even when anaerobic conditions are maintained during blood sampling, continued cellular metabolism in vitro tends to alter the acid-base status of the specimen. For this reason, measurements should be made immediately or the specimen should be cooled (e.g., by immersing the syringe in crushed ice) before it is transported to the laboratory. Even with this precaution, measurements should be made within 1 hour after sampling.

Both hydrogen ion concentration (pH) and carbon dioxide tension can be measured directly by standard electrochemical techniques. Bicarbonate concentration is generally estimated from the total carbon dioxide (tCO_2) released from an acidified serum

Table 4-1. Equivalent Values for pH and Hydrogen Ion Concentration

pH	$[H^+]$ nEq/L
7.70	20
7.65	22
7.60	25
7.55	28
7.50	32
7.45	35
7.40	40
7.35	45
7.30	50
7.25	56
7.20	63
7.15	71
7.10	79
7.05	89
7.00	100
6.95	112
6.90	126
6.85	141
6.80	158

sample; approximately 95 percent of the carbon dioxide released is derived from bicarbonate ions under virtually all circumstances. Measurement in the same blood sample of any two of the three acid-base variables is, of course, sufficient to permit calculation of the third. Normal acid-base values are as follows:

Plasma $[HCO_3^-]$	24–26 mEq/L
$PaCO_2$	39–43 mm Hg
Plasma $[H^+]$	39–42 nEq/L
pH	7.38–7.41

II. Definitions and terminology

A. Acidemia and alkalemia. Acidemia and alkalemia signify increase and decrease in hydrogen ion concentration, respectively (or decrease and increase in pH). Abnormalities of acid-base equilibrium can be initiated by changes in either $PaCO_2$ or plasma bicarbonate concentration. When an increase or decrease in $PaCO_2$ initiates the disturbance, it is referred to as **respiratory acidosis** or **respiratory alkalosis,** respectively. When changes in bicarbonate concentration initiate the disturbance, it is called **metabolic acidosis** or **metabolic alkalosis.** Each initiating (primary) process, whether respiratory or metabolic, sets in motion secondary physiologic responses that alter the level of the opposing variable. The metabolic disturbances produce a ventilatory response that rapidly alters $PaCO_2$ and minimizes the impact on acidity. The respiratory disturbances result in an immediate titration of tissue buffers that acutely alters the level of bicarbonate. If the respiratory disturbance is prolonged (a few days or more), changes in renal acid excretion and bicarbonate reabsorption occur that result in additional adjustments in acid-base equilibrium. The respiratory disturbances are, therefore, classified as either acute or chronic. In the absence of confounding factors, each of these secondary physiologic responses (ventilatory, buffer, and renal) is roughly proportional to the magnitude of the initiating, primary disorder. Thus, a range of anticipated physiologic responses can be anticipated for each class of acid-base disturbance.

B. Simple and mixed acid-base disturbances. A **simple** acid-base disturbance denotes the presence of one primary process, coupled with its appropriate physiologic response. A **mixed** acid-base disturbance refers to the coexistence of two or more primary processes. Since these processes may have either additive or nullifying effects on plasma acidity, mixed acid-base disturbances may produce extreme deviations in hydrogen ion concentration on the one hand, or minor or undetectable deviations on the other hand.

III. Recognition of acid-base disturbances

A. Clinical settings. The presence of an acid-base disturbance can never be definitely established without appropriate laboratory confirmation. Nevertheless, there are certain clinical settings in which acid-base disturbances occur so frequently that the index of suspicion should be quite high (Table 4-2).

B. Clinical signs. Occasionally, an acid-base disturbance is first suspected on the basis of clinical signs. Thus, acidemia may present as hypotension, hypercapnia as obtundation, and alkalemia as paresthesias, tetany, or convulsions. Hyperventilation may be the first clue to the presence of metabolic acidosis or primary respiratory alkalosis. It is much more frequently the case, however, that acid-base disturbances are discovered serendipitously because of abnormalities in bicarbonate concentration detected by routine serum electrolyte determinations.

Table 4-2. Clinical Settings Commonly Associated with Acid-base Disturbances

	Metabolic		Respiratory	
Clinical Setting	Acidosis	Alkalosis	Acidosis	Alkalosis
Sepsis	X			X
Renal failure	X			
Cardiopulmonary arrest	X		X	
Gastric-suction/vomiting		X		
Diarrhea	X			
Small-bowel or biliary drainage	X			
Diabetes mellitus with ketonuria	X			
Airway obstruction			X	
Chronic obstructive pulmonary disease			X	
Hepatic insufficiency	X			X
Recent alcoholic binge	X			X
Drugs				
Diuretics (overt, surreptitious)		X		
Carbonic anhydrase inhibitors (glaucoma)	X			
Amphotericin B	X			
Ammonium chloride	X			
Salicylates (overdose)	X			X
Sedatives (overdose)			X	
Poisons				
Methanol	X			
Ethylene glycol	X			
Paraldehyde	X			

Table 4-3. Anticipated Relations Among Acid-base Values in Simple, Uncomplicated Disorders

Disorder	Primary Change	Secondary Response	Net Effect	Average Relation*
Metabolic acidosis	$\downarrow[HCO_3^-]$	$\downarrow PaCO_2$	$\uparrow[H^+]$ ($\downarrow$pH)	$\Delta PaCO_2 = 1.2\ \Delta[HCO_3^-]$
Metabolic alkalosis	$\uparrow[HCO_3^-]$	$\uparrow PaCO_2$	$\downarrow[H^+]$ ($\uparrow$pH)	$\Delta PaCO_2 = 0.7\ \Delta[HCO_3^-]$
Respiratory acidosis	$\uparrow PaCO_2$	$\uparrow[HCO_3^-]$	$\uparrow[H^+]$ ($\downarrow$pH)	Acute: $\Delta[H^+] = 0.75\ \Delta PaCO_2$ Chronic: $\Delta[HCO_3^-] = 0.35\ \Delta PaCO_2$
Respiratory alkalosis	$\downarrow PaCO_2$	$\downarrow[HCO_3^-]$	$\downarrow[H^+]$ ($\uparrow$pH)	Acute: $\Delta[H^+] = 0.75\ \Delta PaCO_2$ Chronic: $\Delta[HCO_3^-] = 0.50\ \Delta PaCO_2$

*In these relations it is assumed that acid-base values are given in the following units of measure: $PaCO_2$, mm Hg; $[HCO_3^-]$, mEq/L; $[H^+]$, nEq/L.

IV. Low plasma bicarbonate concentration. Some reduction in ... centration (total CO_2) is a characteristic feature of both me... piratory alkalosis (Table 4-3). These two possibilities can ofte... reasonable certainty on the basis of the clinical setting (see ... fact that only metabolic acidosis can reduce plasma bicarbona... (i.e., less than 10 mEq per liter). As a general rule, however, it ... obtain measurements of pH and $PaCO_2$ not only to verify the clinic... also to assess the adequacy of the secondary physiologic responses. A low bicarbonate in association with some degree of acidemia is dia... abolic acidosis, whereas a low bicarbonate and alkalemia signify respiratory alkalosis.

A. Metabolic acidosis (low $[HCO_3^-]$, high $[H^+]$). It is convenient to divide the causes of metabolic acidosis into two groups—those associated with a normal unmeasured anion concentration (anion gap) and those associated with an elevated unmeasured anion concentration (Table 4-4). The unmeasured anion concentration can be defined for practical purposes as the difference between serum sodium concentration and the sum of the serum chloride and bicarbonate (total CO_2) concentrations. Defined in this way, the normal anion gap ranges from 8 to 12 mEq per liter. Metabolic acidosis associated with a normal undetermined anion concentration results from the loss of bicarbonate, disproportionate renal tubular dysfunction, or the addition of hydrochloric acid to the body fluids. By contrast, metabolic acidosis associated with an elevated undetermined anion concentration results from an overproduction of endogenous acid or from renal insufficiency.

1. Normal anion gap (hyperchloremia)

a. Loss of bicarbonate. Loss of bicarbonate from the gastrointestinal tract (e.g., profuse diarrhea, drainage of pancreatic or biliary juice) or from the kidney (e.g., carbonic anhydrase inhibition) results in a hyperchloremic metabolic acidosis. A similar form of metabolic acidosis may be seen with obstructed ileal loop bladders or with ureterosigmoidostomies, which may result in intestinal absorption of urinary chloride in exchange for extracellular bicarbonate.

b. Renal tubular acidosis. Renal tubular acidosis results from specific renal tubular defects in bicarbonate or hydrogen ion transport or both. Unlike glomerular function in patients with severe renal failure, glomerular function may be normal or near normal with renal tubular acidosis. Two main types of renal tubular acidosis are recognized: distal (classic, type 1, gradient limitation) and proximal (type 2, bicarbonate wasting).

Table 4-4. Causes of Metabolic Acidosis

Normal Undetermined Anion Concentration	Elevated Undetermined Anion Concentration
Loss of bicarbonate	Overproduction of organic acids
Diarrhea	Lactic acidosis
Small bowel losses	Diabetic ketoacidosis
Ureterosigmoidostomy	Prolonged starvation
Ileal loop bladder (too long or obstructed)	Alcoholic ketoacidosis
Carbonic anhydrase inhibitors	Salicylate intoxication
Disproportionate failure of renal tubular function	Methyl alcohol ingestion
Renal tubular acidosis	Ethylene glycol ingestion
Tubulo-interstitial renal disease	Paraldehyde ingestion
Addition of hydrochloric acid	Renal insufficiency
Ammonium chloride	Uremic acidosis
Lysine—HCl	Acute renal failure
Arginine—HCl	

(1) **Distal renal tubular acidosis.** In distal renal tubular acidosis, the terminal segments of the nephron are unable to sustain a large transepithelial hydrogen ion concentration gradient. As a consequence, urinary hydrogen ion concentration remains relatively low (pH greater than 5.5) even after acid loading. Both the acidosis and the frequently associated hypokalemia generally are corrected by daily alkali therapy. Growth retardation in youngsters can also be corrected by adequate alkali administration. Distal renal tubular acidosis may be primary (idiopathic) or secondary. Among the disorders frequently associated with secondary distal renal tubular acidosis are hyperglobulinemic states, Sjögren's syndrome, sickle cell disease, hypercalcemia, amphotericin toxicity, toluene toxicity (glue or paint sniffing), and lithium toxicity.

(2) **Proximal renal tubular acidosis.** In proximal renal tubular acidosis, the proximal tubule is unable to to sustain a normal rate of bicarbonate reabsorption. The urinary acidification process in the distal nephron is normal but may be obscured by the increased delivery of bicarbonate from the proximal tubule. Even large doses of administered bicarbonate may be ineffective in fully correcting the acidosis because the administered alkali is not conserved by the kidney and escapes rapidly into the urine. Proximal renal tubular acidosis is frequently associated with other proximal tubular transport defects (e.g., Fanconi's syndrome) and may be seen either in association with certain errors of metabolism (cystinosis, Wilson's disease) or as a consequence of heavy metal toxicity, outdated tetracycline, multiple myeloma, dysproteinemia, nephrotic syndrome, or transplant rejection. A mild form of proximal renal tubular acidosis may be seen in primary or secondary hyperparathyroidism.

c. **Tubulo-interstitial renal diseases.** Tubulo-interstitial renal diseases (pyelonephritis, analgesic abuse nephropathy, acute or chronic transplant rejection) are often accompanied by hyperchloremic metabolic acidosis because of the presence of tubular dysfunction out of proportion to glomerular insufficiency. A mild degree of hyperchloremic acidosis often accompanies hyporeninemic hypoaldosteronism associated with mild diabetic or interstitial renal disease.

d. **Administration of ammonium chloride.** Administration of ammonium chloride or of the cationic amino acids, lysine and arginine (e.g., some forms of parenteral nutrition), can cause hyperchloremic acidosis because these substances yield hydrochloric acid when metabolized.

2. **Increased anion gap**

a. **Lactic acidosis.** Lactic acidosis is a very frequent cause of life-threatening metabolic acidosis. The overproduction of lactic acid results most often from an interference with oxidative metabolism. Because hepatic use of lactate produced by peripheral tissues can regenerate the bicarbonate ion dissipated by this acid, the presence of hepatic dysfunction, which is frequent in patients with lactic acidosis, may contribute importantly to the severity of the acid-base disturbance. Lactic acidosis may occur in association with severe tissue hypoxia (shock, low cardiac output states, very severe anemia) bowel infarction, alcoholism, diabetes mellitus (with or without ketoacidosis), and certain types of leukemia. Lactic acidosis may develop without a recognized cause ("spontaneous"), especially in chronically ill, debilitated patients. A firm diagnosis can be made only if the serum lactate level is found to be elevated. Even in the absence of a lactate determination, however, a strong presumptive diagnosis can be advanced if the undetermined anion concentration is clearly elevated and all of the other recognized causes of anion gap acidosis have been excluded.

The only satisfactory treatment for lactic acidosis is removal of the underlying cause. The efficacy of oxidizing agents (methylene blue) or potent vasodilators (sodium nitroprusside) as a means of improving the redox state of cells remains to be confirmed. Large quantities of sodium bicarbonate

are frequently required to offset the acid load and may lead to marked hyperosmolality and serious vascular congestion; if diuretic agents fail to promote adequate sodium and water losses, dialysis may be required to prevent volume overload during alkali administration.

b. **Diabetic ketoacidosis.** Diabetic ketoacidosis is a major cause of anion gap metabolic acidosis. The fatty acid metabolites, acetoacetic acid and beta-hydroxybutyric acid, are the major acids produced in uncontrolled diabetes. The diagnosis of diabetic ketoacidosis is most reliably confirmed by a positive nitroprusside reaction (Acetest) in the serum. This test provides a semiquantitative assay for acetoacetate but does not detect beta-hydroxybutyrate. Low-dose insulin therapy has proved to be as reliable as high-dose therapy in correcting the acid-base disturbance of uncontrolled diabetes.

Patients with diabetic ketoacidosis are occasionally found to have a coexisting element of lactic acidosis. When this occurs, a marked discrepancy may be noted between the increment in unmeasured anions (and decrement in bicarbonate) and the degree of positivity in serum nitroprusside reaction. This discrepancy can arise not only from the presence of lactate but also from a preponderance of beta-hydroxybutyrate, because of the diminished oxidative potential of the tissues.

Example: A patient with insulin-dependent diabetes enters the hospital in shock following a myocardial infarction. The blood sugar is 500 mg per deciliter; the serum sodium is 140, potassium 4.8, chloride 105, and bicarbonate 8 mEq per liter. The serum nitroprusside reaction is only 1+ in a 1 : 2 dilution. These data strongly suggest that diabetic ketoacidosis is *not* the only form of acidosis present; the anion gap is markedly elevated at 27 mEq per liter (140 − [105 + 8] mEq/L), but the nitroprusside reaction is only weakly positive. The clinical setting is in keeping with the presence of lactic acidosis from hypotension. Indeed, a measured lactate level was 12 mEq per liter (normal is less than 2 mEq per liter).

c. **Starvation.** Starvation is also characteristically associated with an increased breakdown of fatty acids, and a mild ketoacidosis is frequently seen.

d. **Alcoholic ketoacidosis.** Alcoholic ketoacidosis can occur after a period of heavy alcohol abuse. A history of protracted vomiting is often obtained. A preponderance of beta-hydroxybutyric acid is typically seen. Because direct measurement of this acid is not readily available, the diagnosis is usually made by exclusion.

e. **Overdosage.** Overdosage with several potential poisons may result in a severe metabolic acidosis, caused by the overproduction of various (largely unidentified) endogenous acids. Such potential poisons include salicylates (particularly in young children but also in adults), methanol, ethylene glycol, and paraldehyde.

f. **Renal insufficiency.** Renal insufficiency results in metabolic acidosis not because of an overproduction of endogenous acids but because of a diminished capacity of the few remaining tubules to reabsorb filtered bicarbonate and to generate sufficient urinary ammonium. The elevated undetermined anion concentration characteristically seen is the consequence of a reduction in glomerular function, which leads to a retention of a large variety of filterable anions (e.g., sulfates and phosphates).

3. **Simple metabolic acidosis versus mixed acid-base disturbances.** Because metabolic acidosis often occurs in complex clinical circumstances, it is not uncommon for it to be present in the company of other acid-base abnormalities. Such mixed acid-base disturbances can usually be detected by a careful analysis of the acid-base values and of the pattern of serum electrolytes. The presence of an independent primary respiratory disturbance tends to distort the relation between $PaCO_2$ and plasma $[HCO_3^-]$ ordinarily observed in simple metabolic acidosis. The degree of secondary hypocapnia accompanying stable metabolic acidosis is roughly proportional to the magnitude of the steady-state bicarbonate decrement; on the average, each mEq per liter reduction in plasma bicarbonate

concentration is associated with a 1.0 to 1.3 mm Hg reduction in $PaCO_2$. However, during the rapid onset of severe metabolic acidosis, the abrupt fall in plasma bicarbonate may outstrip the secondary decrement in $PaCO_2$, giving rise to extreme elevations in plasma hydrogen ion concentration. Similarly, during the rapid repair of severe metabolic acidosis, a normal or near normal level of plasma bicarbonate may be restored before hyperventilation subsides, resulting in a marked reduction in plasma hydrogen ion concentration (i.e., alkalemia). Excluding such transient circumstances, if respiratory adjustments fall short of the anticipated level (i.e., if $PaCO_2$ is higher than expected for a given decrement in plasma bicarbonate), an element of respiratory acidosis can be diagnosed; conversely, if respiratory adjustments appear excessive (i.e., if $PaCO_2$ is lower than expected), an independent element of primary respiratory alkalosis can be diagnosed.

a. Metabolic acidosis and respiratory alkalosis

Example: A patient with gram-negative septicemia is found to be in shock and to have rapid, deep respirations. Arterial blood studies reveal a $PaCO_2$ of 15 mm Hg, a pH of 7.35 ($[H^+]$, 45 nEq per liter), and a plasma bicarbonate concentration of 8 mEq per liter. Plasma bicarbonate is 16 mEq per liter below normal (24 − 8 mEq/L) as a result of metabolic acidosis, presumably on the basis of lactic acid overproduction. Thus, one might expect a reduction in $PaCO_2$ of approximately 19 mm Hg just as the result of the physiologic response to this degree of metabolic acidosis (16 mEq/L × 1.2 mm Hg per mEq/L = 19 mm Hg). The actual reduction in $PaCO_2$ is about 25 mm Hg (40 − 15 mm Hg). This discrepancy between the observed and expected degrees of hyperventilation signifies an independent process stimulating ventilation and thus evidences a mixed disturbance in which metabolic acidosis and respiratory alkalosis coexist. This particular mixed disturbance is encountered with some frequency in patients with gram-negative sepsis.

b. Metabolic acidosis and metabolic alkalosis. The coexistence of metabolic acidosis and metabolic alkalosis can be diagnosed by the pattern of serum electrolytes if the component of acidosis is due to the overproduction of endogenous acid (see Table 4-3). Under these circumstances, the increment in unmeasured anion concentration above the normal value of 8 to 12 mEq per liter is greater than the decrement in plasma HCO_3 below its normal value of 24 to 26 mEq per liter; this discrepancy signifies that plasma bicarbonate has been titrated to its observed value from a level higher than normal and, thus, that a metabolic alkalosis is also present.

Example. A patient with chronic alcoholism is evaluated after several days of profuse vomiting. Laboratory studies reveal serum sodium 135, potassium 3.0, chloride 80, and bicarbonate 12 mEq per liter. Arterial blood pH is 7.27 ($[H^+]$, 54 nEq per liter), and $PaCO_2$ is 27 mm Hg. It is evident that a moderately severe metabolic acidosis is present and that its cause is in the increased anion gap category. Indeed, alcoholic ketoacidosis largely due to beta-hydroxybutyric acid was documented. Careful analysis, however, demonstrates that the anion gap is 43 mEq per liter (135 − [80 + 12] mEq/L), which is at least 30 mEq per liter higher than normal. This is an elevation much greater than would be required to account for a reduction in bicarbonate from its normal level of 24 mEq per liter to its present value of 12 mEq per liter. Thus, bicarbonate must have been much higher than normal (i.e., a metabolic alkalosis must have been present) at the onset of the metabolic acidosis. The patient's history suggests that this "hidden" alkalosis resulted from vomiting. Specifically, the serum bicarbonate must have started at 42 mEq per liter and then decreased to 12 mEq per liter as the hydrogen ions accompanying the 30 mEq per liter increment in anion were buffered.

4. Therapeutic principles. Treatment of metabolic acidosis centers around removal of the underlying cause when possible and provision of adequate amounts of bicarbonate when necessary. If plasma bicarbonate is only moderately depressed (plasma $[HCO_3^-]$ greater than 15 mEq/L), and if the cause of the acidosis can be treated or is self-limited, bicarbonate replacement therapy may not be necessary, because the normal kidney can replenish bicarbonate stores over a period of several days. If the cause of the acidosis cannot be eliminated (e.g., chronic renal failure), long-term alkali therapy may be necessary. Bicarbonate or an organic anion capable of conversion to bicarbonate (e.g., citrate) may be administered orally for this purpose in a dose adjusted empirically to maintain the desired plasma bicarbonate concentration.

If bicarbonate concentration is markedly depressed (plasma $[HCO_3^-]$ to less than 10 mEq/L), the intravenous administration of sodium bicarbonate may be required even if the underlying cause can be removed quickly (e.g., diabetic acidosis). As a general rule, such therapy should be designed to repair only one-half of the total bicarbonate deficit over the initial 12 hours of treatment, to avoid the consequences of abrupt changes in extracellular acid-base equilibrium. When this precaution is observed, tetany, altered mental status, and convulsions rarely occur.

In estimating the amount of bicarbonate required to produce a desired increment in plasma bicarbonate concentration, an apparent space of distribution of approximately 40 percent of body weight is ordinarily used.

Example: Body weight 70 kg, apparent space of distribution 0.4 × 70 = 28 liters. Plasma bicarbonate concentration 10 mEq per liter, desired increment in bicarbonate concentration 7 mEq per liter. Therefore, 7 mEq/L × 28 L = 196 mEq.

Such estimates of bicarbonate requirements serve only as rough guidelines and must be adjusted to suit individual circumstances. This is particularly true when increased acid production or bicarbonate losses continue during the period of therapy or when plasma bicarbonate is severely reduced (plasma $[HCO_3^-]$ less than 5 mEq/L). If cardiac or renal function precludes administration of adequate amounts of bicarbonate (with sodium), it may be necessary to institute peritoneal dialysis or hemodialysis.

Complications of alkali therapy include the following:

a. Sodium and volume overload, because of the large quantity of sodium bicarbonate that may be required.
b. Hypernatremia, because of the hypertonic nature of the sodium bicarbonate solutions used.
c. Hypokalemia, resulting from a shift of potassium from extracellular to intracellular fluid. This complication is particularly likely to occur in patients who have lost body potassium because of their underlying conditions (e.g., diabetes, diarrhea).
d. Post-treatment alkalosis. Alkalemia may occur during the course of treating metabolic acidosis because of overzealous administration of alkali; metabolism of organic anions (e.g., acetoacetate, lactate), which yield endogenous alkali; and persistent hyperventilation due to lingering acidosis within the central nervous system.

B. Respiratory alkalosis (low $[HCO_3^-]$, low $[H^+]$). Although a reduction in plasma bicarbonate concentration may be the first indication of the presence of respiratory alkalosis, this change in plasma composition is a manifestation of the secondary physiologic response to respiratory alkalosis and not a clue to its cause or a measure of its severity. $PaCO_2$ must be measured directly or calculated (from plasma bicarbonate and hydrogen ion concentration) to assess the severity of the disturbance.

1. Causes of respiratory alkalosis. Any process that stimulates alveolar ventilation—with the exception of acidemia—will result in primary respiratory alkalosis. The multiple causes of this condition can be classified as follows:

a. Central nervous system disease
   (1) Anxiety, hysteria
   (2) Cerebrovascular accident
   (3) Trauma
   (4) Infection
   (5) Brain tumor

b. Pulmonary diseases
   (1) Pulmonary emboli
   (2) Mild pulmonary edema
   (3) Pneumonia
   (4) Ventilation-perfusion imbalance with hypoxia
c. Metabolic disorders
   (1) Fever
   (2) Salicylate intoxication
   (3) Hepatic insufficiency
   (4) Gram-negative septicemia
   (5) Pregnancy

2. **Acute versus chronic respiratory alkalosis.** Many causes of respiratory alkalosis are short-lived. In these instances the acid-base disturbance is manifested by the primary decrement in $PaCO_2$ and a small, secondary decrement in bicarbonate concentration that results from the titration of nonbicarbonate tissue buffers. A decrement in bicarbonate of 3 to 4 mEq per liter may be expected to occur within several minutes after $PaCO_2$ is lowered to 20 to 25 mm Hg. The resulting change in plasma hydrogen ion concentration is roughly proportional to the change in PCO_2; on the average, each mm Hg reduction in $PaCO_2$ in acute respiratory alkalosis results in a fall in plasma hydrogen ion concentration of approximately 0.75 nEq per liter.
   Less commonly, respiratory alkalosis lingers long enough (a few days or more) for secondary renal adjustments in bicarbonate concentration to occur. Such chronic forms of respiratory alkalosis are especially likely to occur in patients with hepatic insufficiency, chronic salicylate intoxication, chronic hypoxic states, and central nervous system neoplasms. When secondary renal adjustments are fully expressed and a new steady state is maintained, the average reduction in plasma bicarbonate concentration is approximately 0.5 mEq per liter for each mm Hg reduction in $PaCO_2$.
3. **Treatment of respiratory alkalosis.** The only satisfactory treatment of this acid-base disturbance is removal of the underlying cause.

V. Elevated plasma bicarbonate concentration. An elevated plasma bicarbonate concentration is a characteristic feature of both metabolic alkalosis and respiratory acidosis (see Table 4-2). The clinical setting in which an elevated plasma bicarbonate is found often suffices to distinguish between these two possibilities. Patients with respiratory acidosis usually have evident pulmonary disease by history, physical examination, or chest x-ray. The magnitude of the bicarbonate increment may also be helpful. Values greater than 40 mEq per liter almost never occur in response to hypercapnia alone, even when renal adaptation is complete; such high levels, therefore, signify the presence of metabolic alkalosis. Any doubt about which class of acid-base disturbance is responsible for an elevated bicarbonate can be resolved by measuring pH and/or $PaCO_2$. A high bicarbonate in association with some degree of alkalemia is diagnostic of metabolic alkalosis; a high bicarbonate and acidemia signify respiratory acidosis.

A. Metabolic alkalosis (high $[HCO_3^-]$, low $[H^+]$)

1. **Causes of metabolic alkalosis.** The causes of metabolic alkalosis can be divided into two major subgroups, sodium chloride responsive and sodium chloride resistant, on the basis of the pathogenetic mechanisms involved (Table 4-5).
   a. **Sodium chloride responsive.** The most frequently encountered mechanism responsible for sustained metabolic alkalosis is the loss of body chloride out of proportion to the loss of sodium. When this occurs, heightened renal sodium conservation (due to a reduction in the effective extracellular fluid volume) accelerates the rate of renal sodium bicarbonate reabsorption, because filtered sodium is no longer accompanied by a normal complement of chloride. This discrepancy between the renal avidity for sodium and the availability of chloride explains the sustained alkalosis seen with gastric losses, with use of potent diuretics (furosemide, ethacrynic acid, thiazides, organic mercurials), and after abrupt relief of chronic hypercapnia. In each of these conditions, a diagnostic hallmark is the virtual absence of urinary chloride (unless, of course, diuretic action is still present). A prerequisite to correction of this form of metabolic alkalosis is the administration of adequate amounts of chloride, usually with potassium and, if needed, sodium.

Table 4-5. Causes of Metabolic Alkalosis

Sodium Chloride Responsive	Sodium Chloride Resistant
Vomiting	Hyperaldosteronism
Gastric suction	Bartter's syndrome
Use of certain diuretics	Cushing's syndrome
Abrupt relief of chronic hypercapnia	Severe potassium depletion
	Licorice ingestion

   b. **Sodium chloride resistant.** The second major mechanism accounting for sustained metabolic alkalosis is a direct stimulation of renal bicarbonate reabsorption. Whenever the balance between sodium chloride and sodium bicarbonate reabsorption is shifted in favor of bicarbonate, the kidney sustains an increase in bicarbonate concentration and a decrease in plasma chloride concentration, irrespective of the daily electrolyte intake. This mechanism plays an important role in the sustained metabolic alkalosis typically found in states of hyperadrenocorticism; these states include primary aldosteronism, Bartter's syndrome, and Cushing's syndrome (especially that produced by ectopic ACTH production). Occasionally, very severe potassium depletion (serum potassium, 2 mEq per liter or less) may produce a similar picture. Because plasma anion composition in these conditions, just as in the normal state, is largely unaffected by the level of salt intake, ingested sodium chloride is rejected by the kidney and appears quantitatively in the urine. Hence, these forms of metabolic alkalosis are typically associated with abundant urinary chloride.
2. **Simple metabolic alkalosis versus mixed acid-base disturbances.** The coexistence of primary respiratory acid-base disturbances and metabolic alkalosis can be diagnosed when $PaCO_2$ is out of the range ordinarily encountered in patients with simple metabolic alkalosis. In the absence of complicating acid-base disturbances, the respiratory response to metabolic alkalosis results in a change in $PaCO_2$ that is roughly proportional to the increment in plasma bicarbonate concentration. Specifically, in simple metabolic alkalosis, each mEq per liter increment of bicarbonate appears, on the average, to evoke a 0.5 to 0.8 mm Hg increment in $PaCO_2$. Patients with metabolic alkalosis who manifest levels of $PaCO_2$ higher than can be accounted for by this relation are likely to have independent respiratory acidosis. Conversely, patients with metabolic alkalosis whose $PaCO_2$ falls below the anticipated level manifest some stimulus to ventilation and suffer from independent respiratory alkalosis.
   Example: A patient with far-advanced hepatic cirrhosis has been treated with potent diuretic agents and a salt-restricted diet because of ascites and edema. Laboratory studies reveal plasma bicarbonate 38 mEq per liter, $PaCO_2$ 42 mm Hg, and pH 7.59 ($[H^+]$, 26 nEq/L). It is evident that metabolic alkalosis, presumably resulting from diuretic treatment, dominates the acid-base disorder. However, the 14 mEq per liter increment in plasma bicarbonate (38 − 24 mEq/L) should be associated with at least a 7 mm Hg increment in $PaCO_2$ if the anticipated degree of secondary hypoventilation is present (14 mEq/L × 0.5 mm Hg/mEq/L). The observed increment in $PaCO_2$ is only 2 mm Hg (42 − 40 mm Hg). This discrepancy between the predicted and the observed increments in carbon dioxide tension signifies the presence of some stimulus to ventilation and, thus, provides evidence for an independent respiratory alkalosis superimposed on the underlying metabolic alkalosis.

3. **Therapeutic principles.** The key to the correction of sodium chloride–responsive forms of metabolic alkalosis is the provision of adequate dietary or parenteral chloride. Because potassium deficits are almost universally present, potassium supplements administered as the chloride salt are generally advisable in addition to sodium chloride to correct any volume depletion. Sodium chloride–resistant forms of metabolic alkalosis respond to treatment of the underlying disease.

B. Respiratory acidosis (high [HCO_3^-], high [H^+]). Although an increase in plasma bicarbonate concentration may be the first clue to the presence of respiratory acidosis, the diagnosis is more often suggested by the clinical setting (see Table 4-2). Because the increment in plasma bicarbonate in this condition reflects the secondary physiologic responses to the underlying primary hypercapnia, it does not provide an index of the severity of the acid-base disturbance. A value for $PaCO_2$ should be obtained by direct measurement or by calculation (from plasma bicarbonate and hydrogen ion concentration) to confirm the diagnosis and to characterize the acid-base disturbance fully.

1. **Causes of respiratory acidosis.** Any process other than alkalemia that produces alveolar hypoventilation results in respiratory acidosis. The causes can be divided into three categories, as follows:
   a. Central nervous system disease
      (1) Sedative overdose
      (2) Respiratory arrest
      (3) Primary alveolar hypoventilation
      (4) Brain tumor
   b. Pulmonary disease
      (1) Acute airway obstruction
      (2) Chronic obstructive pulmonary disease
      (3) Severe pneumonia
      (4) Severe pulmonary edema
      (5) Pneumothorax
      (6) Respiratory muscle disease
      (7) Restrictive disease of the thorax
   c. Metabolic disease: myxedema, hypophosphatemia
2. **Acute versus chronic respiratory acidosis.** Many of the common causes of respiratory acidosis result in abrupt, short-lived hypercapnia. The acid-base disturbance under these circumstances is characterized by the initiating increment in $PaCO_2$ coupled with a small, secondary increment in bicarbonate concentration due to the titration of nonbicarbonate tissue buffers. This buffer response is generally of small magnitude, accounting for only a 2 to 3 mEq per liter increase in plasma bicarbonate even when $PaCO_2$ is increased by 30 mm Hg or more. As a consequence, there is a striking increase in plasma hydrogen ion concentration. On the average, each mm Hg increment in $PaCO_2$ in acute respiratory acidosis results in a 0.75 nEq per liter increment in plasma hydrogen ion concentration.

   In chronic respiratory acidosis (most often the consequence of chronic obstructive lung disease), secondary renal responses result in a more marked increase in plasma bicarbonate concentration. The mean increment in bicarbonate concentration in patients fully adapted to chronic hypercapnia is approximately 0.3 to 0.4 mEq per liter for each mm Hg increment in $PaCO_2$. The coexistence of metabolic acid-base disturbances in patients with primary respiratory acidosis can be assessed by determining whether the level of plasma bicarbonate concentration corresponds to the level anticipated for the observed degree and duration of hypercapnia.

   Example: A patient with long-standing lung disease has a $PaCO_2$ of 55 mm Hg and a plasma bicarbonate concentration of 37 mEq per liter. The increment above the normal $PaCO_2$ is approximately 15 mm Hg (55 − 40 mm Hg). Thus, one might anticipate an increment in plasma bicarbonate concentration of approximately 6 mEq per liter just on the basis of chronic hypercapnia (15 mm Hg × 0.4 mEq/L/mm Hg). The observed increment in bicarbonate concentration, however, is 12 mEq above normal (37 − 25 mEq/L). This discrepancy between the observed and anticipated levels of bicarbonate signifies an independent process augmenting plasma bicarbonate and, thus, supports mixed acid-base disturbance in which an element of metabolic alkalosis is present.
3. **Treatment of respiratory acidosis.** Optimal treatment of respiratory acidosis is directed at removing the underlying cause. Tracheal intubation and mechanical ventilation may be required to reverse life-threatening hypercapnia (and hypoxia). Pharmacologic stimulants have not proved to be especially helpful in assisting patients with either acute or chronic carbon dioxide retention.

Suggested Reading

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5

The Patient With Disorders of the Serum Calcium and Phosphate

Zalman S. Agus, Stanley Goldfarb, and Alan Wasserstein

Disorders of the Serum Calcium

I. **Plasma forms of calcium.** Calcium exists in plasma in several different forms. Much of the circulating plasma calcium is bound to protein (~40 percent), and the remainder exists as either the free or ionized form (50 percent) or bound to complexing ions such as citrate and phosphate (5 to 15 percent). Although the free, ionized form is the only physiologically active one, most laboratories do not measure it directly but instead measure the total calcium. This fact is important in assessing disorders of the serum calcium level, because the serum ionized calcium may vary independently of the total calcium. Thus, hypoalbuminemia is associated with a reduction in the total calcium because of a reduced protein-bound component, but the ionized calcium level is normal, and the patient exhibits no symptoms referable to hypocalcemia. Conversely, alkalosis increases binding of ionic calcium to protein, thereby increasing the fraction of the total calcium that is protein bound and reducing the ionized calcium concentration; the patient, therefore, exhibits signs and symptoms of hypocalcemia, but the total calcium as determined in the laboratory is normal.

II. **Regulation of ionized serum calcium.** Regulation of the ionized serum calcium level is accomplished at three levels. Calcium is absorbed from the gastrointestinal tract principally under the influence of vitamin D and its metabolites; deposited in bone; released from bone; and excreted by the kidneys. Bone deposition and release of calcium are for the most part regulated by vitamin D, parathyroid hormone (PTH), and the serum phosphate. The renal excretion of calcium is in turn determined by the serum calcium level and the level of PTH. Increased levels of PTH result in increased reabsorption of filtered calcium in distal portions of the nephron (Fig. 5-1). Virtually all of the clinical disorders of serum calcium result from disturbances in either gastrointestinal absorption or bone resorption, with the kidney playing a secondary role.

III. **Hypercalcemia**

A. **Causes.** With the advent of the autoanalyzer and routine determination of serum calcium levels, recognition of hypercalcemia has become more common. The causes of hypercalcemia can be subdivided into two basic categories—increased gut absorption and increased bone resorption. The most common causes of hypercalcemia are malignancy and hyperparathyroidism, and granulomatous disorders such as sarcoidosis, tuberculosis, and berylliosis run a distant third (Table 5-1).

1. **Primary hyperparathyroidism.** In the majority of instances (80 to 85 percent), hyperparathyroidism is associated with a single adenoma. In a smaller number of patients there is hyperplasia of two or more glands. Hyperplasia is frequently observed in familial hyperparathyroidism and in the multiple endocrine neoplasia syndrome.
2. **Malignancies.** Malignancy can be associated with hypercalcemia through several pathogenetic mechanisms. Metastases to bone can cause local dissolution and release of calcium. In myeloma and lymphoma and perhaps other tumors as well, the recently discovered osteoclast-activating factor may mediate such bone dissolution. Although ectopic secretion of PTH in malignancy has been suspected for many years, recent evidence suggests that this mechanism occurs

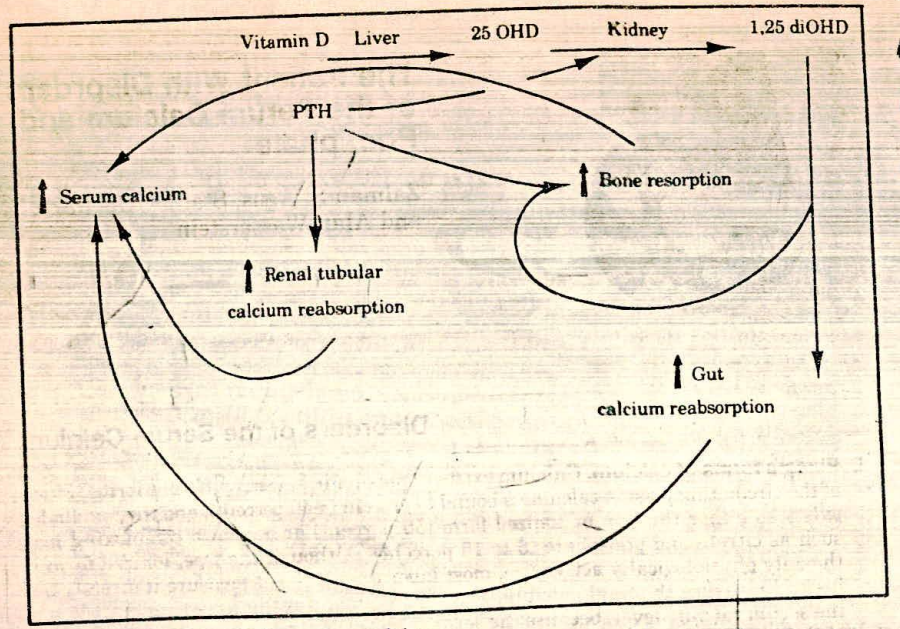

Fig. 5-1. Regulation of the serum calcium.

Table 5-1. Causes of Hypercalcemia

Hyperparathyroidism
Adenoma
Hyperplasia
Multiple endocrine neoplasia syndrome
Familial
Malignancy associated
Metastatic resorption of bone
Secretion of PTH-like substance
Osteoclast activation factor
Prostaglandins
Hormonal therapy of breast cancer
Granulomatous disorders
Sarcoidosis
Berylliosis
Tuberculosis
Histoplasmosis
Coccidioidomycosis
Familial hypocalciuric hypercalcemia
Paget's disease
Addison's disease
Thyrotoxicosis
Vitamin D intoxication
Milk-alkali syndrome
Immobilization
Thiazides
Recovery from acute renal failure (e.g., 2° rhabdomyolysis)
Postrenal transplant

rarely, if ever. Rather, a substance that is immunologically distinct from PTH but shares certain physiologic actions (hypercalcemia, decreased renal tubular phosphate absorption) may account for so-called humoral hypercalcemia of malignancy. Finally, hypercalcemia has been associated with prostaglandin production in several types of solid tumors, but the relative incidence of this mechanism remains to be determined.

3. **Increased gastrointestinal absorption of calcium.** Increased gastrointestinal absorption of calcium plays the predominant role in the genesis of the hypercalcemia of vitamin D intoxication and the granulomatous disorders. There is evidence that the mechanism of increased absorption in sarcoidosis (and possibly other granulomatous disorders) may be increased production of 1,25 dihydroxycholecalciferol, 1,25 $(OH)_2D$, the active metabolite of vitamin D. The incidence of hypercalcemia in sarcoidosis is approximately 10 percent, but hypercalciuria is very common in this disorder.
4. **Other causes.** Familial hypocalciuric hypercalcemia (FHH) is characterized by hypercalcemia (usually asymptomatic), hypocalciuria (fractional calcium excretion less than 1 percent), and hypercalcemia in family members. Although serum PTH levels may be mildly elevated, parathyroidectomy is of no value; this condition should be excluded before parathyroid exploration, particularly if hypercalcemia is asymptomatic.
   Thyroid hormone acts directly on bone to increase resorption. It commonly causes hypercalciuria and, less often, hypercalcemia. At least two mechanisms may be important in the hypercalcemia of milk-alkali syndrome. There is obviously an increase in calcium intake and subsequent gut absorption. Additionally, alkalosis stimulates the renal tubular reabsorption of filtered calcium, and this mechanism probably potentiates the development of hypercalcemia in this syndrome. The mechanism of the hypercalcemia that is occasionally seen in Addison's disease is unknown, but volume depletion with increased concentration of protein-bound calcium is one likely factor. Deficiency of glucocorticoid hormone may also enhance bowel calcium absorption as mediated by 1,25 $(OH)_2D$.
   Other causes of increased bone resorption that may cause hypercalciuria and, less frequently, hypercalcemia include Paget's disease and immobilization. Administration of thiazides can be associated with the development of hypercalcemia. In normal persons there is only a slight, transient elevation of serum calcium, which is due to concentration of serum protein from fluid loss and a decrease in urinary calcium excretion associated with volume contraction, as well as a possible direct effect of thiazides on renal tubular calcium reabsorption. In patients with accelerated bone resorption due to hyperparathyroidism, immobilization, Paget's disease, or vitamin D administration, thiazides seem to potentiate the underlying bone dissolution and may be associated with the development of frank hypercalcemia.

B. Signs and symptoms. Because hypercalcemia is itself a manifestation of an underlying disease process, several signs and symptoms that may be associated with hypercalcemia are manifestations of the primary process, whereas others relate to the hypercalcemia per se.

1. Signs and symptoms associated with **hypercalcemia** include:
   - **a.** Anorexia
   - **b.** Nausea and vomiting
   - **c.** Constipation
   - **d.** Polyuria, nocturia, and polydipsia
   - **e.** Hypertension
   - **f.** Confusion, stupor, and coma
   - **g.** Acute and chronic renal insufficiency
   - **h.** Nephrolithiasis
   - **i.** Metastatic calcification
   - **j.** Peptic ulcer disease, pancreatitis
   - **k.** Electrocardiographic changes

2. Signs and symptoms associated with **underlying disease processes** include:
   - **a.** Hyperparathyroidism: anemia, myopathy, hyperchloremic acidosis, hypophosphatemia, bone disease, pseudogout
   - **b.** Sarcoidosis: disturbances on chest x-rays, rash, lymphadenopathy
   - **c.** Systemic manifestation of malignancy
   - **d.** Thyrotoxicosis

   Hypercalcemia in and of itself may produce a symptom complex characterized by anorexia, nausea and vomiting, constipation, polyuria, nocturia, polydipsia, and central nervous system (CNS) disturbances, including confusion, psychosis, lethargy, stupor, and coma. A serum calcium above 15 mg per deciliter in association with stupor or coma and renal insufficiency (hypercalcemic crisis) is most commonly seen in malignancies but also occurs in hyperparathyroidism. It requires urgent treatment. Hypercalcemia is often associated with hypertension. If the process is prolonged, metastatic calcification and resultant renal insufficiency may ensue. This is most commonly seen in hyperparathyroidism, sarcoidosis, and the milk-alkali syndrome. Other associations with hypercalcemia include peptic ulcer disease and pancreatitis as well as a proximal myopathy that is more commonly associated with hyperparathyroidism. Nephrolithiasis may be associated with any cause of prolonged hypercalcemia and/or hypercalciuria but is more commonly seen in patients with hyperparathyroidism. Laboratory findings are nonspecific, with the exception of ECG and urinalysis. Electrocardiographic manifestations of hypercalcemia include shortening of the Q–T interval and, rarely, serious arrhythmias. The polyuria, nocturia, and polydipsia reflect an inability to concentrate the urine maximally and possibly a primary stimulation of thirst also. Acid-base disturbances that may be seen include a metabolic alkalosis associated with bone dissolution and release of alkali salts, and an increase in bicarbonate reabsorption produced by hypercalcemia. When hyperparathyroidism is present, however, the alkalosis is usually overshadowed by the effect of PTH on the renal tubule to decrease bicarbonate reabsorption, resulting in a hyperchloremic acidosis. Hyperparathyroidism also produces the classic radiologic findings of osteitis fibrosa—subperiosteal resorption of phalanges, "ground-glass" appearance of the skull, and resorption of the distal clavicles.

C. Diagnosis

1. **Indirect demonstration.** In the past, the diagnostic approach to hypercalcemia was oriented toward an indirect demonstration of increased parathyroid hormone activity, including abnormally increased phosphate excretion and evidence of subperiosteal reabsorption. The frequent association of hyperparathyroidism with a hyperchloremic acidosis has also been considered a diagnostic feature. Changes in serum phosphate and chloride have even been combined into a single diagnostic test. A ratio of serum chloride to phosphate exceeding 33 is said to favor hyperparathyroidism; a ratio less than 30, hypercalcemia of other causes. All of these tests are indirect, however, and often there are other factors present that may alter renal phosphate and/or bicarbonate handling independently, thereby adversely affecting the diagnostic accuracy and specificity of these determinations. At present, with the ready availability of the PTH assay, there seems to be less need for these classic tests.
2. **Measurement of plasma immunoreactive PTH.** The diagnostic workup, therefore, should begin with determination of the PTH level. PTH determinations that relate serum PTH to concurrent serum calcium level and provide probabilities for PTH-dependent versus PTH-independent hypercalcemia are commercially available. Assay of the C-terminal fragment of the hormone is most useful in the diagnosis of hyperparathyroidism. Measurement of immunoreactive PTH should be done regardless of the presence of other potential causes of hypercalcemia, because there are clear examples of the coexistence of hyperparathyroidism with a variety of conditions, including sarcoidosis, tuberculosis, thyrotoxicosis,and malignancies.

   The diagnosis of hypercalcemia is almost always evident from the clinical setting, however, and the role of the PTH determination is usually to confirm rather than to make the diagnosis. Thus, the vast majority of patients with hypercalcemia discovered incidentally or during the evaluation of renal calculi have primary hyperparathyroidism. Similarly, the vast majority of patients with hypercalcemia of malignancy have malignancy diagnosed before the hypercalcemia is detected. In the patient with suspected primary hyperparathyroidism, a *frankly elevated* PTH confirms the diagnosis, and parathyroid exploration may be undertaken. However, a urine calcium-creatinine ratio should be obtained to exclude familial hypocalciuric hypercalcemia, particularly if the patient is asymptomatic. If the PTH level is in the normal range ("inappropriate" for the level of hypercalcemia), the diagnosis of primary hyperparathyroidism is still likely, but more definitive proof may be desired before surgery. In such instances, which are more common now because of increasing detection of relatively mild hypercalcemia, sequential PTH determinations usually reveal frankly elevated PTH. Because patients with nonhyperparathyroidal hypercalcemia, particularly nonparathyroidal malignancy, may have PTH levels in the normal range, it is erroneous to base a diagnosis of primary hyperparathyroidism solely on the presence of an "inappropriately" elevated PTH, which is in fact in the normal range. In the patient with malignancy, a frankly elevated PTH does not suggest the presence of ectopic PTH production, but rather concomitant primary hyperparathyroidism. This association is particularly common with certain tumors (e.g., breast carcinoma), and parathyroid exploration may be rewarding even in the presence of known malignancy. A PTH level in the normal range in a patient with hypercalcemia and malignancy is frequently observed, and is probably due to the nonspecificity of the PTH immunoassay. In patients with other causes of hypercalcemia, the diagnosis is usually obvious from the history (e.g., vitamin D intoxication, which is usually iatrogenic), or the clinical picture is dominated by the underlying disease (e.g., thyrotoxicosis, adrenal insufficiency).

   In the occasional cases that remain obscure after serial PTH measurements, several additional diagnostic steps may be employed. The urine calcium-creatinine ratio and results of family members, tests may reveal familial hypocalciuric hypercalcemia. Hypercalcemia of sarcoidosis but not of primary hyperparathyroidism is suppressed by a trial of hydrocortisone (100 mg daily for 1 week). The rare instance in which hypercalcemia is a presenting feature of malignancy should be detected by chest x-ray, urinalysis, serum and urine protein electrophoresis, and stool occult blood. Although weight loss and anemia may occur in primary hyperparathyroidism as well as in malignancy, the presence of these features, and/or repeated failure to document hyperparathyroidism by immunoassay, may necessitate additional diagnostic maneuvers to exclude malignancy. These include an IVP to rule out renal cell carcinoma, abdominal computed axial tomography (CT) scan to exclude occult lymphoma, and perhaps investigation of the gastrointestinal tract.

D. Treatment.

Numerous treatment modalities have been used in the management of hypercalcemia. All have side effects and limitations, and some are more likely to be effective in selected situations.

1. **Phosphate administration.** Calcium can be removed from the blood and deposited at extravascular sites with intravenous phosphate infusion. The usual dose is 20 to 30 mg of elemental phosphorus per kilogram body weight (approximately 50 mMol) over a period of 12 to 16 hours. The response is almost immediate. This treatment is one of the most potent approaches available. Unfortunately, the extravascular deposition of calcium and phosphate can occur anywhere in the body, including the heart and kidney, and the use of intravenous phosphate has been associated with renal cortical necrosis, cardiac arrest, and sudden death. For these reasons, its use is not recommended.

   Oral phosphate therapy, particularly in patients with a reduced serum phosphate, is a much safer form of therapy and may be effective by reducing both calcium gut absorption and bone resorption. It is usually given as 1.5 to 3.0 gm of elemental phosphorus per day in divided doses (Phospho-soda 600 mg phosphorus per 5 ml of solution, or Neutra-Phos 250 mg phosphorus per cap-

sule). Serum calcium usually begins to fall within 24 to 48 hours after administration. Oral phosphate therapy should never be used in patients with an increased serum phosphate, because the risk of extravascular calcification is markedly increased.

2. **Calcitonin and mithramycin.** Several agents that seem to reduce bone resorption as a primary action are available. Calcitonin, given as 4 units per kilogram of body weight intravenously followed by subsequent doses of 4 units per kilogram subcutaneously at 12 to 24 hours, often lowers serum calcium to or toward normal within several hours after administration. Approximately 20 to 25 percent of patients do not respond, however. In those who do respond, continued use may be limited by the rapid development of resistance; this resistance may be avoidable, however, with concomitant steroid administration. Despite these limitations, calcitonin is an attractive agent because of its rapid initial effect and remarkable freedom from side effects. Mithramycin is an antitumor agent that also lowers serum calcium by inhibition of bone resorption. The hypocalcemic dose of 25 μg per kilogram of body weight intravenously is relatively safe, even in the presence of renal failure. Several repeated doses may, however, be associated with the side effects of thrombocytopenia, platelet dysfunction, or hepatic damage. Serum calcium usually begins to fall within 12 to 24 hours after administration, and the effects may persist for 3 to 7 days. Diphosphonates also inhibit bone resorption and have the following two advantages over calcitonin and mithramycin—they can be given orally, and they may ameliorate bone pain in patients with bone metastases. Currently, only etidronate is available in the United States, and this agent causes osteomalacia. Other diphosphonates, which are being used in Europe, do not have this side effect and may soon be available in this country. Indomethacin, by inhibiting prostaglandin synthesis, may eventually prove useful in selected patients with hypercalcemia and malignancy, but at the present time there are not sufficient data to justify its widespread use. In fact, prostaglandin inhibition in the hypercalcemic state can lead to renal failure.
3. **Glucocorticoids.** Glucocorticoids decrease intestinal absorption either directly or via inhibition of vitamin D metabolism; therefore, they are effective in hypercalcemia due to vitamin D intoxication or sarcoidosis. They are also effective in some malignancies (notably, multiple myeloma and breast carcinoma), either by tumoricidal effects or inhibition of bone resorption. Usual dosages are 3 to 5 mg/kg/day of hydrocortisone-equivalent initially, followed by smaller maintenance dosages. In those patients who respond, serum calcium usually begins to fall after 2 to 3 days.
4. **Saline and furosemide.** Finally, urinary calcium excretion can be increased by inhibition of tubular sodium reabsorption at those sites at which sodium and calcium transport appear to be linked. Thus, saline and/or sodium sulfate infusion produces expansion of the extracellular fluid volume and subsequent inhibition of proximal tubular sodium and calcium reabsorption. However, the rapid expansion of the ECF volume may produce volume overload, particularly in elderly patients or in those with underlying cardiovascular disease. A useful adjunct to this type of therapy is the simultaneous use of a diuretic that acts in the loop of Henle. This serves to potentiate calciuria markedly by inhibiting calcium and sodium transport at a site downstream from the proximal tubule. In addition, natriuresis prevents overload of the cardiovascular system. Use of the diuretic before the induction of volume expansion may be self-defeating, because resultant natriuresis will produce contraction of the ECF volume, increased proximal tubular reabsorption of sodium and calcium, and consequent aggravation of hypercalcemia. Therefore, an initial priming saline infusion of 1 to 2 liters over 1 hour should be given. The approach is as follows:
   a. Begin with a priming dose of 1 to 2 liters saline IV over 1 hour.
   b. Give furosemide 40 to 80 mg IV, and repeat every 2 to 3 hours.
   c. Measure urine volume every hour and urine sodium-potassium concentration every 4 to 6 hours.
   d. Replace urine volume with saline and added potassium chloride.
   e. If hypercalcemia is prolonged, add magnesium (15 mg per hour).

   Once diuretics are given, urinary losses of sodium and potassium must be measured and replaced. Sodium sulfate is theoretically more calciuric than saline because of the formation of calcium sulfate complexes that are not reabsorbed by the tubule. Sodium sulfate has not proved to be more effective than saline, however, and its use is often complicated by hypernatria, because it is most often prepared as an isotonic hypernatremic solution.
5. **EDTA administration.** EDTA also increases urinary calcium excretion. Its principal virtue, however, is that by complexing with calcium in the blood before excretion, it reduces the ionized calcium level immediately. EDTA, 15 to 50 mg per kilogram over 4 hours, is probably the most effective immediate therapy for hypercalcemia. Unfortunately, there has been a significant incidence of nephrotoxicity associated with EDTA administration in high doses. For this reason, its use should be restricted to life-threatening situations in which immediate reduction of the ionized calcium level is critical.

E. Therapeutic approach

1. **Acute hypercalcemia.** Therapy of acute symptomatic hypercalcemia of any grade of severity begins with volume expansion, which alone may be adequate in mild-to-moderate hypercalcemia. After ECF volume expansion is achieved, the addition of furosemide at intervals commensurate with the severity of hypercalcemia additionally enhances calciuria. Additional therapy depends on the severity and urgency of the clinical picture. Severe hypercalcemia (greater than 15 mg per deciliter) with acute neurologic, cardiovascular, or renal dysfunction constitutes hypercalcemic crisis and is a medical emergency. In most instances, the addition of mithramycin or calcitonin to saline-furosemide infusion provides adequate acute therapy. Neither agent requires renal function to be effective. Calcitonin has a faster onset of action, although it is less uniformly effective than mithramycin. If after several hours of saline-furosemide diuresis and calcitonin infusion, hypercalcemia greater than 15 mg per deciliter persists and the clinical condition remains unstable, additional therapy is required. In these rare instances, immediate reduction of the serum ionized calcium by infusion of sodium EDTA may be required. Rapid effects can also be obtained with hemodialysis; this is preferred in the patient with oliguric renal failure.
2. **Chronic hypercalcemia.** Management of subacute or chronic mild hypercalcemia is dependent to a certain extent on the cause of the hypercalcemia:
   a. Steroids
      (1) Sarcoidosis
      (2) Multiple myeloma
      (3) Breast cancer (50 percent)
      (4) Vitamin D intoxication
      (5) Immobilization
   b. Oral phosphate
      (1) Hyperparathyroidism (nonsurgical candidates)
      (2) Most malignancies
   c. Mithramycin: If oral phosphate is ineffective or serum phosphate is elevated.

Thus, steroids are most effective in syndromes characterized by increased intestinal calcium absorption and in some malignancies. In other malignancies and in nonsurgical candidates with hyperparathyroidism, oral phosphate therapy is a relatively safe and effective treatment. If the serum phosphate is elevated, however, the use of phosphate is contraindicated, and chronic administration of mithramycin at 5- to 7-day intervals is a reasonable alternative. The use of indomethacin has not been carefully evaluated yet, but it is a potentially useful drug in the management of hypercalcemia because it inhibits prostaglandin production in some malignancies.

Finally, it should be pointed out that parathyroid surgery is the treatment of choice for hyperparathyroidism; chronic medical therapy is indicated only in pa-

tients in whom surgery has been repeatedly unsuccessful or is contraindicated. The management of the patient with asymptomatic mild hypercalcemia detected on routine screening remains controversial. Unless adequate follow-up can be ensured, surgery is usually indicated to avoid the potential complications of bone disease, kidney stones, and renal damage.

IV. Hypocalcemia

A. Causes.

The causes of a reduced serum calcium level are listed in Table 5-2.

1. **Hypoalbuminemia.** Hypoalbuminemia lowers the total serum calcium level by reduction of the fraction that is bound to protein. The ionized fraction is unaffected by this reduction, and the patient is, therefore, asymptomatic. A useful rule of thumb to estimate the contribution of hypoalbuminemia to hypocalcemia is that total serum calcium will fall by 0.8 mg per deciliter for every decrement in serum albumin of 1 gm per liter.
   A reduction in the ionized calcium level usually reflects a disturbance in the production, metabolism, or response to parathyroid hormone or vitamin D, the two principal factors that regulate the ionized calcium level. Additionally, removal of calcium from the serum and deposition in extravascular sites can produce hypocalcemia.
2. **Primary disturbances in the parathyroid system.** Disturbances in the parathyroid hormone system that can produce symptomatic hypocalcemia include decreased production (hypoparathyroidism) or inadequate response to normal circulating levels of parathyroid hormone (pseudohypoparathyroidism). Hypoparathyroidism is most commonly due to surgical injury following thyroid, parathyroid, or radical neck surgery. Rarely, it may be the consequence of infiltrative disease such as iron storage disease, amyloidosis, and metastatic malignancy, or it may occur either sporadically or as a familial idiopathic disorder. Idiopathic hypoparathyroidism most often presents in childhood or early adolescence. It is occasionally associated with other abnormalities such as idiopathic adrenal insufficiency, diabetes mellitus, pernicious anemia, moniliasis, and hypothyroidism. In all of these instances, serum PTH levels are low or undetectable. In contrast, pseudohypoparathyroidism resembles hypoparathyroidism in the clinical features of hypocalcemia and hyperphosphatemia but differs in two important respects. First, because the disease represents a lack of responsiveness to PTH rather than a defect in secretion, serum PTH levels are high and suppressible with calcium administration. Second, pseudohypoparathyroidism is often associated with a unique skeletal developmental abnormality, sometimes called Albright's hereditary osteodystrophy, consisting of short stature, mental retardation, round face, obesity, and a characteristic shortening of the third and fourth metacarpals and metatarsals. The osteodystrophy may occur in the absence of the biochemical abnormalities, in which case the disease is known as pseudopseudohypoparathyroidism. The cause of pseudohypoparathyroidism seems to be a defect in the adenylate cyclase response to parathyroid hormone. Accordingly, the diagnosis is classically made by demonstrating normal or elevated levels of PTH and lack of an increase in urinary 3′5′ adenosine monophosphate (cyclic AMP) after PTH infusion. In rare patients, however, there may be bone resistance to PTH with a normal increase in urinary cyclic AMP.
3. **Hypomagnesemia.** Another interesting cause of hypocalcemia involving the parathyroid hormone system is hypomagnesemia; hypocalcemia in this situation combines the features of both hypoparathyroidism and pseudohypoparathyroidism. Thus, severe hypomagnesemia may decrease secretion of parathyroid hormone as well as inhibit the response of the bone to normal levels of parathyroid hormone. Either or both of these mechanisms may be operative in any given patient, and the PTH level may be low, normal, or elevated. The cardinal features of this disorder are a serum magnesium level below 0.8 mEq per liter or 1 mg per deciliter and a resistance to therapy until the hypomagnesemia has been corrected. The causes of hypomagnesemia include inadequate intake, hyperalimentation, steatorrhea, diarrhea, chronic alcoholism, and nephrotoxicity secondary to aminoglycoside antibiotics or cisplatin. The latter two agents apparently cause urinary magnesium wasting.
4. **Vitamin D deficiency.** A deficiency of the active form of vitamin D may cause hypocalcemia and may occur in a variety of ways. After absorption from the GI tract as a fat-soluble vitamin, or synthesis in the skin under the influence of ultraviolet irradiation, vitamin D_3 is transported to the liver. In the liver, the intermediate form, 25(OH)D is produced; this compound is additionally metabolized by the kidney to produce $1,25(OH)_2D$, the most active metabolite of the vitamin. Vitamin D metabolites both enhance intestinal calcium absorption and potentiate the effect of PTH on bone. Abnormalities anywhere in this chain of events can produce decreased levels of $1,25\ (OH)D_3$ and subsequent hypocalcemia. Nutritional deficiency of vitamin D has almost disappeared in the United States, and gastrointestinal disease is now the most important cause of vitamin D deficiency. Partial gastrectomy, chronic pancreatitis, small bowel disease, intestinal resection and bypass surgery, and steatorrhea are all associated with impaired absorption of vitamin D_3. In addition, liver disease may be associated with decreased production of 25(OH)D from the native vitamin. Drugs such as phenobarbital and phenytoin, which accelerate the metabolism of 25(OH)D to inactive metabolites and make it unavailable for metabolism by the kidney, can produce hypocalcemia; anticonvulsants may also have direct inhibitory effects on intestine and bone. Deficiency of 25(OH)D can also be produced by disturbance of the enterohepatic circulation and with loss into the urine in the nephrotic syndrome. Defective

Table 5-2. Causes of Hypocalcemia

Hypoalbuminemia
Disturbance in parathyroid system
Hypoparathyroidism
Surgical
Infiltrative
Idiopathic
Pseudohypoparathyroidism
Hypomagnesemia
Disturbances in vitamin D system
Decreased intake—nutritional
Decreased absorption—malabsorption
Decreased production of 25(OH)D—liver disease
Increased metabolism of 25(OH)D
Phenobarbital
Phenytoin
Alcohol
Glutethimide
Accelerated loss of 25(OH)D
Nephrotic syndrome
Disturbances of enterohepatic circulation
Decreased production of $1,25(OH)_2D$
Hereditary
Renal disease
Removal of calcium from serum
Hyperphosphatemia
Laxatives
Phosphate enemas
Cytotoxic treatment of leukemias and lymphomas
Rhabdomyolysis
Osteoblastic metastases
Acute pancreatitis

enzyme activity in the kidney, either as a result of renal disease and a reduction in functioning parenchyma or as a hereditary defect (vitamin D–dependent rickets), produces low levels of $1,25(OH)_2D$ and hypocalcemia. Deficiency of PTH may also be associated with diminished $1,25(OH)_2D$. Recently, several cases have been described with the features of vitamin D deficiency but elevated levels of 1,25(OH)D; these patients apparently have target organ resistance to vitamin D metabolites.

5. **Hyperphosphatemia, osteoblastic metastases, and pancreatitis.** Removal of calcium from the serum by deposition elsewhere can be produced by hyperphosphatemia and osteoblastic metastases. Acute hyperphosphatemia can occur with phosphate ingestion (cow's milk in infants, laxatives or enemas containing phosphates, and potassium phosphate tablets) as well as following lysis of cells, as in treatment of acute leukemia or lymphoma or with rhabdomyolysis. Osteoblastic metastases rarely cause hypocalcemia by enhanced bone formation in carcinoma of the breast, prostate, and lung. The hypocalcemia of pancreatitis probably also fits into this category; precipitation of calcium soaps in the abdominal cavity is the major mechanism, and inadequate parathyroid response plays an ancillary role.

B. Signs and symptoms. As with hypercalcemia, the manifestations of hypocalcemia range from the acute, dramatic, and life-threatening to the subtle and misleading that go undiagnosed for many years. The major manifestations of hypocalcemia involve disturbances of the following areas:

1. Psychiatric
2. Neuromuscular
   a. Tetany
   b. Seizures
   c. Intellectual impairment
   d. Extrapyramidal disorders
   e. Myopathy
3. Ectodermal
4. Ocular cataracts
5. Dental
6. Cardiovascular

Tetany, with markedly enhanced neuromuscular irritability, is the hallmark of hypocalcemia. It begins with circumoral and acral paresthesias. Motor manifestations include stiffness, clumsiness, muscle spasms, cramps, and the characteristic carpopedal spasm. Latent tetany may be detected by tapping over the facial nerve to produce a facial twitch (Chvostek's sign), or by inflation of a blood pressure cuff over systolic pressure for 3 minutes to produce carpal spasm (Trousseau's sign). Other manifestations include seizures associated with severe hypocalcemia, mental retardation in children, and dementia or psychosis in adults. Extrapyramidal movement disorders may occur with or without evidence of basal ganglia calcification. Myopathy is due to secondary hyperparathyroidism, phosphate depletion, or vitamin D deficiency, rather than to hypocalcemia per se. In hypoparathyroidism, dermatitis, eczema, and psoriasis may occur associated with coarse, brittle hair and patchy alopecia. Cataracts occur with prolonged hypocalcemia; progression can be prevented with treatment. Characteristic dental abnormalities occur when hypocalcemia is present during early development and include hypoplasia, failure of eruption, defective enamel and root formation, and carious teeth.

Hypotension may complicate acute hypocalcemia, and hypocalcemia may occasionally contribute to the development of frank congestive heart failure due to decreased myocardial contractility. Electrocardiographic manifestations include a characteristic lengthening of the Q—T interval. Hypocalcemia may produce insensitivity to digitalis. Rarely, disordered ventricular conduction with hypocalcemia may progress to ventricular fibrillation.

C. Diagnosis. The diagnostic approach to hypocalcemia is basically a review of the various components of parathyroid hormone and vitamin D metabolism (Fig. 5-2). The first step is verification that the reduction in total calcium reported from the laboratory indicates a reduction in ionized calcium levels. In the absence of direct measurements of this fraction, measurement of the serum albumin level provides a reasonable guide. If the fall in calcium is greater than can be accounted for by a reduction of 0.8 mg per deciliter for each 1 gm per deciliter reduction in serum albumin level, physiologic hypocalcemia can be presumed. The next step is to measure the serum magnesium level. If the magnesium concentration is less than 0.8 mEq per liter or 1 mg per deciliter, hypomagnesmia is likely to be a major factor in the genesis of hypocalcemia. If the magnesium level is not low, the plasma phosphate concentration is helpful. A high serum phosphate suggests hypoparathyroidism; a low value is compatible with secondary hyperparathyroidism due to vitamin D deficiency. Renal failure causes both high serum phosphate and $1,25(OH)_2$ vitamin D deficiency but is readily excluded by the usual measures of renal function. The discrimination between hypoparathyroidism and vitamin D deficiency can be confirmed by measurement of parathyroid hormone levels. A low PTH level is expected in hypoparathyroidism; an elevated level is consistent with either pseudohypoparathyroidism or vitamin D deficiency. The clinical picture should distinguish the latter two syndromes. The presence of the classic osteodystrophy confirms the diagnosis of pseudohypoparathyroidism. Gastrointestinal disease, liver disease, anticonvulsant medication, and/or nephrotic syndrome all point to vitamin D deficiency. In the absence of clinical clues, this differentiation can be made by measuring the circulating levels of 25(OH)D and $1,25(OH)_2D$ and/or by evaluating the urinary cyclic AMP response to PTH infusion. Most instances of vitamin D deficiency are due to malabsorption of vitamin D; few are due to disturbances in the metabolism of 25(OH)D. As assays for the various vitamin D metabolites become more widely available, it will be possible to examine the components of this system more closely. For the present, however, it is sufficient to make the diagnosis of vitamin D deficiency and to institute therapy on that basis.

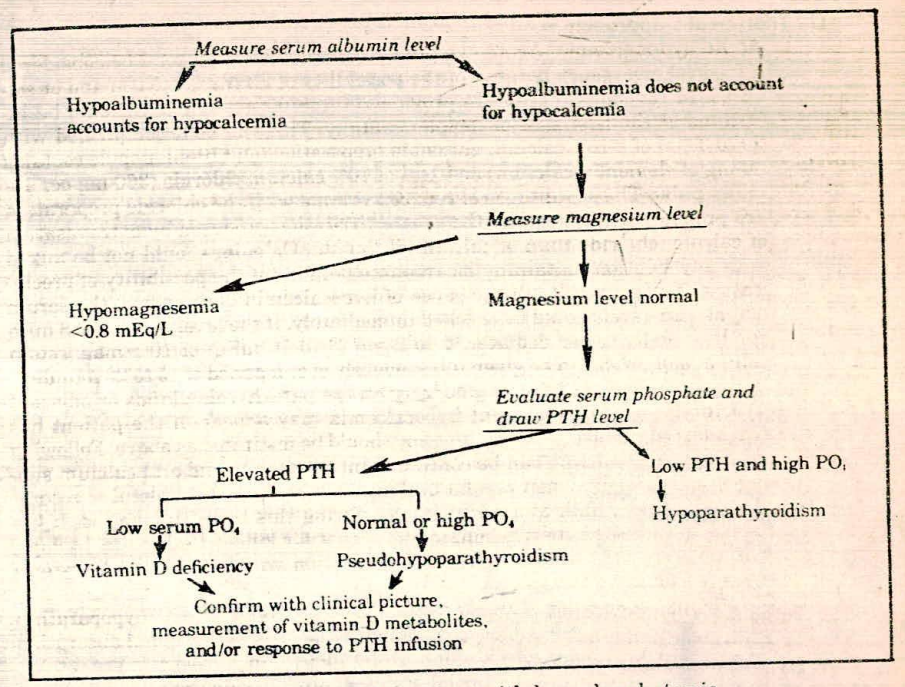

Fig. 5-2. Diagnostic evaluation of the patient with hypophosphatemia.

D. Therapeutic approach

1. **Acute hypocalcemia.** Acute symptomatic hypocalcemia should be considered a medical emergency because of the possibility of laryngeal spasm and/or seizures. Intravenous therapy to provide 200 to 300 mg calcium should be instituted at the first sign of incipient tetany. This can be accomplished with 20 to 30 ml of a 10% calcium gluconate preparation (one 10-ml ampule contains 90 mg of elemental calcium) or 10 ml of 10% calcium chloride (360 mg per 10-ml ampule). The advantages of reduced volume with the chloride preparation are probably outweighed by the greater irritation produced by extravasation of calcium chloride than of calcium gluconate. Calcium should not be mixed with any solution containing bicarbonate because of the possibility of precipitation of calcium salts. If the cause of hypocalcemia is unknown, the serum magnesium level should be checked immediately. If the level is below 0.8 mEq per liter or 1 mg per deciliter, 1 to 2 gm (8 to 16 mEq) of 10% magnesium sulfate solution should be given intravenously over a period of 15 to 20 minutes.
   In the first few days following surgery on the parathyroid glands or adjacent structures, subacute transient hypocalcemia may appear. If the patient has symptoms suggestive of tetany, therapy should be instituted as above. Following acute therapy, calcium can be continued intravenously and oral calcium supplementation begun when regular oral intake is started. It is helpful to restrict phosphorus (i.e., milk and meat) intake during this transition period. If hypocalcemia and/or hyperphosphatemia persist for longer than 10 to 14 days, it is unlikely that normal parathyroid function will return, and long-term therapy should be considered.
2. **Chronic hypocalcemia.** Chronic hypocalcemia, whether due to hypoparathyroidism or vitamin D deficiency, is treated by increasing intestinal absorption of calcium. This is done with vitamin D therapy and increased calcium intake. In hypoparathyroidism, the initial step is to provide calcium in the range of 2 to 4 gm per day, either as calcium lactate (60 mg elemental calcium per 300-mg tablet), calcium gluconate (90 mg per 1-gm tablet), or calcium carbonate (260 mg per 650-mg tablet). If response to this therapy is inadequate and a near normal serum calcium is not achieved, a vitamin D preparation should be added. This can be given either as vitamin D_2, ergocalciferol, 50,000 to 150,000 units or 1.25 to 3.75 mg per day, or dihydrotachysterol (DHT), 0.25 to 0.75 mg per day. These dosages are many times higher than the equivalent physiologic dosage of 100 to 400 units of vitamin D_2 per day required to treat true vitamin D deficiency. In part, the resistance may be due to inadequate production of 1,25(OH)D_2 from 25(OH)D, due to PTH deficiency and hyperphosphatemia. DHT has the advantage of more rapid offset of action if hypercalcemia supervenes. It also bypasses the need for 1-hydroxylation. As experience is gained with the use of 1,25$(OH)_2$D, therapy may be additionally improved. The aim of therapy is to provide a near normal serum calcium, but in the absence of the renal effects of PTH this produces hypercalciuria. Thiazides have been shown to be effective in patients with hypoparathyroidism; the careful use of hydrochlorothiazide may reduce both urinary calcium and the need for vitamin D in this situation.
   In hypocalcemia associated with disorders of vitamin D metabolism, therapy can be individualized. In the usual patient with malabsorption, calcium supplementation and vitamin D therapy, as given above, are appropriate. Dosage of vitamin D ranges from 4000 to 12,000 units per day to high dosages comparable to those required in hypoparathyroidism. In patients with very large requirements, magnesium depletion should be considered. Measurement of 25(OH)D levels may be useful in assessing adequacy of therapy, and 1,25$(OH)_2$D and 25(OH)D (calcifediol) may be particularly useful in conditions in which hepatic 25-hydroxylase activity is compromised and in conditions of excessive external losses of 25(OH)D, such as defects of the enterohepatic circulation or the nephrotic syndrome. Patients taking anticonvulsant medication usually respond to supplementation with 5000 to 10,000 units of vitamin D per day. In the very rare patient with vitamin D–dependent rickets, therapy with 1,25$(OH)_2$D is indicated. The hypocalcemia of renal failure is a special situation in that both deficiency of 1,25$(OH)_2$D and hyperphosphatemia play a role. Renal failure is only rarely associated with symptomatic hypocalcemia, and the therapeutic approach is designed to prevent or treat bone disease. The first step in therapy is reduction of hyperphosphatemia with phosphate-binding antacids. If this is unsuccessful, therapy with oral calcium and then with vitamin D is often required. Dihydrotachysterol or 1,25$(OH)_2$D compounds that bypass the requirement for renal 1-hydroxylation have special merit in this situation. Also, the complication of hypercalcemia is more rapidly reversible with these compounds than with vitamin D.
   Not infrequently, the diagnosis of hypocalcemia is based on a laboratory determination in asymptomatic patients who often present with either bowel disease or liver impairment and chronic alcoholism. In these patients, the decision whether or not to institute therapy should be based on individual assessment. Mild hypocalcemia usually remains asymptomatic in these circumstances, and the principal complication is the potential development of metabolic bone disease because of the associated vitamin D deficiency. If the primary disease responsible for malabsorption can be treated, there is no need for prolonged therapy with vitamin D. In a patient with irreversible disease with expectation of a prolonged course or in a patient with symptomatic bone disease, treatment with vitamin D (approximately 1500 units) is clearly indicated. In the absence of obvious gastrointestinal disease, a workup is indicated to evaluate the presence of occult steatorrhea or liver disease.

Disorders of the Serum Phosphate

Normal levels for serum phosphate are 3.5 to 4.5 mg per deciliter, whereas total intracellular phosphate concentration (inorganic and organic forms) is nearly 300 mg per deciliter. Because the source of cellular inorganic phosphate is primarily extracellular phosphate, and since the cellular inorganic pool provides phosphate for adenosine triphosphate (ATP) and phospholipid synthesis, the regulation of serum phosphate is critical to cellular function and membrane structure.

I. **External phosphate balance.** Adults are in external phosphate balance. That is to say, intake of phosphate (averaging 1200 mg per day) equals output (800 mg per day via the kidney and 400 mg per day via losses into the GI tract). Diet and the GI tract are not normally important influences on phosphate homeostasis since phosphate is ubiquitous in foods and intake is usually far in excess of GI losses. There is little regulation of gut phosphate absorption; most of dietary intake, massive or meager, is absorbed. The kidney, however, exerts a major influence on phosphate homeostasis. About 9000 mg per day is filtered and available for excretion. Normally, approximately 90 percent is reabsorbed, leaving 800 mg to be excreted daily. However, a rise in parathyroid hormone levels can easily reduce the rate of phosphate reabsorption by 10 percent of the filtered load, which in turn produces a twofold increase in excretion. A fall in PTH levels can lead to a 10 percent rise in phosphate reabsorption by the kidney and acutely reduce output to less than 100 mg per day. Since the total extracellular fluid phosphate content is only 56 mg, it is clear that minor changes in renal phosphate transport may lead to major changes in serum phosphate level. Although these changes are primarily the result of changing PTH levels, PTH-independent defects in renal phosphate transport exist and lead to clinically important disturbances in the serum phosphate level.

II. **Internal phosphate balance.** There is also an internal balance for phosphate. Normally, inorganic phosphate exists in intracellular fluids at a concentration of 3 to 4 mg per deciliter, but total phosphate (organic plus inorganic) may be 300 mg per deciliter. Extracellular fluid levels are 4 percent of this total value. Thus, shifts in phosphate across cell membranes can profoundly alter the serum phosphate level. Various hormones as well as changes in hydrogen ion content of the body fluids may influence this transcellular distribution.

III. Hypophosphatemia

A. Causes. Ten to fifteen percent of hospitalized patients may develop a lower serum phosphate level (less than 2.5 mg per deciliter), and a smaller number may be found with profound hypophosphatemia (less than 1.0 mg per deciliter). Hypophosphatemia can result from either excess external losses (GI tract or kidneys) or redistribution of phosphate from extracellular to intracellular fluids (Table 5-3). Inadequate phosphate intake alone is rarely responsible for severe phosphate depletion, because compensatory mechanisms reduce both renal excretion and GI secretion. The renal response is quite rapid, but the GI response may take several weeks. Inadequate diet may cause mild-to-moderate depletion but does not produce marked hypophosphatemia.

1. **Gastrointestinal disturbances.** Gastrointestinal losses of phosphate sufficient to induce hypophosphatemia can be produced with protracted diarrhea or ingestion of large amounts of aluminum-containing antacids. Aluminum binds to phosphate (either dietary or secreted) in the GI tract and produces net losses of phosphate from the body.
   Hypophosphatemia in gastrointestinal disease is primarily the result of malabsorption. Malabsorption of vitamin D and calcium leads to secondary hyperparathyroidism, which in turn enhances urinary phosphate excretion. Although reduced GI phosphate absorption may also play a role, increased renal excretion is more important in the genesis of hypophosphatemia.
2. **Renal phosphate wasting—intrarenal factors.** Renal phosphate wasting is due to either intrinsic tubular transport abnormalities or inhibition of phosphate reabsorption by extrarenal factors such as hormones, drugs, or acute expansion of the extracellular fluid volume. The two most important forms of intrinsic tubular abnormalities that lead to phosphate wasting are vitamin D–resistant rickets (VDRR), both adult sporadic and familial forms, and variants of Fanconi's syndrome. VDRR in the familial form represents a dominant sex-linked disorder in which phosphate transport across the GI tract and kidney is defective. Hypophosphatemia occurs in early life. The primary clinical manifestations are severe rickets and osteomalacia that do not respond to physiologic doses of vitamin D. A form of this condition occurs sporadically in adults. This latter disorder is quite rare. It is usually associated with tumors of mesenchymal origin, usually sclerosing hemangioma. This tumor may elaborate a substance that, although not structurally similar to parathyroid hormone, may have similar phosphaturic activity.
   Fanconi's syndrome refers to a primary injury to the renal proximal tubule with reduced reabsorption of a number of solutes normally reabsorbed in this segment of the nephron, including bicarbonate, glucose, and amino acids, as well as phosphate. The causes of this lesion include metabolic diseases (cystinosis, Wilson's disease, hereditary fructose intolerance), neoplastic disorders (multiple myeloma), inflammatory diseases (systemic lupus erythematosus), and intoxication (heavy metal poisoning).

Table 5-3. Causes of Hypophosphatemia

Gastrointestinal disturbances
Inadequate intake
Aluminum-containing antacids
Chronic diarrhea
Secondary hyperparathyroidism
Malabsorptive states
Vitamin D deficiency
Primary renal losses
Primary hyperparathyroidism
Vitamin D–resistant rickets
Fanconi's syndrome
Glycosuria
Diuretics
Extracellular fluid volume expansion
Redistribution
Insulin administration
Acute respiratory alkalosis
Catecholamine administration

3. **Renal phosphate wasting—extrarenal factors.** Renal phosphate wasting due to extrarenal factors primarily represents forms of hyperparathyroidism. In both primary and secondary hyperparathyroidism (due to GI disturbances or dietary vitamin D deficiency), elevated circulating levels of PTH chronically depress renal tubular phosphate reabsorption and lead to hypophosphatemia. The level of serum phosphate seen in these conditions is usually between 2.0 and 2.5 mg per deciliter. Severe hypophosphatemia is uncommon.
   Certain other extrarenal factors may lead to phosphate wasting. Perhaps the most important of these is glycosuria. Glucose and phosphate compete for reabsorption in the proximal tubule. During hyperglycemia, renal phosphate reabsorption may be reduced. This may contribute to the prominent hypophosphatemia seen during the therapy of unstable diabetes mellitus. Certain diuretics, such as acetazolamide and metolazone, may reduce proximal tubular phosphate reabsorption in a manner similar to the inhibition of phosphate reabsorption that occurs during acute expansion of the extracellular fluid volume with saline- or bicarbonate-containing solutions.
4. **Redistribution of phosphate.** Hypophosphatemia may be produced by redistribution of phosphate from the extracellular to the intracellular fluid. This occurs with stimulation of glycolysis and formation of large quantities of phosphorylated compounds. Glucose infusion, insulin administration, or respiratory alkalosis has this effect. Hypophosphatemia is an inevitable consequence of parenteral hyperalimentation unless phosphate supplementation is provided. Marked hypophosphatemia is commonly seen in the treatment of diabetic ketoacidosis. Catecholamine administration also stimulates cellular phosphate uptake. The mechanism is unknown.
5. **Hypophosphatemia of alcoholism.** Perhaps the most common setting of marked hypophosphatemia is the hospitalized alcoholic patient. Multiple factors contribute to the pathogenesis of this syndrome. Before hospitalization, inadequate phosphate intake, chronic diarrhea, and secondary hyperparathyroidism (due to calcium and vitamin D deficiency and/or malabsorption) combine to produce a baseline state of phosphate depletion. On admission, the alcoholic is usually treated with glucose-containing intravenous solutions that stimulate cellular phosphate uptake. Respiratory alkalosis develops as withdrawal from alcohol and delirium tremens begin. The consequence of this sequence of events is severe hypophosphatemia, often most marked 12 to 24 hours after admission.

B. Signs and symptoms. Since inorganic cellular phosphate depends on extracellular fluid phosphate as its source, the consequences of hypophosphatemia may be the same whether phosphate is actually lost from the body fluids (urine or stool) or enters cells in an organic form. The primary disturbance is cellular ATP deficiency, due to both disordered adenine metabolism and reduced high-energy phosphate bond formation. In general, severe hypophosphatemia (less than 1.0 to 1.5 mg per deciliter) is required to produce acute clinical symptoms.
The organ systems most profoundly affected by hypophosphatemia are muscle (skeletal and cardiac), hematopoietic, central nervous system (CNS), and bone.

1. **Muscle.** A skeletal myopathy may occur in hypophosphatemia with elevated creatine phosphokinase (CPK) levels and profound weakness. This disturbance has led to alveolar hypoventilation and respiratory failure according to at least one report.

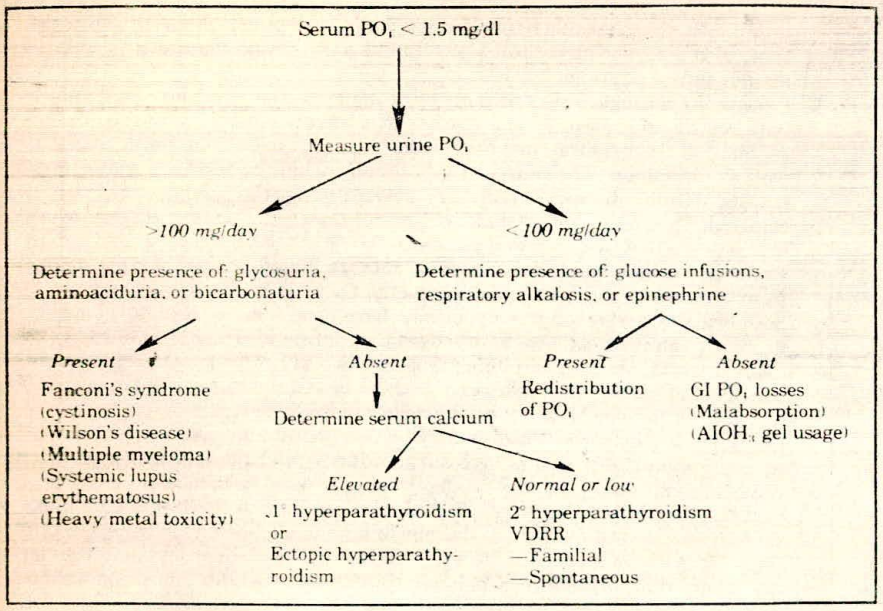

Fig. 5-3. Diagnostic evaluation of the patient with hypophosphatemia.

2. **Hematopoietic.** Reduced red blood cell survival, reduced white cell function (phagocytosis), and reduced platelet adhesiveness have all been reported in hypophosphatemia but are almost always of a minor degree and subclinical in nature.
3. **CNS.** Neurologic dysfunction manifested by obtundation, coma, and, rarely, seizures has also been noted in severe hypophosphatemia, particularly in patients with multisystem disease or severe trauma.
4. **Bone.** Osteomalacia has been shown to occur with severe, prolonged hypophosphatemia. The deficiency of ATP induced by phosphate depletion may be a relative one. For example, resting muscle may not undergo rhabdomyolysis with phosphate deficiency, but vigorous activity may quickly stress cells beyond their ATP reserves and lead to tissue damage. Also, patients who have a modest degree of phosphate deficiency may become severely symptomatic when cellular glucose uptake is stimulated by glucose or insulin administration.

C. Diagnosis. The differential diagnosis begins with assessment of urinary phosphate excretion (Fig. 5-3). The kidney removes phosphate from the urine rapidly when the filtered load of phosphate begins to fall. In normal people, phosphate is virtually eliminated from the urine below a phosphate level of 2.0 mg per deciliter. In a patient with marked hypophosphatemia, urinary excretion of greater than 100 mg per day (corresponding to a urinary phosphate concentration of 5 to 10 mg per deciliter) is inappropriate and indicates renal phosphate wasting, which is due to either a tubular defect or increased levels of parathyroid hormone. Hyperparathyroidism (primary or secondary) is distinguished by measurement of the PTH level. The various tubular syndromes can then be identified by the presence or absence of other components of proximal tubular dysfunction, such as glycosuria, bicarbonaturia, and aminoaciduria.

If urinary phosphate excretion is appropriately low, the differential diagnosis includes GI losses and redistribution of phosphate associated with respiratory alkalosis and glucose infusion. The former is corroborated by a history of gastrointestinal disease or the use of aluminum hydroxide gels.

D. Therapeutic approach. All patients with marked hypophosphatemia should be treated. The route and rate of therapy, however, are a source of controversy. The first principle of therapy is to correct the underlying disturbance. In more than 60 percent of hospitalized patients, glucose infusions are the cause of hypophosphatemia. In the majority of the remaining patients, respiratory alkalosis due to sepsis, pulmonary disease, anxiety, alcohol withdrawal, or fever will be present. In these circumstances, correction of the primary disorder may preclude the need for specific phosphate supplements. In some patients, however, obtundation, coma, seizure, respiratory failure, and congestive heart failure may coexist with and be attributable to hypophosphatemia. In this case, therapy with phosphate supplements is indicated. Unfortunately, because of a highly variable patient response, no regimen for intravenous phosphate therapy is completely safe. If hyperphosphatemia occurs, deposition of calcium phosphate complexes in soft tissues, blood vessels, and other viscera, as well as severe hypocalcemia, may result. This untoward reaction may occur whenever the solubility product of [Ca] × [HPO_4] exceeds 60.

1. **Oral phosphate.** The preferred route of therapy is oral administration of phosphate, since it is less likely to cause acute, severe hyperphosphatemia. The dosage for the treatment of severe hypophosphatemia should not exceed 2000 mg per 24 hours in four divided doses. Serum phosphate should be monitored once every 24 hours and phosphate repletion halted when serum phosphate rises above 2.5 mg per deciliter. (Phospho-soda contains 650 mg phosphate per 5 ml).
2. **Intravenous phosphate.** If oral therapy cannot be employed, then intravenous phosphate may be used. The dosage should never exceed 2 mg per kilogram of body weight over 6 hours, with monitoring of serum phosphate level every 6 hours until the level rises to 2.5 mg per deciliter. The prophylactic use of intravenous phosphate is justified only in the setting of total parenteral nutrition, for which studies have shown the need for 450 mg of phosphate for each 1000 kcal infused. In other conditions in acutely ill, unstable patients, intravenous phosphate supplementation is indicated only in the emergency therapy of severe, symptomatic hypophosphatemia.

   Prophylactic intravenous phosphate therapy has been suggested as a useful adjunct to the management of diabetic ketoacidosis. The acute reversal of acidosis reduces oxygen delivery (Bohr effect), and superimposition of reduced 2,3 diphosphoglycerate (DPG) levels due to hypophosphatemia may additionally impair tissue oxygenation. However, prospective studies now show no clinical benefit to routine, prophylactic phosphate infusions in patients being treated for diabetic ketoacidosis. Therefore, oral phosphate administration is the preferred regimen when normal dietary intake of phosphates cannot be otherwise achieved.

IV. Hyperphosphatemia

A. Causes. In the steady state, the level of urinary excretion is the major determinant of the serum phosphate. In normal people, because of efficient renal excretion, serum phosphate does not increase during periods of increased phosphate intake even with an increase in intake to 4000 mg per day. Above that level, only small rises occur, provided that phosphate intake is distributed over a 24-hour period. If the increased intake is concentrated within a 2- to 3-hour period, hyperphosphatemia will transiently result. There are three circumstances in which renal excretion is insufficient to prevent hyperphosphatemia (Table 5-4).

1. **Massive phosphate infusion.** Acute elevation of serum phosphate by massive infusion into the extracellular fluid from either exogenous or endogenous sources may exceed the ability of the kidney to excrete phosphate. Exogenous souces include oral phosphate supplementation, enemas, or laxatives. Severe hyperphosphatemia (greater than 15 mg per deciliter) has been reported in children receiving hypertonic phosphate enemas. Recent studies have shown that the use of recommended quantities of phosphate-containing laxatives in adults may acutely and transiently raise serum phosphate to 7 to 8 mg per deciliter. Endogenous causes of increased phosphate include acute rhabdo-

Table 5-4. Causes of Hyperphosphatemia

Massive phosphate infusion
Endogenous
Cytotoxic therapy
Rhabdomyolysis
Exogenous
Phosphate enemas
Laxative abuse
Decreased glomerular filtration rate
Increased tubular reabsorption
Hypoparathyroid disorders
Acromegaly
Thyrotoxicosis
EHDP
Sickle cell anemia
Tumoral calcinosis

EHDP = ethane-1-hydroxy-1, 1-diphosphonate.

myolysis secondary to a wide variety of disorders, including trauma, hyperthermia, and narcotic overdosage. In this setting, acute renal failure may also occur as a result of myoglobinuria, so that underexcretion of phosphate may be present as well. Several recent reports have shown that severe hyperphosphatemia may occur following cytotoxic therapy of a variety of leukemias and lymphomas. It has been suggested that pretreatment of these patients with a low phosphate diet and aluminum hydroxide therapy would reduce the phosphate load imposed by the acute cell breakdown with cytotoxic therapy. Unfortunately, phosphate depletion induces an adaptive increase in the renal phosphate reabsorptive capacity. This increase in reabsorption is independent of the serum phosphate and would, therefore, markedly impair the ability of the kidney to excrete an acute phosphate load. Thus, although the intracellular phosphate content may be reduced with a depleting regimen, marked hyperphosphatemia may still occur. This approach, therefore, is not recommended.

2. **Decreased glomerular filtration rate.** Reduction of glomerular filtration rate (GFR) is the second circumstance associated with inability of renal excretion to maintain a normal serum phosphate. A decrease in GFR below 25 ml/min/m^2 in either acute or chronic renal failure is associated with hyperphosphatemia if dietary intake is in the normal range (800 to 1200 mg per day). The degree of hyperphosphatemia achieved in this setting is modest, 5 to 6 mg per deciliter. More severe degrees of renal insufficiency or the combination of mild renal insufficiency and increased phosphate intake are associated with more marked hyperphosphatemia. Even in severe oligoanuric failure, a serum phosphate of greater than 10 mg per deciliter implies the presence of tissue breakdown or excessive phosphate intake.
3. **Increased tubular reabsorption.** Hyperphosphatemia can also be produced by an increase in the tubular reabsorptive capacity for phosphate. Even though the filtered load is normal, the kidney excretes less phosphate as the tubules reabsorb an increased fraction of the filtered load. Increased phosphate reabsorptive capacity occurs in a variety of clinical settings. By far the most common mechanism is a reduction in parathyroid hormone activity (see p. 70). Whether due to absence of parathyroid glands or to resistance to the renal tubular effects of PTH (pseudohypoparathyroidism), hyperphosphatemia is a classic manifestation. If phosphate intake is excessive, serum phosphate may rise additionally and exacerbate the hypocalcemia. Growth hormone and thyroid hormone directly stimulate tubular phosphate reabsorption; thus, both acromegaly and thyrotoxicosis may be associated with mild-to-moderate hyperphosphatemia. Disodium ethane-1-hydroxy-1, 1-diphosphonate (EHDP), a diphosphonate recently approved for use in the therapy of Paget's disease of bone, is a potent stimulator of renal tubular phosphate reabsorption and is often associated with moderate hyperphosphatemia. Tumoral calcinosis is a disorder, usually familial, characterized by hyperphosphatemia, normocalcemia, and deposition of large calcium phosphate masses around large joints. Recent studies have shown that this rare condition is due to a primary increase in renal tubular phosphate reabsorption.

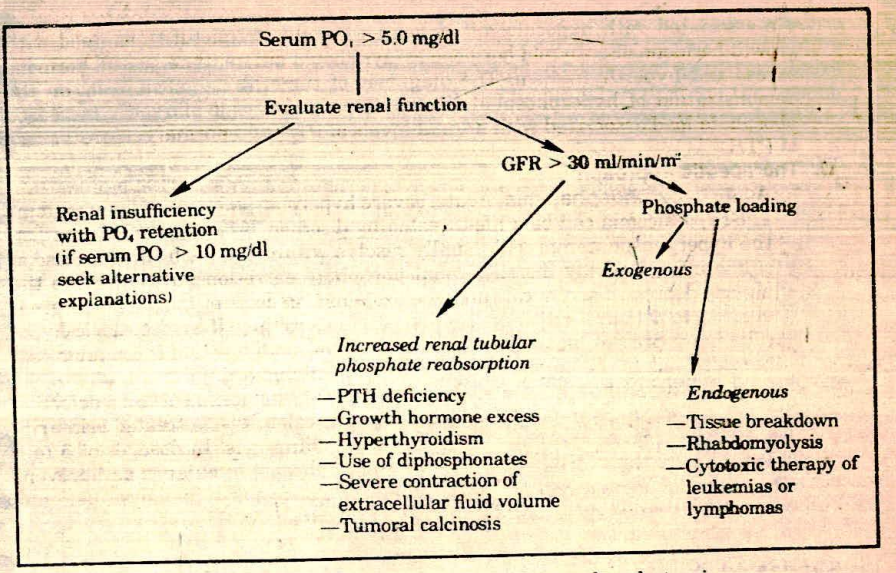

Fig. 5-4. Diagnostic evaluation of the patient with hyperphosphatemia.

B. **Signs and symptoms.** The principal effect of an elevation of serum phosphate is the formation of insoluble calcium phosphate complexes. The symptoms that are observed relate to the resultant hypocalcemia and metastatic soft tissue calcifications. An acute rise in serum phosphate may, therefore, be associated with tetany, hypotension, and acute organ dysfunction, including acute renal failure and cardiac arrest due to calcium phosphate deposition. Chronic hyperphosphatemia, as seen in renal failure, also depresses bone resorption and intestinal calcium absorption and additionally aggravates hypocalcemia. Secondary hyperparathyroidism ensues, and the resulting osteitis fibrosa and myopathy may be the presenting features. In the absence of parathyroid hormone, as in hypoparathyroidism, hypocalcemia predominates in the symptomatology of chronic hyperphosphatemia.

C. **Diagnosis.** Hyperphosphatemia is due to either defective excretion or massive overload (Fig. 5-4). The latter, whether from endogenous or exogenous sources, should be immediately obvious from the history and physical examination. Even in the absence of an appropriate history (and even in the presence of renal failure), increased serum phosphate of greater than 10 mg per deciliter implies the presence of increased phosophate load. Surreptitious laxative and enema abuse are often associated with hypocalcemia or volume contraction. Measurements of serum levels of CPK will reveal rhabdomyolysis.

Chronic mild-to-moderate hyperphosphatemia in the absence of an obvious source of phosphate implies a defect in renal excretion of phosphate, due to either renal failure or increased tubular reabsorption. In the absence of renal failure, the differential diagnosis includes the various forms of hypoparathyroidism, thyrotoxicosis, acromegaly, and tumoral calcinosis. Most forms of hypoparathyroidism

are associated with hypocalcemia, whereas the clinical picture combined with growth hormone and thyroid hormone assays should differentiate growth hormone excess and hyperthyroidism. The diagnosis of tumoral calcinosis rests on the demonstration of hyperphosphatemia in the absence of a markedly increased phosphate load associated with normal levels of PTH and normal responsiveness to PTH.

D. Therapeutic approach

1. **Acute hyperphosphatemia.** Acute, severe hyperphosphatemia with symptomatic hypocalcemia can be a life-threatening disorder. If renal function is intact, the hyperphosphatemia will usually resolve within 6 to 12 hours. The use of saline infusions may increase renal phosphate excretion but will dilute the already depressed serum calcium. Acetazolamide in doses of 15 mg per kilogram every 3 to 4 hours will increase phosphate excretion. If symptomatic hypocalcemia is present, however, and particularly if renal function is compromised, hemodialysis is the only effective therapy available.
2. **Chronic hyperphosphatemia.** Chronic hyperphosphatemia due to defective renal excretion, as in renal failure or tumoral calcinosis, is treated primarily with a low phosphate diet and aluminum binding gels. In dosages of 5 to 6 gm per day, these drugs produce a negative phosphate balance and prevent hyperphosphatemia. Hypophosphatemia should be avoided. In dialysis patients, predialysis values of 4 to 5 mg per deciliter are acceptable.

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6 The Patient With Renal Stones

Fredric L. Coe

In carrying out their regulatory functions, the kidneys must eliminate from the body not only calcium but substances such as oxalic acid and phosphorus, with which calcium forms highly insoluble salts. At the same time, the kidneys must eliminate uric acid, which is a metabolic end product in humans and is also very insoluble. The amounts of urine available to dissolve these insoluble materials are limited by adaptation to terrestrial life, which requires the kidneys to conserve water efficiently. Most of the time, presumably because of successful evolution, the kidney is able to achieve a balance between the demands for the excretion of insoluble materials and those for water conservation. Even in a normal person, however, occasional calcium oxalate or uric acid crystals are observed during a routine urinalysis, illustrating the extent to which supersaturation may occur in the course of everyday life.

Some people, because of a tendency to overexcretion of calcium or uric acid, peculiarities of diet, or fundamental metabolic derangements, tend to eliminate excessive amounts of insoluble materials in their urine. In these people crystalluria is much more frequent than in normal people, and stones tend to form on the surfaces of the renal papillae. Sometimes these stones break loose, occlude the ureteral orifice, and produce pain and hematuria. In some people the stones remain anchored to the papillary tips, producing a picture of nephrocalcinosis. Crystalluria is often intermittent and is not always present in patients who form macroscopic stones, but the two tend to go together and to arise from the same causes.

The approach to the patient with renal stone disease is essentially twofold. First, a thorough metabolic investigation should be made to determine whether there is overexcretion of divalent minerals. Next, treatment efforts are directed against disorders that are found.

In rare instances hereditary disturbances of the renal tubule lead to the elimination in the urine of cystine, an amino acid that is insoluble in urine and consequently forms crystals and stones. The finding of a cystine stone dictates the diagnosis of cystinuria, for these stones never occur in the absence of this condition.

There is also a special category of stone disease in which the urinary tract becomes infected with organisms that possess urease, an enzyme that can hydrolyze urea to ammonium. The spontaneous liberation of ammonium raises the urine pH and causes precipitation of struvite, the triple salt of magnesium, ammonium, and phosphate. Struvite stones are never produced by metabolic disorders; they are produced only by urinary infection.

Even in patients who form cystine and struvite stones, metabolic evaluation cannot be abridged because multiple stone types are often passed. In addition, patients who form stones of calcium or uric acid have a high risk of subsequent urinary infection and development of struvite stones.

I. Clinical setting. Renal stone disease has a prevalence in the American population of approximately 5 cases per 1000 people. This figure is derived principally from hospital discharges. It probably understates the true prevalence because only a fraction of renal stone attacks require hospitalization. Although calcium stones occur in men more frequently than in women—the sex ratio approaches 2 : 1 or 3 : 1—infection stones of struvite occur far more often in women than in men. Cystine stones, which are caused by an inherited renal tubular disorder, occur with equal frequency in the two sexes. Calcium stones are very uncommon in children.

Although the prevalence and attack rates vary geographically, stones are virtually ubiquitous in the Western world. In the United States, as well as in the rest of the Western Hemisphere, there are "stone belts," in which stone disease is particularly prevalent. These geographic clusterings, however, have been of less clinical and investigative interest than was initially hoped, and the reasons for them have never been elucidated. Abnormal levels of calcium or other minerals in the water supplies, although long suspected, have never been documented. Differences in trace element concentrations in foods, variations in soil chemistry, and other hypotheses also have failed to gain support. About the only clear geographic risk factor is that of climate; stone disease tends to occur more frequently in the hot and dry areas of the world. This increase affects not only calcium stones but also uric acid stones. The presumed reason is chronic dehydration, which forces the kidney to eliminate normal or, in some instances, abnormal amounts of insoluble material in lower than average volumes of urine.

II. **Signs and symptoms.** As long as the stones remain attached to the renal papillae, where they usually tend to form, they produce no symptoms except hematuria. Renal stones are one of the commonest causes of hematuria, along with urinary tract and renal neoplasia, renal cysts, and urinary tract and renal infections. Once free to move in the urinary stream, however, a stone can produce pain from acute obstruction of the renal collecting system anywhere from the ureteropelvic junction to the ureterovesical junction. The pain, which arises because of increasing pressure and consequent dilatation of the kidney and urinary collecting system, is usually known as renal colic. It tends to begin suddenly. Over a period of approximately 30 minutes it reaches a plateau of intensity and then remains constant and often of unbearable severity. In general, a pain that begins in the flank area and does not change its location reflects an obstruction anywhere along the urinary system, but a pain that begins in the flank area and then moves downward, along the radiation path of the ureter, which is essentially along the lateral and anterior abdomen, almost always indicates a stone that has moved down the ureter. Stones that lodge at the ureterovesical junction frequently present without renal colic, but rather with symptoms suggesting urinary infection (i.e., dysuria, frequency, and urgency). The reason for these symptoms is irritation of the bladder trigone. Stones at this location may also cause pain that radiates into the testicle or vulva on that side.

Frequently, stones are asymptomatic and are discovered on routine radiographic assessment for another condition. Apart from uric acid stones, renal stones are radiopaque—cystine stones because of the sulfur they contain, calcium stones because of their calcium content, and struvite stones because of their magnesium content. In general, calcium stones tend to present as small, densely radiopaque objects; cystine stones are slightly less radiopaque and have "soft" edges; struvite stones frequently form laminated, branching "staghorn" calculi.

Physical examination rarely reveals important findings except for those of urinary obstruction or infection. The obstructed kidney tends to be tender and may be enlarged enough to palpate. If urinary infection has supervened in an obstructed kidney, there may well be signs of perinephric inflammation, including muscle spasm and costovertebral angle tenderness. Tenderness along the path of the ureters is an infrequent sign even if the ureter is dilated by a distal stone. In patients who have a stone at the ureterovesical junction and who present with symptoms of lower urinary tract infection, the absence of bladder tenderness is often a striking negative finding.

III. **Types of stone disease.** Four main types of stones are encountered in clinical practice (Table 6-1); calcium stones predominate, and a majority of these are composed of or contain calcium oxalate. Whatever their composition, stones are organized masses of crystals that grow on the surfaces of the renal papillae whenever the excretory burden of poorly soluble materials is excessive for the volume of urine that is available to dissolve them. In the cases of calcium and cystine stones, the main causes are overexcretion of calcium, uric acid, or oxalate, or of cystine, respectively. Uric acid stones can be caused by overexcretion of uric acid, but an abnormally low urine pH is usually more important in pathogenesis. Struvite stones are produced only by bacteria that possess the enzyme urease and, therefore, are a result of urinary infection.

Table 6-1. Types of Renal Stones

Major Constituent	Crystal Type	Approximate Percent of All Stones
Calcium		75
	Calcium oxalate	
	Hydroxyapatite ($CaPO_4$)	
	Brushite	
Uric acid	Uric acid	5
Cystine	Cystine (amino acid)	1
Struvite—carbonate	$MgNH_4PO_4$ and $CaCO_3$	20

A. **Calcium stones.** Hypercalciuric states, hyperuricosuria, and hyperoxaluria are the main remediable causes of calcium stones.

1. **Hypercalciuria.** Hypercalciuric states that cause calcium stones include:
   a. Idiopathic hypercalciuria
   b. Primary hyperparathyroidism
   c. Renal tubular acidosis (including acetazolamide use)
   d. Sarcoidosis
   e. Cushing's syndrome
   f. Immobilization
   g. Calcium-alkali excess (calcium phosphate stones)
   h. Vitamin D excess
   i. Hyperthyroidism
   j. Paget's disease

   The most common cause is idiopathic hypercalciuria, which appears to be inherited as a mendelian dominant trait and is present in nearly one-half of patients with calcium stones. Primary hyperparathyroidism, in which hypercalciuria is due to hypercalcemia from parathyroid hormone excess, is present in about 5 percent of patients with renal stones. All other hypercalciuric states are uncommon causes of stone disease.

2. **Hyperuricosuria.** Hyperuricosuria, usually due to excessive purine intake in the form of meat, fish, and poultry, causes calcium stones frequently, in about 20 percent of patients probably by producing crystals of uric acid or its sodium salt that act as seed nuclei upon which calcium oxalate can deposit.

3. **Hyperoxaluria.** Hyperoxaluric states that cause calcium stones include:
   a. Intestinal disease (Crohn's disease, malabsorption)
   b. Ileal resection
   c. Jejuno-ileal bypass
   d. Vitamin C excess
   e. Dietary oxalate excess
   f. Primary hyperoxaluria

   Diseases of the ileum or ileal resection or bypass produces severe hyperoxaluria. Although this cause of calcium stone disease is becoming better recognized and perhaps even more common because of the increase in the number of patients with jejuno-ileal bypass during the past decade, intestinal oxaluric states are present in only a small percentage of all patients with renal stones. Frequently, mild hyperoxaluria from diet (rhubarb, tea) or excessive vitamin C intake may contribute to stone disease in patients with other disorders. Primary hyperoxaluria is very rare. In this condition stones begin in childhood, followed by a gradual rise of stone disease. Elevated urine pH can also contribute to calcium stones, because apatite or calcium phosphate (but not oxalate) crystallizes readily in alkaline urine; this is especially important in hereditary distal renal tubular acidosis.

B. Uric acid stones. Uric acid is weakly acidic, with a dissociation constant (pK_a) of 5.35. In a urine of that pH, 50 percent of the uric acid is dissociated into urate and protons. The undissociated acid is very insoluble compared to urate and forms stones, whereas urate forms stones very rarely. Therefore, low urine pH is a critical factor in producing uric acid stones, and such stones rarely form and persist in an alkaline urine. Patients with gout and members of families that are afflicted with an inherited tendency toward uric acid stones elaborate a very acid urine (Table 6-2), whose average pH is below 5.5 or even below 5.0 in extreme circumstances, for reasons that are not fully understood. Urine pH is also low in patients with an ileostomy or colostomy, whose drainage is alkaline. Loss of colon function raises urine uric acid excretion, because about one-third of the daily production of uric acid normally is degraded by colonic bacteria. Low urine volume, secondary to hot climate, intestinal disease, or habitual low fluid intake, also lowers urine pH, as protonated urine buffers are rendered more concentrated. Perhaps the only situation in which uric acid stones form despite a normal urine pH is in the Lesch-Nyhan syndrome, in which uric acid overproduction is so extreme, and hyperuricosuria is so massive, that the concentration of undissociated uric acid exceeds the solubility limit at even a normal pH.

C. Cystine stones. Cystine, an amino acid, also has a solubility that depends on pH, but its dissociation constant is so high that its solubility does not increase until urine pH rises above 7.4. In cystinuria, throughout the physiologic pH range, urine is so saturated with cystine that stone formation is frequent. The basis for cystinuria is a hereditary defect of amino acid transport by the brush border membranes of the renal proximal tubules involving cystine, arginine, ornithine, and citrulline. Intestinal transport of these amino acids is also defective, but the intestinal defect is clinically trivial. There is no cause for cystine stones except cystinuria.

D. Struvite stones. Abnormal urine pH is critical to the formation of these stones, because struvite ($MgNH_4PO_4$) contains PO_4^{3-}, which is present only at a high pH, above 8.0; another requirement is that urine [NH_4^+] be high. The kidney itself cannot produce so alkaline a urine that also contains appreciable concentrations of NH_4^+; this combination occurs only when bacteria that possess urease colonize the urinary tract and generate ammonia from urea; the urea hydrolyzes to NH_4^+ and raises the pH to above 8.0. At that pH not only does struvite crystallize spontaneously, but calcium carbonate crystals also form and intermingle with the struvite; thus these stones always contain both minerals.

IV. Evaluation of the patient

A. Clinical assessment. The main goals of clinical assessment are to characterize the seriousness of stone disease and to search for clues to causes. The history and physical examination are critical because treatment must be chronic if it is to be effective, and it must be based on a complete understanding of the patient's health status. Most of the time, however, little of direct therapeutic relevance

Table 6-2. Causes of Uric Acid Stones

Causes	Hyperuricemia	Hyperuricosuria	Low Urine pH	Low Urine Volume
Gout	yes	±	yes	no
Familial	no	no	yes	no
Climate	no	no	±	yes
Ileostomy	±	±	yes	yes
Colostomy	no	±	yes	yes
Lesch-Nyhan syndrome	yes	yes	no	no
Low fluid intake (habitual)	no	no	±	yes

± = trait occurs only some of the time.

will be found in the examining room. Most stone formers, especially those with calcium stone disease, are otherwise well, and the cause of their stones is detectable only in the laboratory. The clinical assessment of the patient with nephrolithiasis includes:

1. **Stone disease characteristics**
   a. Numbers of stones passed, removed, or visualized
   b. Current stone burden: radiograph of the kidneys, ureters, bladder
   c. Stone morbidity: hospitalization, cystoscopy, surgery, urinary infection
   d. Damage from stones: loss of kidney substance, permanent urinary drainage abnormality, azotemia
   e. Family history of stones, especially stone type
   f. Types of stones formed by the patient: crystallographic analyses
2. **Symptomatic causes of stones**
   a. Hyperparathyroidism: peptic ulcer, bone disease, pancreatitis
   b. Renal tubular acidosis: bone pain, waddling gait
   c. Sarcoidosis: hilar lymphadenopathy, hepatosplenomegaly, erythema nodosum
   d. Other: immobilization, Paget's disease, Cushing's syndrome, vitamin D excess, vitamin C excess, hyperthyroidism, excess purine intake, alkali excess, bowel disease, urinary tract infection (always obtain past culture results), episodes of dehydration, history of low fluid intake.

B. Urinalysis

1. **Hematuria.** Hematuria is common in nephrolithiasis and may reflect the presence of stones even when stones cannot be visualized radiographically. Red cell casts, however, indicate glomerular disease as the cause of the hematuria.
2. **Leukocyturia.** Leukocyturia usually reflects the presence of urinary tract or renal infection. Severe proteinuria is not produced by renal calculi per se, but it can be produced by some causes of stones. For example, tubulo-interstitial renal disease from hypercalcemia, as in primary hyperparathyroidism, or from severe hyperoxaluria can cause excessive excretion of low-molecular-weight proteins, such as β_2 microglobulin or lysozyme, and very modest albuminuria—no more than 500 mg per 24 hours. Renal calculi and more severe albuminuria may be associated with renal disease secondary to hypertension, hypercalcemia, or some underlying chronic renal disorder. Stone disease itself does not cause casts.
3. **Crystalluria.** Crystalluria (Figs. 6-1 and 6-2 [color insert]) is diagnostically important only in certain specific situations. Cystine crystals, which are flat hexagonal plates, occur only in heterozygous or homozygous cystinuria. Struvite crystals, rectangular prisms that resemble coffin lids, occur only when the urine is infected with urea-splitting bacteria. The other crystals can occur in normal urine. Calcium oxalate monohydrate forms round discs that resemble red cells and may be connected in pairs, like dumbbells. Calcium oxalate dihydrate forms in the shape of pyramids, (they look as though a pyramid is standing on a mirror). Calcium phosphate crystals, either apatite or octocalcium phosphate, usually look like nondescript fine dust, because the crystals are too small to be resolved by the light microscope. Brushite ($CaHPO_4$), however, produces flat rectangular crystals that look like thin boards or laths. Uric acid usually forms a fine dust that may be red if it adsorbs uricine, a red pigment normally present in urine. Uric acid dihydrate is uncommon in urine; it forms rhomboid crystals that are large and easily recognizable. Although the finding of calcium oxalate, calcium phosphate, or uric acid crystals should arouse suspicions about the probable cause of stones in a patient, any of these crystals can be found in the urine of normal people.

C. Metabolic evaluation (Table 6-3)

1. **Timing of outpatient workup.** Hypercalcemia, hypercalciuria, hyperoxaluria, hyperuricosuria, and abnormal urine pH are all detected by measurements made on serum and 24-hour urine collections. Three collections are recommended, despite the cost and time involved, because treatment of chronic disease usually results from a positive diagnosis. The urine collections are a mirror

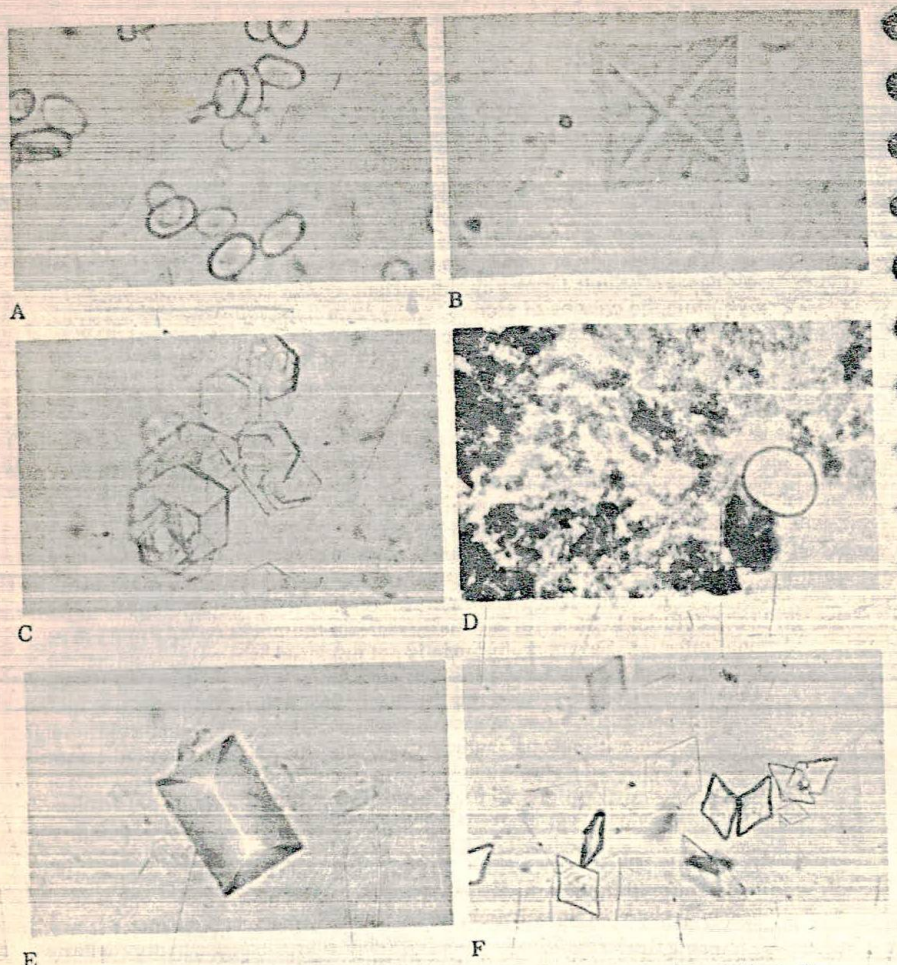

Fig. 6-1. Crystals in urine sediment. **A.** Calcium oxalate monohydrate (40×). **B.** Calcium oxalate dihydrate (40×). **C.** Cystine (40×). **D.** Amorphous calcium phosphate (40×). **E.** Struvite (40×). (Figs. A–E courtesy of Jacob Lemann, Jr., M.D.) **F.** Uric acid (40×). (Courtesy of Jerome P. Kassirer, M.D.)

of life-style and should, therefore, be collected while the patient is leading his or her life as was usual when stones were being produced. There are endless problems in obtaining useful collections of urine. New diets that have been suggested by friends and relatives or by a physician and embraced as treatment of stones must be discarded in favor of the old one. The high fluid intake that most patients begin after recovery from a stone (and gradually give up as time goes on) must also be willfully set aside for the collections. There is no sense in collecting urine soon after surgery or even hospitalization, because patients often regain their appetites only after a few months have elapsed. It is often difficult to wait, because patients are anxious for treatment to stave off a recurrence; however, stone disease is very chronic and a misleading study, done in haste, can do much harm. The very worst and most regrettable error is to

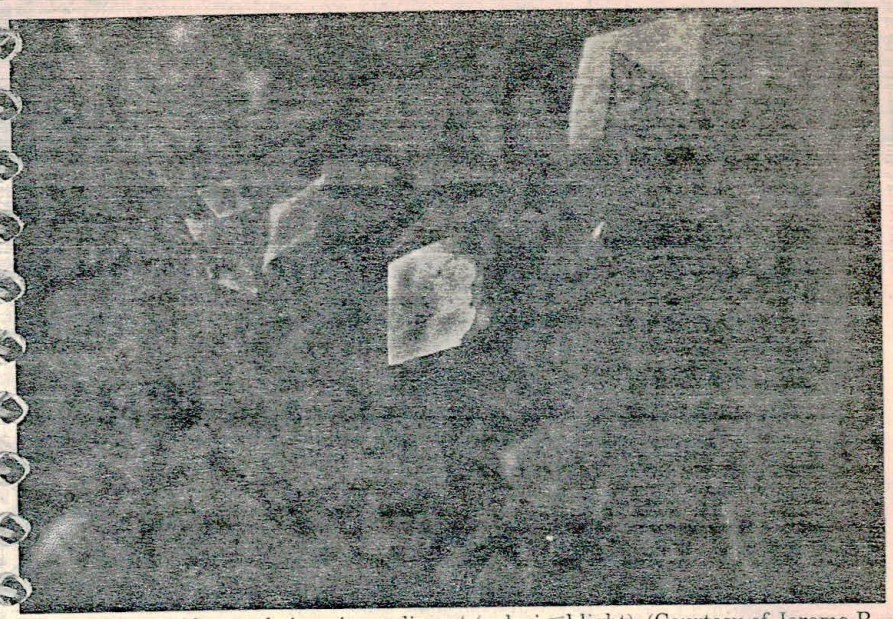

Fig. 6-2. Uric acid crystals in urine sediment (polarized light). (Courtesy of Jerome P. Kassirer, M.D.)

Table 6-3. Metabolic Assessment of the Patient With Nephrolithiasis

Test	Serum[a]	24-Hour Urine	Fresh Urine Aliquot
Calcium	3	3	
Uric acid	3	3	
Creatinine	1	3	
Oxalate	—	3	
Phosphate	1	1	
pH	—	3	
Sodium	1	1	
Potassium	1	—	
Chloride	1	—	
CO_2 content	1	—	
Cystine screening[b]	—	—	1
Urinalysis	—	—	1

[a]Sera drawn at the conclusion of each 24-hour collection; numbers represent number of separate samples suggested.
[b]Nitroprusside reaction; detects above 75 mg/L of cystine.

do the workup in the hospital, for convenience, insurance purposes, or any other reason. No one can eat, drink, and get about normally in a hospital, so urine data are as artificial and divorced from real life as possible.

2. **Collection techniques.** There is some art in the actual techniques of collecting samples. First of all, the physician must be in charge and everything done through his or her office. Four-liter plastic containers, with a molded handle, as wide a mouth as possible, and a metal or plastic screw cap that does not leak, are most suitable. There should be a label for the collection times and name of the patient. A teaspoon of thymol crystals is used as a preservative; it is worthwhile to have a brief list of written instructions for the collection. Patients find it difficult to understand that the collection is begun by voiding into the toilet, not into the container; the intuitive action is to void into the container, thus producing an erroneous overcollection. It is human nature to be chagrined when the container is still nearly empty at the end of the day and to drink extra water to fill it up. Patients should be warned that the bottle is large enough to accommodate almost anyone and that few will fill it even halfway. The office staff must also understand this. Finally, there is the "impossible" problem of collecting at least two of the urine samples during regular weekdays at work and at least one on Sunday. Every executive and professional is sure such an indignity is not intended for him or her; people who work in a factory or on a construction site think the physician must not be serious—after all, there just is not unlimited bathroom time, teachers assure the physician that the classroom is not the place for urine-collecting jugs; and so forth. However, everyone does manage to collect and, judging from the constancy of sequential urines, collect well or at least consistently.

D. **Interpretation of metabolic data.** Overexcretion is defined using upper limits of normal (Table 6-4). Criteria are given both in terms of absolute amounts and normalized for body weight and for urine creatinine excretion, which tends to parallel muscle mass. Although the 3 serum calcium concentration measurements must be interpreted using the normal for the laboratory that performed them, values above 10.3 mg per deciliter should be viewed with suspicion, especially if all three are high. It is useful to summarize metabolic data in clear diagnostic categories, such as hypercalcemia, hypercalciuria, hyperuricosuria, or hyperoxaluria, using Table 6-4 as a guide, and then go on to the finer details. The interpretation and analysis of hypercalcemic states, of which primary hyperparathyroidism is the most important when one is concerned with renal stone disease, are discussed elsewhere (see Chap. 5, sec. III).

1. **Hypercalciuria.** The differential diagnosis of hypercalciuria is presented in Table 6-5. Primary hyperparathyroidism, always a hypercalcemia state, is discussed in Chapter 5, section III. Renal tubular acidosis is detected because of hyperchloremia (serum chloride above 108 mEq/L) and low carbon dioxide content (serum carbon dioxide below 24 mM); urine pH values will all be above 5.5 in the hereditary distal tubular form of the disease, but can be lower in proximal tubular forms. Given such findings, the diagnosis of renal tubular acidosis must be confirmed with an acid loading test (see Chap. 4, sec. IV). The diagnosis of idiopathic hypercalciuria requires clinical exclusion of all other possible hypercalciuric states.

Table 6-4. Upper Limits of Normal for Excreted Materials

Material	mg/24 hr		mg/kg/24 hr	mg/gm creatinine/24 hr
	Male	Female		
Calcium	300	250	4	150
Uric acid	800	750	—	—
Oxalate	50	50	0.73	—
Cystine	—	—	—	60*

*Heterozygous cystinurics, who rarely produce cystine stones, excrete between 60 and 300 mg/gm creatinine/24 hr; homozygous cystinurics excrete above 300 mg/gm creatinine/24 hr.

Table 6-5. Differential Diagnosis of Hypercalciuria

Cause	Serum Calcium	Other Serum Values	Usual Stone Type
Idiopathic hypercalciuria*	Normal	Normal	Calcium oxalate and/or calcium phosphate
Primary hyperparathyroidism	High	Hypophosphatemia, occasionally hyperchloremic acidosis	Calcium oxalate and/or calcium phosphate
Renal tubular acidosis	Normal	Hyperchloremic acidosis	Calcium phosphate

*Sarcoidosis, Cushing's syndrome, alkali abuse, immobilization, vitamin D excess, hyperthyroidism, Paget's disease, rapidly progressive bone disease, and malignant tumors (which cause hypercalciuria though not stones) must be excluded on clinical grounds.

2. **Hyperuricosuria.** The presence of hyperuricosuria can facilitate calcium stone formation whatever other cause of stones may also be present. There is no differential diagnosis of hyperuricosuria except whether it is due to dietary intake or to endogenous overproduction. This distinction usually need not be based on testing but can be inferred from the dietary history. If purine intake from meat, fish, and poultry is very high, diet must be contributing to hyperuricosuria even if it is not the sole cause, and change of diet is a rational first step in treatment. If there is no obvious surplus of dietary purine, a change in diet is not indicated.
3. **Hyperoxaluria.** Intestinal causes are obvious from history and physical examination, because they include Crohn's disease, ileal resection, jejuno-ileal bypass, and primary states of fat malabsorption. The site of excessive oxalate absorption appears to be the colon, because ileostomy or colostomy prevent hyperoxaluria. Fat malabsorption favors excessive colonic oxalate absorption by enhancing the formation of calcium soaps of fatty acids in the bowel lumen, leaving an abnormally high fraction of dietary oxalate, which usually combines with calcium to form insoluble salts, free for absorption. In addition, some fatty acids can enhance the permeability of colonic mucosa to oxalate. Bile salt malabsorption allows excessive bile salts to reach the colon, where they may increase mucosal permeability. It is important to question patients about dietary oxalate excess (Table 6-6), as well as the use of vitamin C, which enhances oxalate production in some people. The onset of stones in childhood, followed by severe stone disease and azotemia, suggests primary hyperoxaluria.
4. **Uric acid stones.** The most important question is whether stones are pure uric acid or admixed with calcium. In the latter case, in which either mixed stones or both calcium and uric acid stones are present, the patient must be treated as though two independent stone diseases were present, because treatment directed at only one will often result in continued formation of the other. The interpretation of hyperuricemia, hyperuricosuria, low daily urine volume, and low urine pH is summarized in Table 6-2.
5. **Cystine stones.** Even more than pure uric acid stones, cystine stones are a diagnosis in themselves, because cystinuria is always present. The cystine screening test, however, readily detects heterozygous carriers of the cystinuria gene whose cystine excretional, though elevated, is not high enough to produce stones. For this reason, a positive test calls for measurement of 24-hour cystine

Table 6-6. Common High Oxalate Foods

0.1% Oxalate by Weight	0.02% Oxalate by Weight
Beets	Blackberries
Beet tops	Blueberries
Dried figs	Concord grapes
Lime peel	Red currants
Nuts	Gooseberries
Parsley	Oranges (and peel)
Rhubarb	Raspberries
Spinach	Strawberries
Swiss chard	Beans (green and wax)
Black tea	Carrots
Chocolate	Celery
Cocoa	Roasted coffee
	Endive
	Okra
	Green onions
	Green peppers
	Sweet potatoes

excretion but is not in itself a basis for diagnosis or treatment. Similarly, the finding of cystine crystals in the urine should arouse suspicion and lead to measurement of cystine excretion, but may reflect only the heterozygous carrier state.

V. **Treatment**

A. **Calcium stones.** The treatment of primary hyperparathyroidism and of renal tubular acidosis is discussed elsewhere (see Chap. 4, sec. IV, and Chap. 5, sec. III).

1. **Idiopathic hypercalciuria (Fig. 6-3)**

a. **Thiazide therapy.** The best available treatment for idiopathic hypercalciuria and recurrent stones is a thiazide diuretic agent. When used chronically, drugs of this class decrease urine calcium excretion and prevent stone recurrence. A convenient drug is trichlormethiazide, 2 mg twice daily. At this dosage, which is one-third of the full dose, potassium replacement is rarely necessary. A high salt intake lessens the hypocalciuric effectiveness of thiazide and is a common cause of treatment failure, so sodium excretion must be measured along with calcium and creatinine in follow-up, 24-hour urine collections. It is best to reassess calcium excretion after 8 weeks of initial treatment and 8 weeks after any change in thiazide dosage or salt intake. Thereafter, a yearly follow-up is desirable. A blood sample should be obtained for calcium and potassium with each 24-hour urine collection. Occasional patients develop a maculopapular or urticarial skin rash from thiazide derivatives and must then discontinue the medication.

b. **Low calcium diet.** A low calcium diet is an alternative to a thiazide diuretic for those patients who have formed only a single stone. The best way to determine if diet will work in a given patient is to place the patient on a conventional low calcium diet of about 500 mg per day, which is essentially a diet free of dairy products. If urine calcium excretion falls into the normal range, the treatment has been successful. Persistent hypercalciuria could reflect extremely efficient intestinal calcium absorption or a renal tubule leak of calcium; in either event, diet alone is not a realistic therapy.

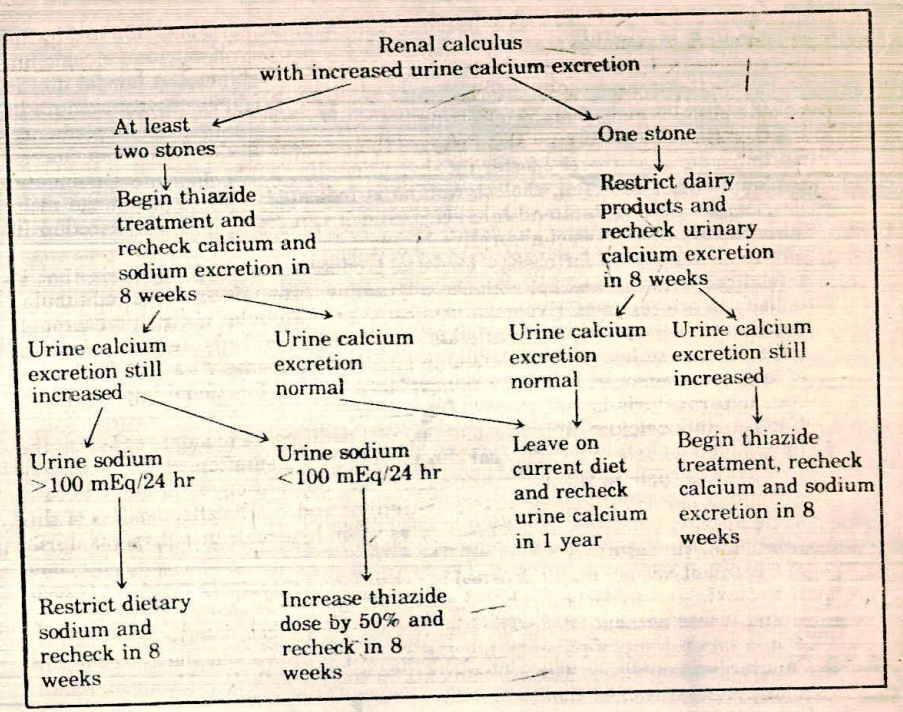

Fig. 6-3. Treatment of idiopathic hypercalciuria.

c. **Cellulose phosphate.** A more extreme restriction of intestinal calcium absorption can be accomplished with cellulose phosphate, an ion-exchange resin. Given orally, the resin binds calcium in the lumen of the bowel, preventing its absorption, and the calcium and resin are eliminated in the stool. This drug can cause chronic calcium depletion in patients with defective renal calcium conservation because it restricts calcium absorption severely. Under ideal research conditions, renal hypercalciuria can be distinguished from absorptive hypercalciuria, but the tests are complicated and open to dispute. Furthermore, cellulose phosphate is not yet available as a standard drug and is still mainly of research interest.

2. **Hyperuricosuria.** Since diet is the main problem in most patients with hyperuricosuria, a reduction of purine intake from meat, fish, and poultry is an ideal treatment. Usually it is difficult for patients to change their habits, and many fail to do so, at least right away. For this reason, with a patient who has severe recurrent stone disease, allopurinol may be instituted, 100 mg twice daily, to provide protection during a period of dietary adjustment that may last 1 to 2 years. Some of these patients are unwilling or unable to do without the drug; others eventually can be treated by diet alone. Given a patient who has formed only one stone, however, diet is a proper first treatment. Naturally, diet will not work when there is endogenous overproduction of uric acid, and hyperuricosuria will persist despite ingestion of a diet that is not excessive in purine content.

3. **Hyperoxaluria.** Dietary sources of excess oxalate should be reduced or eliminated, as should the use of vitamin C supplements, whatever the cause of hyperoxaluria. Intestinal hyperoxaluria, from ileal resection, ileal bypass, or intrinsic ileal disease, can be treated initially with oral calcium supplementation, because calcium absorption usually is subnormal and the surplus cal-

cium mainly precipitates oxalate in the bowel lumen and is eliminated in the feces. A reasonable starting dosage is 3 gm per day of calcium, as calcium carbonate, taken in two divided doses, one after each meal. A low fat diet is also helpful, because unabsorbed fatty acids form complexes with calcium in the bowel lumen, thereby offsetting the benefits of oral calcium supplements. Certain fatty acids may also increase the permeability of the colonic mucosa to oxalate and thereby foster its absorption. If calcium supplementation and low fat diet both fail, cholestyramine is indicated. This ion-exchange resin adsorbs both oxalate and bile acids, and it can reduce oxalate excretion in almost all instances of absorptive hyperoxaluria.

Intestinal bypass for obesity tends to produce severe hyperoxaluria that is difficult to reverse except with cholestyramine. Azotemia and acquired tubular defects are common. Hyperoxaluria causes intratubular obstruction through the formation of masses of calcium oxalate crystals, and interstitial deposits of calcium oxalate lead to tubulo-interstitial renal disease. As a rule, the bypass should be removed if there is any evidence of renal functional impairment or if hyperoxaluria is refractory to treatment.

4. **Idiopathic calcium lithiasis.** When no metabolic cause of stones is found, the best available treatment is oral phosphate supplementation, at a daily dosage of 2 gm of phosphorus in four divided doses. In addition, as in every form of stone disease, adequate hydration is recommended. The effectiveness of this treatment is not as well documented as when hypercalciuria, hyperoxaluria, and hyperuricosuria are reversed. The course of stone disease during phosphate treatment has not been published in detail for a large group of patients except in two instances. In both, phosphate was given in a dosage of only 1 gm daily, and it was without effect. The higher dosage has been described as effective in a large group of patients, but the clinical details about the patients have never been published. Other treatments, including methylene blue, magnesium, or pyridoxine supplementation, are untested and cannot be recommended.

B. Uric acid stones

1. **Alkali administration.** Whatever their cause, uric acid stones are first treated by raising the urine pH into the normal range through oral alkali supplementation. The pH of the 24-hour urine should be between 6.0 and 6.5; individual voidings should all have a pH of above 5.5 and below 7.0. Sodium bicarbonate tablets (10-grain tablets each contain 7.2 mEq of base) are given at a dosage of 0.5 mEq base per kilogram of body weight in four divided doses, one on arising, one at bedtime, and the other two between meals. The patient should be given pH test paper, so that the pH of individual voidings can be recorded; the dosage of alkali may then be raised or the timing of doses altered until control throughout the day is achieved.
2. **Allopurinol administration.** Hyperuricosuria above 1000 mg per 24 hours requires treatment with allopurinol; 100 mg twice daily usually is sufficient. If purine intake is very high, a reduction to, but not below, normal is also prudent. Modest hyperuricosuria, between 800 and 1000 mg per day, should be treated with allopurinol only if alkali treatment fails to control stone disease, or if alkali cannot be used properly because of heart failure or intestinal disease. Otherwise, a reduction of dietary purine intake is sufficient.

   Intestinal disease may pose special problems. Adequate urine volume can be difficult to achieve when diarrhea is severe or when a colostomy or an ileostomy is present, because intestinal fluid losses are high. Furthermore, a large fluid intake may be poorly tolerated by patients with bowel disease because the volume of diarrhea or the drainage from an ileostomy or colostomy may rise, and abdominal pain may ensue. Alkali also may be poorly tolerated, because of abdominal distention and bloating, yet urine pH tends to be very low because of intestinal bicarbonate loss. When these problems are present, allopurinol should be used even if the urine uric acid excretion rate is normal. Naturally, fluids and alkali should be used up to the limit of tolerance.
3. **Acetazolamide.** Acetazolamide (Diamox) has a useful role in special cases. If given in two to four doses of 250 mg daily it causes sustained bicarbonaturia; thus sodium bicarbonate can be given despite heart failure or hypertension. Given as 250 mg at bedtime, the drug will raise the overnight urine pH. In patients whose first morning urine is very acid despite alkali treatment, this measure can be of critical value.

C. Cystine stones. The primary treatment is sufficient water to produce a urine volume that will dissolve the amount of cystine excreted daily. Since cystine dissolves to the extent of almost 300 mg per liter in urine, the required urine volume can be calculated if cystine excretion is quantified. As a rule, at least 3 liters of urine are needed daily, and urine flow must be as high at night as during the day. Alkali treatment of limited value because cystine solubility begins to increase only above pH 7.4, and so elevated a pH can be attained only by administering very large doses of base, above 2 to 4 mEq/kg/day. D-penicillamine, which produces soluble complexes with cysteine and thereby aids greatly in preventing cystine precipitation, is an ideal agent except for an extraordinary frequency (above 40 percent) of hypersensitivity reactions, ranging from skin rash to nephrotic syndrome. Because it is a potent antigen, the drug is best reserved for patients whose stone disease cannot be controlled with high fluid intake and aklali.

D. Struvite stones

1. **Surgical considerations.** Struvite stones must be removed if they produce persistent obstruction of the ureter or ureteropelvic junction, intractable pain, serious renal infection, or clinically important bleeding. Otherwise, surgery should be delayed, because recurrence is very frequent and subsequent surgery to remove recurrent stones is technically difficult and carries a high risk of nephrectomy. Renacidin infusion into the pelvis at the time of surgery may prevent recurrence.
2. **Medical treatment.** Because the stones are infected foreign bodies, it is unrealistic to expect to eradicate urinary infections. The best course is to suppress infection by the chronic administration of methenamine mandelate (Mandelamine) or the combination of sulfamethoxazole and trimethoprim (Bactrim or Septra). Acute exacerbations of infection are best treated with a 3-week course of an antibiotic to which the organism is sensitive at that time; a new urine culture must be obtained with each such episode to assess antibiotic sensitivity. Patients with struvite stones frequently have had metabolic stone disease in the past and harbor specific causes of such stones. These should be treated to forestall the formation of new stones.

Suggested Reading

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7

The Patient With Urinary Tract Infection

L. Barth Reller

Urinary tract infections are exceeded in frequency among ambulatory patients only by respiratory and gastrointestinal tract infections. Bacterial infections of the urinary tract are the commonest cause of both community-acquired and nosocomial infections in patients admitted to hospitals in the United States. The prognosis and management of urinary tract infections, however, depend on the site of infection and any predisposing factors.

I. **Definitions.** Some definitions are necessary, since infection of the urinary tract may result from microbial invasion of any of the tissues extending from the urethral orifice to the renal cortex. The first useful distinction is betweeen **upper** (kidney) and **lower** (bladder, prostate, and urethra) **urinary tract** infections. Although the infection and resultant symptoms may be localized at one site, the presence of bacteria in the urine **(bacteriuria)** places the entire urinary system at risk of invasion by bacteria. Significant bacteriuria is defined as the presence of 100,000 or more colony-forming units (cfu) of bacteria per milliliter of urine. Although lesser colony counts can be of diagnostic importance, bacteriuria commonly implies a colony count of greater than or equal to 10^5 bacteria per milliliter of urine.

The basic clinical entities included in the category of urinary tract infections are the following. **Pyelonephritis** is nonspecific inflammation of the renal parenchyma. **Acute bacterial pyelonephritis** is a clinical syndrome characterized by chills and fever, flank pain, and constitutional symptoms caused by bacterial invasion of the kidney. **Chronic bacterial pyelonephritis** is long-standing renal infection with healed residua or smoldering foci and persistent bacteriuria; symptoms often are absent. Infections confined to the bladder **(cystitis)**, the urethra **(urethritis)**, and the prostate **(prostatitis)** commonly cause dysuria, frequency, and urgency. Recurrence of urinary tract infection is the result of either relapse or reinfection. It is clinically important to make this distinction. **Relapse** is the recurrence of bacteriuria, with or without symptoms, with the same infecting microorganism, which has persisted despite treatment. In contrast, **reinfection** is recurrence of infection with a different, usually drug-susceptible, microorganism. Relapse occurs more commonly after treatment of bacterial pyelonephritis or prostatitis than after treatment of cystitis. Most episodes of cystitis and urethritis are due to reinfection. **Asymptomatic bacteriuria** is an important clue to the presence of infection somewhere in the urinary tract; however, the importance of the infection and the need for treatment depend on the age, sex, and underlying condition of the patient.

II. **Clinical setting.** To foster both prompt recognition and possible prevention, and understanding of the epidemiology of urinary tract infections (who gets them and why) is particularly important for primary care physicians. In Figure 7-1 are shown the major risk periods during life for symptomatic urinary tract infections and the increasing prevalence of asymptomatic bacteriuria that accompanies aging.

A. **Asymptomatic bacteriuria.** In the absence of instrumentation, asymptomatic bacteriuria in men is rare until after the age of 60 years. In noncatheterized, institutionalized elderly men the prevalence of bacteriuria exceeds 20 percent. The cumulative prevalence of asymptomatic bacteriuria in women increases about 1 percent per decade throughout life. All pregnant women should be examined for bacteriuria, since proper treatment lowers the subsequent incidence of acute pyelonephritis in the third trimester from about 30 percent to 3 percent. In the

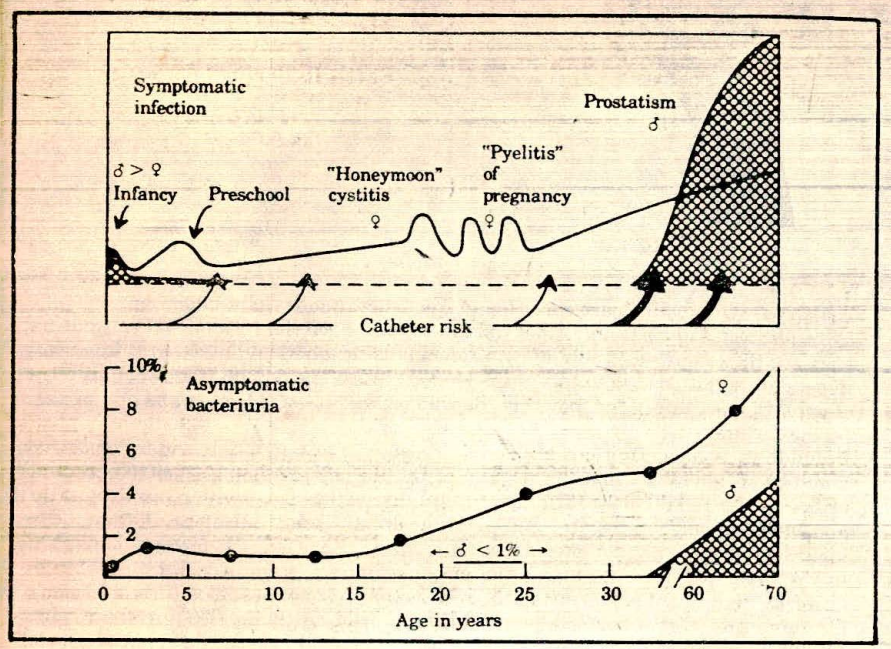

Fig. 7-1. Frequency distribution of symptomatic urinary tract infections and prevalence of asymptomatic bacteriuria by age and sex. (Modified from the original concept of Jawetz. From C. M. Kunin. *Detection, Prevention and Management of Urinary Tract Infections* [3rd ed.]. Philadelphia: Lea & Febiger, 1979.)

absence of any symptoms, a systematic search for covert bacteriuria in other population groups has not proved to be worth the cost. Why more women acquire bacteriuria with increasing age is not known. Prostatic hypertrophy and an increased likelihood of instrumentation is thought to account for the bacteriuria of older men. Differences between men and women in the rates of bacteriuria have been attributed to the shorter female urethra and its proximity to the vaginal and rectal mucosae and their abundant microbial flora.

B. Symptomatic urinary tract infections. Symptomatic urinary tract infections occur in all age groups. Among newborns and infants, boys are affected more often than girls. When the urinary tract is the source of neonatal sepsis, serious underlying congenital anomalies are frequently present. During childhood persistent bacteriuria, with or without repeated symptomatic episodes, occurs in a small group (less than 2 percent) of school girls. Such girls, and also school boys with bacteriuria, should have a urologic evaluation to detect correctable structural abnormalities when urinary tract infections are documented.

Sexually active women have a markedly increased risk for episodes of cystitis. In the absence of prostatitis, bacteriuria and symptomatic urinary tract infections are unusual in men. At any age, however, both sexes may develop symptomatic infections in the presence of the following risk factors:

1. Obstruction to urine flow
   - a. Congenital anomalies
   - b. Renal calculi
   - c. Ureteral occlusion (partial or total)
2. Vesicoureteral reflux
3. Residual urine in bladder
   - a. Neurogenic bladder
   - b. Urethral stricture
   - c. Prostatic hypertrophy

4. Instrumentation of urinary tract
   - a. Indwelling urinary catheter
   - b. Catheterization
   - c. Urethral dilatation
   - d. Cystoscopy

Most often bacteria ascend the urethra to initiate infection in the urinary tract. Bacteria may also reach the renal parenchyma by the hematogenous or lymphatic route.

III. Clinical features

A. Acute urethral syndrome. The cardinal symptoms of frequency and dysuria occur in over 90 percent of ambulatory patients with acute urinary tract infections. One-third to one-half of all patients with frequency and dysuria, however, do not have significant bacteriuria. These patients have the acute urethral syndrome, which can mimic both bladder and renal infections. Vaginitis, urethritis, herpes infections, and prostatitis are common causes of the acute urethral syndrome. Certain additional signs and symptoms help to differentiate these clinical entities from urinary tract infections, which can be diagnosed with certainty only by quantitative cultures of urine.

1. **Vaginitis.** About 20 percent of women in the United States have an episode of dysuria each year, and one-half of these seek medical care. The presence of vaginal discharge and irritation makes vaginitis the likely cause of dysuria, unless a concomitant urinary tract infection can be confirmed by culture. *Candida albicans*, the commonest specific cause of vaginitis, can be demonstrated readily by culture or by finding yeast cells in a Gram-stained smear of vaginal secretions or in a saline preparation with potassium hydroxide added. Trichomoniasis can be documented with a saline preparation that shows the motile protozoa of *Trichomonas vaginalis*. Nonspecific vaginitis most often is associated with *Gardnerella vaginalis*. A clue to the diagnosis is the presence of many small gram-negative bacilli that adhere to vaginal epithelial cells.
2. **Urethritis.** Acute frequency and dysuria for fewer than 3 days favor a diagnosis of urethritis or urinary tract infection rather than vaginitis. *Chlamydia trachomatis* is now recognized as a common cause of the acute urethral syndrome in women as well as nonspecific urethritis (NSU) in men. Unavailability of practical methods for laboratory confirmation of chlamydial urethritis has led to empiric therapy with tetracycline. *Neisseria gonorrhoeae* is also a widespread cause of urethritis and dysuria. The diagnosis and treatment of gonorrhea are now well standardized. Low-colony-count (100–1000 cfu) infections with coliforms are now a recognized cause of urethritis in symptomatic young women with pyuria.
3. **Herpes infections.** *Herpes virus hominus*, usually type 2, is another sexually transmitted agent that can cause severe dysuria through ulcerations in close proximity to the urethral orifice. The diagnosis of herpes progenitalis can be confirmed by finding giant multinucleated transformed cells in epidermal scrapings stained with Wright's stain (Tzanck smear) or by isolating the virus in tissue culture.
4. **Prostatitis.** Prostatitis is a common affliction of men that more frequently causes dysuria and frequency in middle-aged and younger men than urinary tract infections do. The major categories of prostatitis are acute and chronic bacterial and nonbacterial. Acute bacterial prostatitis is characterized by the sudden onset of chills and fever, urinary frequency and urgency, dysuria, perineal and low back pain, and constitutional symptoms. Rectal examination usually discloses an exquisitely tender, hot, and swollen prostate gland. Enteric gram-negative bacilli, staphylococci, and enterococci are the usual pathogens cultured from prostatic secretions or urine or both. A hallmark of chronic prostatitis is relapsing urinary tract infections. Frequency, dysuria, nocturia, and low back and perineal pain are the usual symptoms. Nonbacterial prostatitis is the most common form of chronic prostatitis. Of unknown cause, it mimics chronic bacterial prostatitis clinically; however, bacteriologic cultures of urine and prostatic secretions are sterile.

B. Urinary tract infections. Fortunately, despite the mimicking syndromes, infections of the urinary tract can be established objectively and economically with quantitative cultures of urine obtained from patients with characteristic, albeit nonspecific, signs and symptoms. Acute uncomplicated urinary tract infections occur mainly in women of childbearing age. The presenting features are only suggestive of the site of infection. Although patients may present with classic symptoms of cystitis (dysuria, frequency, and suprapubic discomfort) or acute bacterial pyelonephritis (flank pain and tenderness, chills and fever, and nausea and vomiting), accurate localization requires laboratory studies (see sec. IV). Patients with acute infection of the upper urinary tract commonly have lower tract symptoms; however, the reverse is much less common.

Flank pains, chills and fever, and nausea and vomiting herald the onset or flare-up of kidney infections in patients with the risk factors outlined above (see sec. II.B). Moreover, those patients with obstruction to urine flow, vesicoureteral reflux, large residual urines in the bladder, or instrumentation of the urinary tract are prone to bacteremia as a complication of their symptomatic bacteriuria. The urinary tract is the most common source of gram-negative bacteremia in hospitals in the United States. Classic hallmarks of bacterial sepsis are shaking chills and fever, often accompanied by circulatory collapse. Confusion is an early manifestation of septic shock. Initially there may be hyperventilation and associated respiratory alkalosis, but metabolic acidosis often ensues. Decreased arterial blood pressure, venous pooling, renal ischemia, and diminished urinary output additionally complicate the clinical picture. Prompt diagnosis and therapy may be lifesaving.

IV. Laboratory diagnosis

A. Urine specimens for culture

1. **Indications.** The diagnosis of urinary tract infection, from simple cystitis to complicated pyelonephritis with sepsis, can be established with certainty only by quantitative cultures of urine. The major indications for urine cultures are:
   a. Patients with symptoms or signs of urinary infections
   b. Follow-up of recently treated urinary infection
   c. Removal of indwelling urinary catheter
   d. Screening for asymptomatic bacteriuria during pregnancy
   e. Patients with obstructive uropathy and stasis, before instrumentation
2. **Methods.** Urine specimens must be cultured promptly, within 2 hours, or be preserved by refrigeration or a suitable chemical additive (e.g., boric acid–sodium formate preservative). Acceptable methods of collection are:
   a. Midstream urine voided into a sterile container after careful washing (water or saline) of external genitalia (any soap must be rinsed away)
   b. Urine obtained by single catheterization or suprapubic needle aspiration of bladder
   c. Sterile needle aspiration of urine from the tube of a closed catheter drainage system (do not disconnect tubing to get specimen)

Not acceptable because of constant contamination and the impossibility of quantitative counts are tips from indwelling urinary catheters and randomly obtained urine without adequate preparation of the patient. The clean-voided, midstream technique of collection is preferred whenever possible to avoid the risk of introducing infection at the time of catheterization, a hazard that is greater in elderly patients confined to bed and in men with condom catheters. Occasionally, suprapubic aspiration of the bladder is necessary to verify infection. This technique has been most helpful in obtaining specimens from possibly septic infants and from adults in whom repeated clean-voided specimens have yielded equivocal colony counts on culture.

B. Microbial pathogens. The usual microbial pathogens isolated from patients with urinary tract infections are listed in Table 7-1. Results of cultures are highly dependent, however, on the clinical setting in which bacteriuria occurs. For example, *Escherichia coli* is found in the urine of 80 to 90 percent of patients with acute cystitis or asymptomatic bacteriuria and no underlying anatomic abnormalities of the urinary tract. Many patients with staghorn calculi of the kidneys

Table 7-1. Microbial Pathogens of Kidney and Bladder

Microorganism	Percentage of Urine Cultures (with $\geq 10^5$ cfu/ml)
Escherichia coli	50–90%
Klebsiella or *Enterobacter*	10–40
Proteus, Morganella, or *Providencia*	5–10
Pseudomonas aeruginosa	2–10
Staphylococcus epidermidis (saprophytidus)	2–10
Enterococci	2–10
Candida albicans	1–2
Staphylococcus aureus	1–2

cfu = colony-forming units.

harbor urea-splitting *Proteus* organisms in their urine. *Klebsiella* and *Enterobacter* infections are commonly acquired in the hospital. *Pseudomonas aeruginosa* and *Candida albicans* are rarely encountered except in patients with indwelling catheters or relapsing infections after multiple courses of antibiotic therapy. The presence of *Staphylococcus aureus* in the urine most often is a clue to concomitant staphylococcal bacteremia, unless there is an underlying risk factor. Although the likely microorganism and usual susceptibility patterns are sufficient to guide initial empiric therapy of uncomplicated cystitis or acute bacterial pyelonephritis, precise therapy requires isolation of the causative bacterium and standardized antimicrobial susceptibility testing by the disk diffusion or the broth or agar dilution method.

C. Interpretation of urine cultures. Because quantitation of bacteriuria is so important clinically, methods for culture of urine must enable the number of colony-forming units of a potential pathogen per milliliter of urine to be assessed. The standard procedure involves use of calibrated bacteriologic loops that deliver a known volume of urine to the surface of agar plates. Proper plating techniques achieve isolated colonies that can be enumerated accurately. A satisfactory alternative for the diagnosis of uncomplicated urinary tract infections is the dip-slide method, which is particularly well suited for quantitative urine cultures in smaller clinics. Rapid methods based on filtration and colorimetry, bioluminescence, growth kinetics, or biochemical reactions are being used more widely to screen urine specimens for the presence of bacteria. Their sensitivities are in the range of 10^4 to 10^5 cfu per milliliter. The simplest is the paper strip test for detection of leukocyte esterase and nitrite in first-morning urine specimens. These methods are not a substitute for standard cultures in symptomatic patients.

1. **Colony counts.** A basic guide to the interpretation of quantitative cultures of urine is shown in Table 7-2. Colony counts greater than 10^5 cfu per milliliter in properly collected and transported specimens usually indicate infection (Fig. 7-2). Colony counts of 10^3 or fewer cfu per milliliter from untreated patients are uncommon with true urinary tract infections, except in symptomatic young women with pyuria and urethritis. Intermediate counts, especially with mixed flora, usually imply poor collection or delayed transport and culture. Brisk diuresis may reduce transiently an otherwise high colony count.
2. **Suprapubic needle aspiration.** Any growth from urine obtained by suprapubic needle aspiration may be important. Use of a 0.01-ml quantitative loop for culturing aspirated urine permits detection of as few as 100 cfu per milliliter. Two or more colonies (equal to or less than 200 cfu/ml) of the same microorganism ensures the purity of growth from such specimens and permits standardized antimicrobial susceptibility testing. Similar criteria should be used for patients who are receiving antimicrobials at the time of culture. Except

Table 7-2. Interpretation of Urine Cultures

Quantitation (cfu/ml urine)	Probability of True Infection: Clean-Voided Specimen (%)	Probability of True Infection: Catheterized Specimen (%)
<10,000	2	2
10,000 to 100,000	5	50
>100,000	80	95

cfu = colony-forming units.
Source: L. B. Reller, S. A. Sahn, and R. W. Schrier (Eds.), *Clinical Internal Medicine*. Boston: Little, Brown, 1979.

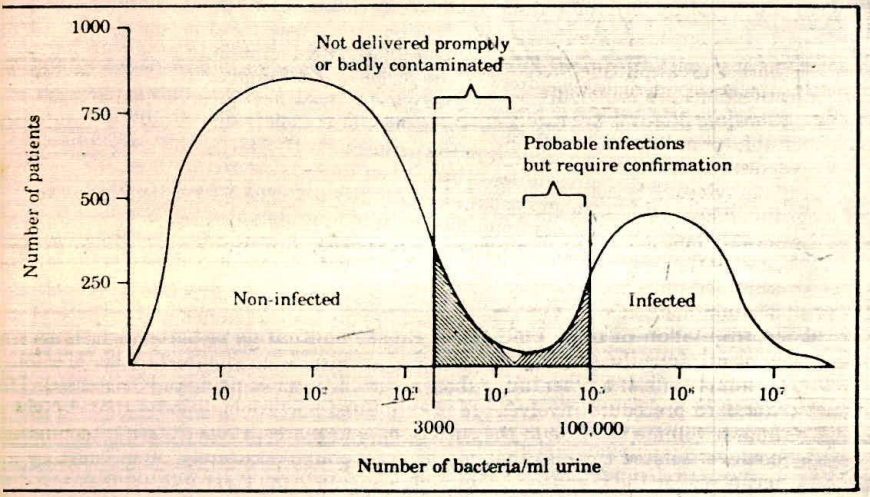

Fig. 7-2. Results of quantitative bacterial counts from cultures of urine specimens. From W. Brumfitt and A. Percival. Pathogenesis and laboratory diagnosis of non-tuberculous urinary tract infection: A review. *J. Clin. Pathol.* 17:482, 1964.)

in unusual circumstances, the isolation of diphtheroids, alpha-hemolytic streptococci, and lactobacilli indicates contamination of the urine specimen with vaginal or periurethral flora.

3. **Prostatic secretions.** In men the distinction between a urinary source and prostatic focus of infection must be made. Figure 7-3 diagrams the procedure for obtaining voided urine and expressed prostatic secretions in partitioned segments that enable proper interpretation. VB_1 is the first 10 ml of voided urine, and VB_2 is the midstream specimen of urine obtained before prostatic massage. Subsequently, the expressed prostatic secretions (EPS) are collected before the final voided urine specimen (VB_3). When the bacterial colony counts in the urethral culture (VB_1) exceed by tenfold or more those of the midstream (VB_2) and prostatic cultures (EPS and VB_3), the urethra is the source of the infection. The diagnosis is bacterial prostatitis if the quantitative counts of the prostatic specimens (EPS and VB_3) exceed those of the urethral (VB_1) and midstream (VB_2) samples. A urinary tract infection with a prostatic origin,

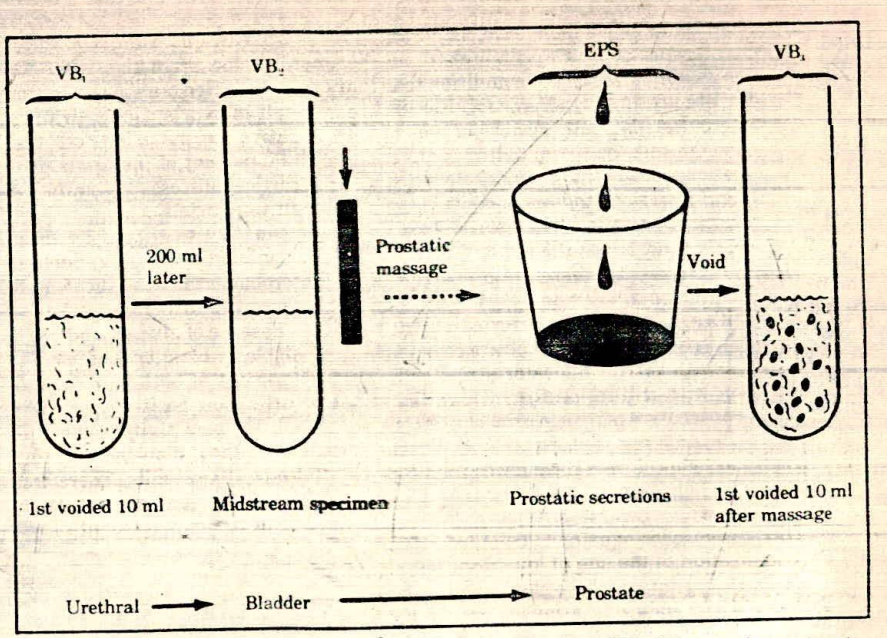

Fig. 7-3. Localization of infection with segmented cultures of the lower urinary tract in men. (From E. M. Meares and T. A. Stamey. Bacteriologic localization patterns in bacterial prostatitis and urethritis. *Invest. Urol.* 5:492, 1968. Copyright © 1968, The Williams & Wilkins Co., Baltimore.)

or vice versa, is indicated by colony counts of 10^5 or more cfu per milliliter of the same microorganism in all four specimens.

D. **Microscopic examination of urine.** Procedures for the microscopic examination of urine are not yet standardized; nonetheless, visualization of bacteria, leukocytes, and epithelial cells in urine can provide some useful information. The advantages of microscopic analysis are immediate availability and low cost. The disadvantages, depending on the method, are lack of sensitivity or specificity or both. Only properly collected and processed specimens for quantitative urine cultures can provide a precise diagnosis.

The microscopic examination can be done on either unspun urine or the centrifuged sediment. A critical comparison of these two techniques is not available. The presence of squamous epithelial cells and mixed bacterial flora indicates contamination and the need for a repeat specimen.

1. **Unspun urine.** When fresh, unspun urine from patients with significant ($>10^5$ cfu/ml) bacteriuria is examined microscopically (×1000), 90 percent of specimens show one or more bacteria and 75 percent of specimens show one or more white blood cells (WBCs) per oil-immersion field.
2. **Centrifuged sediment.** When 10 ml of urine is centrifuged in a standard 15-ml conical tube for 5 minutes at 2500 revolutions per minute in a clinical centrifuge, three or four drops of the sediment are examined under a coverslip at high power (×400) in diminished light. Patients with significant bacteriuria almost always show bacilli in the urinary sediment, whereas only about 10 percent of patients with less than 10^5 cfu per milliliter show bacteria. About 60 to 85 percent of patients with significant bacteriuria have 10 or more WBCs per high-powered field (HPF) in the sediment of midstream-voided urine; however, about 25 percent of patients with negative urine cultures also have pyuria (10 or more WBCs per HPF). Since only about 40 percent of patients with

pyuria have 10^5 or more bacteria per milliliter of urine by quantitative culture, the presence of pyuria in a midstream specimen has low predictive value for significant bacteriuria. In addition to urinary tract infection, any of the causes of acute urethral syndrome (see sec. **III.A**) can result in pyuria. Genitourinary tuberculosis is another cause of pyuria with negative routine urine cultures, although mycobacterial cultures are positive in 90 percent of instances. Analgesic nephropathy, perinephric abscess, renal cortical abscess, disseminated fungal infection, and appendicitis may also result in pyuria.

E. Biochemical tests for bacteriuria. Two metabolic capabilities shared by most bacterial pathogens of the urinary tract are utilization of glucose and reduction of nitrate to nitrite; these are properties of all Enterobacteriaceae. Since small amounts of the glucose and nitrate are normally present in urine, the presence of significant numbers of bacteria in urine results in absence of glucose and presence of nitrite. Dipstick devices are commercially available for both types of testing. Studies with nitrite indicator strips show that 85 percent of both women and children with culture-confirmed significant bacteriuria show positive results if three consecutive morning urine specimens are tested. The sensitivity of the glucose utilization test is about 90 to 95 percent in patients without diabetes mellitus. Both biochemical tests have fewer than 5 percent false-positive results. Therefore, these biochemical tests can be used by patients or parents after proper instruction to determine when quantitative cultures are needed in the management of recurrent episodes of urinary tract infection.

F. Localization of the site of infection. The site of infection in the urinary tract has great therapeutic and prognostic importance. Upper urinary tract infection (pyelonephritis) indicates a much greater likelihood of underlying uropathy (e.g., congenital anomalies, renal stones, ureteral occlusion, vesicoureteral reflux, neurogenic bladder, or prostatic hypertrophy) or previous instrumentation (see sec. **II.B.4**). Relapses with the same, often multiple-antibiotic-resistant bacteria are common with pyelonephritis or chronic bacterial prostatitis. Treatment is long (10 to 14 days minimum) and may be arduous. On the other hand, cystitis rarely is complicated and treatment can be short (single-dose) and usually is easy.

Unfortunately there is no ready way to distinguish between upper and lower urinary tract infections by simple laboratory tests. The difficulty in making this distinction reliably on clinical grounds alone has been discussed (see sec. **III.B**). Older, indirect methods (e.g., serum antibodies, urine concentration test, and urinary beta-glucuronidase activity) are neither sensitive nor specific. The newer **antibody-coated bacteria test** has been useful in research studies. It has not become established in routine practice, however, because of lack of standardized methods, expense, and difficulties in interpretation in children, catheterized patients, and men with prostatitis. Direct methods for localization (e.g., ureteral catheterization, renal biopsy, and the bladder washout technique) are hazardous or expensive or both. Fortunately, eradication of bacteriuria with single-dose therapy in symptomatic patients with uncomplicated disease is a practical method for presumptive localization of infection to the bladder or urethra.

G. Radiography and other diagnostic procedures. The principal role of radiographic and urologic studies in patients with urinary tract infections is to detect vesicoureteral reflux, renal calculi, and potentially correctable lesions that obstruct urine flow and cause stasis. Uncomplicated reinfections (cystitis and urethritis) in females that respond to single-dose antimicrobial therapy are not an indication for radiographic and endoscopic investigation of the urinary tract. Infants, boys, and men with first episodes and girls and women with relapsing urinary tract infections should have an intravenous pyelogram (IVP) with postvoiding radiographs. For a detailed evaluation of the ureterovesical junction, bladder, and urethra, a voiding cystourethrogram and measurement of the residual urine after voiding may be necessary. If vesicoureteral reflux is present after acute infection has been treated, a urologist should be consulted. Cystoscopy may be warranted. Renal calculi can usually be detected on a plain radiograph of the abdomen. Intravenous pyelography confirms the presence and location of calculi, detects radiolucent stones (less than 10 percent of renal calculi), and discloses the degree of obstruction and dilatation.

Ordinarily, radiographic studies should not be done during acute infections. Gram-negative bacilli have the ability to impede ureteral peristalsis, and transient abnormalities of the IVP are common with acute pyelonephritis. These include hydroureter, vesicoureteral reflux, diminished pyelogram, loss of renal outline, and renal enlargement. Acute pyelonephritis with an obstructed ureter is a surgical emergency. A perinephric abscess also requires surgical drainage. These complications, however, are best detected initially by ultrasound and by computed tomography, respectively. To avoid radiocontrast-induced acute renal failure, excretory urography and other radiocontrast studies should be avoided whenever possible in patients, especially elderly ones, with a serum creatinine above 1.5 mg per deciliter, diabetes mellitus, or dehydration.

V. Treatment of urinary tract infection

A. Principles underlying therapy and follow-up. The basic principles for effective management of urinary tract infections are outlined below.

1. Asymptomatic patients should have colony counts greater than or equal to 10^5 per milliliter on at least two occasions before treatment is considered.
2. Unless symptoms are present, no attempt should be made to eradicate bacteriuria until catheters, stones, or obstructions are removed.
3. Selected patients with chronic bacteriuria may benefit from suppressive therapy.
4. A patient who develops bacteriuria as a result of catheterization should have treatment to re-establish a sterile urine.
5. Antimicrobials used for treatment should be the safest and least expensive agents to which the causative microorganisms are susceptible.
6. Efficacy of treatment should be evaluated by urine culture 1 week after completion of therapy.

The success and ease of treatment depends on absence or correction of any obstruction to urine flow and on removal of foreign bodies (stones and catheters) whenever possible. In the natural history of most uncomplicated urinary tract infections, the acute symptoms usually resolve over several days to a week, regardless of therapy. Therefore, it is important to obtain follow-up urine cultures 1 to 2 weeks after completion of antimicrobial therapy to insure eradication of the infection. If symptoms are not resolving within 48 hours, urine cultures should be obtained to evaluate the efficacy of the prescribed treatment. It should be noted, however, that antimicrobial therapy based on results of standardized susceptibility testing rarely fails. Failure is usually due to (a) undrained abscess, foreign body (intravenous or urinary catheter), or obstruction to drainage; (b) drug fever; or (c) the wrong diagnosis. The most useful oral antimicrobials for treatment of bacteriuria and the approximate costs of therapy are listed in Table 7-3.

B. Treatment of asymptomatic bacteriuria. Asymptomatic bacteriuria should be sought routinely and treated in all pregnant women. Short-acting sulfonamides or ampicillin for 10 days usually suffices, since almost all of these infections are caused by sensitive *Escherichia coli*. This approach can prevent about 80 to 90 percent of cases of antepartum acute pyelonephritis. Girls with recurrent bacteriuria, due to either relapse or reinfection, should be treated regardless of symptoms as well as evaluated urologically. Asymptomatic bacteriuria in men and nonpregnant women, a common condition in the elderly, does not appear to cause renal damage in the absence of obstructive uropathy or vesicoureteral reflux. Therefore, repeated attempts to clear the bacteriuria with antimicrobials seem unwarranted; they may only select for more resistant microorganisms and create a need for more toxic and costly antibiotics should the patient subsequently develop symptoms. Instrumentation of the genitourinary tract should be avoided in patients with asymptomatic bacteriuria or, if necessary, done under the cover of prophylactic antimicrobial therapy.

Table 7-3. Most useful antimicrobials for treatment of urinary tract infections

	Infections	
Antimicrobial	Adult Oral Dosage	Approximate Cost (10-day course)*
Sulfisoxazole	0.5–1 gm every 6 hours	$ 3–7
Trimethoprim	100 mg every 12 hours	$ 7–8
Trimethoprim-sulfamethoxazole	2 tablets (80 mg/400 mg each) every 12 hours	$ 6–14
Ampicillin	500 mg every 6 hours	$ 8–19
Amoxicillin	250 mg every 8 hours	$ 7–11
Nitrofurantoin	50–100 mg every 6 hours	$ 2–14
Tetracycline	250–500 mg every 6 hours	$ 4–14
Cephalexin or cephradine	250–500 mg every 6 hours	$25–55
Carbenicillin	382–764 mg every 6 hours	$29–58

*The cost of antimicrobials varies greatly between generic and trade-name products as well as from pharmacy to pharmacy. The approximate costs noted were derived from *The Medical Letter on Drugs and Therapeutics: Handbook of Antimicrobial Therapy* (rev. ed.), 1984, pp. 63–64.

C. Treatment of cystitis—single-dose therapy. Acute cystitis and low-colony-count coliform urethritis are almost exclusively diseases of females, mostly sexually active women between the ages of 15 and 45 years. Although reinfection is common, complications are rare. There is now appreciable evidence that infections truly confined to the bladder or urethra respond as well to single-dose therapy as to conventional therapy for 10 days. Indeed, response to single-dose therapy *implies* a lower urinary tract infection. All of the following oral regimens for adult, nonpregnant women have been shown to give over 90 percent success: amoxicillin, 3 gm; sulfisoxazole, 2 gm; or trimethroprim-sulfamethoxazole, four tablets (80 mg of trimethoprim and 400 mg of sulfamethoxazole per tablet). This is an important breakthrough in the management of uncomplicated cystitis and coliform urethritis, because all patients were treated formerly with the standard 10 to 14 days of therapy. A logical approach would be to treat all patients with acute lower urinary tract symptoms with single-dose therapy and to repeat the urine culture in 48 to 72 hours. Patients with persistent bacteriuria would then get an additional 10 to 14 days of therapy. All patients should get a subsequent follow-up urine culture 1 to 2 weeks after cessation of treatment to document successful treatment. Since 80 to 90 percent of episodes of acute cystitis are caused by sensitive strains of *E. coli*, any of the less expensive antimicrobials listed in Table 7-3 should prove effective, unless susceptibility testing discloses a resistant microorganism. Symptomatic pyuria without bacteriuria in an otherwise healthy young person suggests chlamydial urethritis.

D. Management of recurrent cystitis (reinfections). Some women, especially those whose periurethral and vaginal epithelial cells support attachment of coliform bacteria more avidly, suffer from recurrent episodes of cystitis in the absence of recognized structural abnormalities of the urinary tract. In these women a single dose of an antimicrobial after sexual intercourse or nightly at bedtime has been shown to reduce significantly the frequency of episodes of cystitis from an average of 3 per patient-year to 0.1 per patient-year. Effective single-dose regimens include nitrofurantoin, 50 or 100 mg; penicillin G potassium, 250 mg; trimethoprim-sulfamethoxazole, 40 and 200 mg; and cephalexin, 250 mg. Although antimicrobial prophylaxis is effective and usually safely tolerated for months to years, single-dose therapy for acute cystitis makes prophylaxis more expensive and possibly more hazardous for most patients because of alterations in fecal and vaginal bacterial flora. Lastly, a behavioral regimen that stresses regular, complete emptying of the bladder has been shown to be effective in preventing reinfection and recurrent cystitis.

E. Treatment of acute bacterial pyelonephritis. The occurrence of flank pain, chills and fever, and nausea and vomiting with or without dysuria suggests acute bacterial pyelonephritis. In this clinical setting, blood cultures as well as quantitative cultures of urine should be obtained. Whether or not ambulatory patients should be admitted to the hospital for treatment depends in part on a subjective assessment of toxicity, likely compliance with therapy, and the home situation. When the assessment is doubtful, the patient should be treated in the hospital, at least until there has been a clear response to therapy. This policy also applies to patients with known underlying uropathies, since complications are more common in these patients.

1. **Outpatient therapy.** Ampicillin, amoxicillin, and trimethoprim-sulfamethoxazole are the drugs of choice for initial therapy of pyelonephritis in outpatients. After culture results and susceptibility tests are available, a full 10- to 14-day course of antimicrobial therapy may be completed with the least expensive drug to which the patient's microorganism is susceptible.
2. **Inpatient therapy.** Patients who require admission to the hospital should be treated initially with parenteral (intramuscular or intravenous) gentamicin or tobramycin (1.5 to 2 mg/kg every 8 hours, with appropriate alteration of the dose interval if the serum creatinine exceeds 1 mg/dl) if the urine shows gram-negative bacilli on microscopic examination. If gram-positive cocci are seen in the urine, intravenous ampicillin (1 gm every 4 hours) should be given in addition to the aminoglycoside to cover the possibility of enterococcal infection while awaiting the results of urine and blood cultures and antimicrobial susceptibility tests. If no complications ensue and the patient becomes afebrile, the remaining days of a 10- to 14-day course can be completed with oral therapy. The urinary tract is a common source of sepsis and bacteremic shock in patients with underlying uropathies. As with other patients in septic shock, intravenous fluids must be given to maintain adequate arterial perfusion, which usually results in a urinary output in excess of 50 ml per hour. Mortality may be reduced by massive pharmacologic doses of corticosteroids (3 mg/kg of dexamethasone or 30 mg/kg of methylprednisolone given as a single bolus infusion through a central venous catheter over 10 to 20 minutes and repeated once only after 4 hours if needed). Failure to respond to seemingly appropriate therapy suggests the possibility of undrained pus. Examination by ultrasound or computed tomography may disclose an obstructed ureter or perinephric abscess, both of which require surgical drainage.

F. Management of recurrent renal infections (relapses). Chronic bacterial pyelonephritis is one of the most refractory problems in clinical medicine; relapse rates are as high as 90 percent. The entity is a heterogeneous one with multiple underlying factors.

1. **Risk factors.** To improve the success rate, it is of utmost importance that any correctable lesion be repaired, that obstructions to urine flow be relieved, and that foreign bodies (e.g., indwelling urinary catheters or renal staghorn calculi) be removed if possible. If the risk factors cannot be corrected, long-term eradication of bacteriuria is almost impossible. To attempt eradication in such instances leads only to emergence of more resistant strains of bacteria or fungi; consequently, one must be resigned to treatment of symptomatic episodes of infection and to suppression of bacteriuria in selected patients.
2. **Acute symptomatic infection.** The treatment of acute symptoms and signs of urinary tract infection in a patient with chronic renal bacteriuria is the same as for patients with acute bacterial pyelonephritis. Urine cultures are important to detect a possible change in antimicrobial susceptibility of the infecting microorganism. Toxic patients should also have blood cultures.
3. **Prolonged treatment.** Some patients with relapsing bacteriuria after 2 weeks of therapy will respond to 6 weeks of antimicrobial therapy; this is especially true of patients with no underlying structural abnormalities and of men with normal prostatic examinations. Patients who fail the longer therapy, who have repeated episodes of symptomatic infection, or who have progressive renal disease despite corrective measures are candidates for suppressive chemotherapy.

4. **Suppressive therapy.** Patients selected for suppressive therapy should have 2 to 3 days of specific high-dose antimicrobial therapy to which their infecting bacteria are susceptible to reduce the colony counts in their urine. The preferred agent for long-term suppression is methenamine mandelate, 1 gm four times daily in adults. To be most effective the pH of the urine should be maintained below 5.5; this can be accomplished with ascorbic acid, 500 mg two to four times daily. Alternatively, the dosage of methenamine mandelate alone can be increased to 8 gm or even 12 gm per day. The dosage should be adjusted to the minimal amount required to keep the urine free of bacteria. To avoid metabolic acidosis the dosage of methenamine mandelate must be reduced in patients with renal insufficiency, in whom 2 gm per day may suffice; it should not be used at all unless the creatinine clearance exceeds 10 ml per minute.
5. **Prognosis.** Although a common cause of appreciable morbidity, urinary tract infections do not play a major role in the pathogenesis of end-stage renal disease. Patients who come to renal dialysis or transplantation because of chronic bacterial pyelonephritis almost always have an underlying structural defect. Most often the lesion is chronic atrophic pyelonephritis associated with vesicoureteral reflux that started in infancy. The role of surgical correction of vesicoureteral reflux is not clear despite years of debate; what is certain, however, is the importance of meticulous control of infection in children to prevent progressive renal scarring and renal failure by early adulthood.

G. Treatment of prostatitis

1. **Acute bacterial prostatitis.** Acute bacterial prostatitis is commonly accompanied by acute cystitis, which enables recovery of its causative pathogen by culture of voided urine. Massage of an acutely inflamed prostate gland often results in bacteremia; therefore, this procedure should be avoided unless the patient is already receiving effective antibiotic therapy. The drug of choice is the combination of trimethoprim-sulfamethoxazole (co-trimoxazole) in the dosage given in Table 7-3; treatment should be given for 30 days to prevent chronic bacterial prostatitis. If co-trimoxazole cannot be given, parenteral gentamicin or tobramycin (see sec. **V.E.**) plus ampicillin should be used as outlined for acute bacterial pyelonephritis until results of cultures and susceptibility testing are known. After acute symptoms subside, a suitable oral antibiotic can be given in full dosage for at least 30 days. Urethral catheterization should be avoided. If acute urinary retention develops, drainage should be by suprapubic needle aspiration or, if prolonged bladder drainage is required, by a suprapubic cystostomy tube placed under local anesthesia.
2. **Chronic bacterial prostatitis.** The hallmark of chronic bacterial prostatitis is relapsing urinary tract infection. It is most refractory to treatment. Although erythromycin with alkalinization of the urine has been effective against susceptible gram-positive pathogens, most instances of chronic bacterial prostatitis are caused by gram-negative enteric bacilli. Co-trimoxazole is the drug of choice. About 75 percent of patients improve and 33 percent are cured with 12 weeks of co-trimoxazole therapy (two tablets twice daily). For patients who cannot tolerate co-trimoxazole, nitrofurantoin, 50 or 100 mg once or twice daily, can be used for long-term (6 to 12 months) suppressive therapy.

H. Recommendations for the care of urinary catheters. Urinary catheters are valuable devices for enabling drainage of the bladder, but their use is associated with an appreciable risk of infection in the urinary tract. For a single (in and out) catheterization the risk is small (1 to 2 percent); however, bacteriuria occurs in virtually all patients with indwelling urinary catheters within 3 to 4 days unless placement is done under sterile conditions and a sterile, closed drainage system is maintained (Fig. 7-4). The use of a neomycin-polymyxin irrigant does not prevent catheter-associated infections.

Urinary catheters are the single commonest cause of nosocomial infections and are responsible for more than 5000 deaths from gram-negative sepsis each year in the United States. Explicit recommendations for the prevention of catheter-associated urinary tract infections, formulated by the Center for Disease Control, are given below.

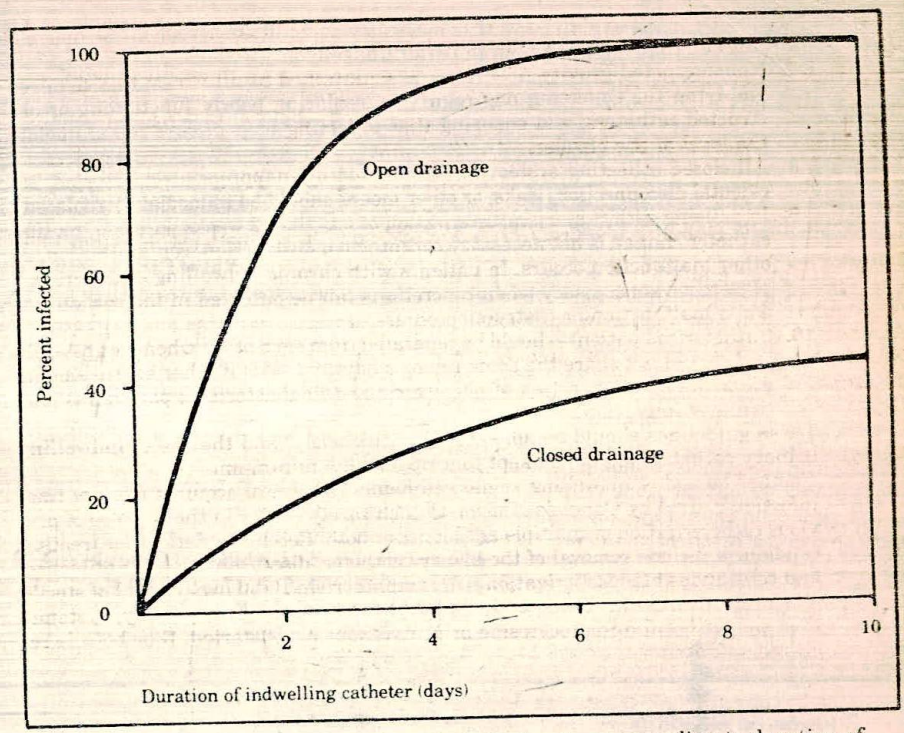

Fig. 7-4. Prevalence of bacteriuria in catheterized patients according to duration of catheterization and type of drainage system. (From R. J. Fass, A. S. Klainer, and R. L. Perkins. Urinary tract infection: Practical aspects of diagnosis and treatment. *J.A.M.A.* 225:1509, 1973. Copyright 1973, American Medical Association.)

1. Indwelling urinary catheters should be used only when absolutely necessary; they should never be used solely for nurse or physician convenience, and they should be removed as soon as possible.
2. Catheters should be inserted only by adequately trained personnel; if practical, a team of individuals should be given responsibility for catheter insertion and maintenance.
3. Urinary catheters should be aseptically inserted utilizing proper sterile technique and the following sterile equipment: gloves, a fenestrated drape, sterile sponges and an iodophor solution for periurethral cleansing, a lubricant jelly, and an appropriate-sized urinary catheter. Following insertion, catheters should be properly secured to prevent movement and urethral traction.
4. Once- or twice-daily perineal care for catheterized patients should include cleansing of the meatal-catheter junction with an antiseptic soap; subsequently, an antimicrobial ointment may be applied.
5. A sterile closed drainage system should always be used. The urinary catheter and the proximal portion of the drainage tube should not be disconnected (thus opening the closed system) unless required for irrigation of an obstructed catheter. Sterile technique must be observed whenever the collecting system is opened and catheter irrigation is done; a large-volume sterile syringe and sterile irrigant fluid should be used and then discarded. If frequent irrigations are necessary to ensure catheter patency, a triple-lumen catheter permitting continuous irrigation within a closed system is preferable.
6. Small volumes of urine for culture can be aspirated from the distal end of the catheter with a sterile syringe and 21-gauge needle; the catheter must

first be prepared with tincture of iodine or alcohol. Urine for chemical analyses can be sterilely obtained from the drainage bag.

7. Nonobstructed gravity flow must be maintained at all times; this requires emptying the collecting bag regularly, replacing poorly functioning or obstructed catheters, and ensuring that collecting bags *always* remain below the level of the bladder.
8. All closed collecting systems contaminated by inappropriate technique, accidental disconnection, leaks, or other means should be immediately replaced.
9. In patients with urinary catheterization of less than 2 weeks duration, routine catheter change is not necessary except when obstruction, contamination, or other malfunction occurs. In patients with chronic indwelling catheters, replacement is necessary when concretions can be palpated in the catheter or when malfunction or obstruction occurs.
10. Catheterized patients should be separated from each other whenever possible and should not share the same room or adjacent beds if other arrangements are available. Separation of bacteriuric and nonbacteriuric patients is particularly important.

These guidelines should be adhered to meticulously, and the use of indwelling urinary catheters should be kept to a responsible minimum.

Another hazard of indwelling urinary catheters is hospital-acquired urinary tract infection caused by *Candida albicans*, which rarely occurs in the absence of previous catheterization or multiple antibiotics or both. Recommendations for treating candiduria include removal of the urinary catheter, discontinuation of antibiotics, and continuous bladder irrigation with amphotericin B (50 mg/1000 ml of sterile water via a three-way catheter for 24 hours for 5 days). Occasionally, systemic therapy with oral 5-fluorocytosine or intravenous amphotericin B or both is required.

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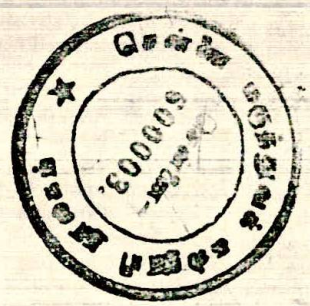


8 The Patient With Proteinuria or an Abnormal Urinary Sediment

Antoine M. de Torrenté
and Robert J. Anderson

Examination of the urine is one of the simplest and most rewarding laboratory methods in clinical medicine. Urine is usually abundant and readily obtained, and the method of examination is simple. Such tests, although lacking in specificity, are usually sensitive in detecting renal parenchymal or urinary tract disease. An abnormal urinary sediment or proteinuria should never be dismissed until a reasonable explanation has been found. A variety of treatable diseases (e.g., renal parenchymal infection, especially tuberculous; allergic interstitial nephritis, analgesic nephropathy, and certain immune complex nephritides) that, if left unchecked, can lead to chronic renal failure may be discovered. An early manifestation of a curable renal neoplasm may be hematuria. The urinary sediment and the 24-hour quantitative protein excretion can also be used, with other tests of renal function, to ascertain positive or negative responses to therapy. Urinalysis is an invaluable tool in screening for a wide variety of diseases affecting the urinary tract and in monitoring their course; therefore, it should be performed in every patient as routinely as blood pressure is measured and height and weight are recorded.

Since almost all diseases of the urinary tract may be accompanied by either proteinuria and/or an abnormal sediment, an abnormal sediment can never be diagnostic. The physician confronted with an abnormal urine sediment has to use other means of investigation, including history, physical examination, and laboratory and radiologic investigations, to arrive at a specific diagnosis.

I. **Collection of urine.** For routine urinalysis a random specimen is adequate. The best results are usually obtained on an early morning specimen, which usually has a high osmolality and low pH, a setting that prevents rapid dissolution of formed elements and casts. A concentrated urine specimen is also more sensitive to test for proteinuria.

   A. **Male patients.** To avoid unnecessary contamination of the urine specimen, the foreskin should be retracted in uncircumcised men, the meatus cleaned with a gauze pad moistened with water, and a "clean catch" midstream specimen voided into a clean container.

   B. **Female patients.** In women the labia should be spread apart, the meatus cleaned as described above, and a "clean catch" midstream specimen obtained. This method, although somewhat cumbersome, avoids heavy contamination by epithelial cells and debris that may obscure meaningful findings. In general, urinary sediment examination is of little value during the menstrual period even after insertion of vaginal tampons. Red cell or white cell casts, however, cannot be explained by contamination with menses.

II. **Examination of urine**

   A. **Urine color.** Urine is normally clear or amber. A listing of causes of abnormal urine color is in Table 8-1.

   B. **Urine sediment.** The urine specimen is shaken gently to mix its components. Observation may reveal unusual color or abnormal foaming (proteinuria). Ten milliliters of urine are then poured into a conical centrifuge tube and spun for 3 to 5 minutes at 3000 rpm. About 9 ml of the supernatant are carefully discarded and the sediment suspended in the remaining milliliter. Some nephrologists have recommended that all supernatant be discarded and the remaining "button" be removed gently with a pipette and placed on the slide; this technique may be

Table 8-1. Causes of Abnormal Urine Color

Red
Benzidine (+): RBC, hemoglobin, myoglobin
Benzidine (−): beeturia (a harmless inborn error of metabolism), medications (paraaminosalicylic acid [PAS], Congo red, phenolsulfonphthalein [PSP], senna, phenolphthalein)
Porphyria
Orange
Medications (phenazopyridine [Pyridium], ethoxazene [Serenium], rifampin)
Porphyria
Brown/black
Hemoglobin or myoglobin with alkaline pH (should always be benzidine [+])
Bilirubin (yellow foam)
Medications (L-dopa, methyldopa [Aldomet], phenol, phenacetin)
Melanin (tumor)
Homogentisic acid (alkaptonuria)
Porphyria
Blue/green
Medications (indigo-carmine dyes, methylene blue)
Pseudomonas infection

particularly helpful when a paucity of casts is present. One or two drops of the sediment are then deposited on a microscope slide and examined first at a low magnification (×100) and then at high power (×400). The sediment should be examined immediately, before drying. Staining is usually necessary only with the Gram stain, often best in the area just outside the coverslip. Formed elements and casts are more abundant at the edges of the coverslip. Usually 10 to 15 high power fields (HPF) should be examined and the casts and formed elements expressed as number per HPF. An exact quantitation in a counting chamber is not recommended, since the conditions of collection are so variable. One red blood cell cast per HPF is as important as 20 or 40. The various cells and casts are shown in Figures 8-1 through 8-16.

C. Urine protein. The urine should be checked for protein with the dipstick method. This method employs the alteration of an indicator dye by protein and is sensitive to about 30 mg of albumin per deciliter. The method, however, does not detect light-chain proteins and some other globulins. Other low-molecular-weight proteins excreted in tubular diseases also may not be detected by the dipstick method. If light-chain or low-molecular-weight proteins are suspected, the sulfosalicylic acid test should be performed on the urine as follows: Eight drops of 20% sulfosalicylic acid are added to 2 ml of urine. A white cloud of precipitate indicates a positive test. The sulfosalicyclic acid test is more sensitive than the dipstick method but is less specific (Table 8-2). A highly concentrated (specific gravity greater than 1.030) early morning normal urine may contain trace to 1+ protein by the dipstick method. The findings in a normal early morning urine are:

1. **Protein:** 0 to 1+
2. **Epithelial cells:** occasional per HPF (may be numerous in females)
3. **Crystals:** occasional per HPF
4. **Red blood cells:** 0 to 5 per HPF
5. **White blood cells:** 0 to 3 per HPF
6. **Casts:** hyaline, occasional per HPF

Proteinuria

I. General patient evaluation. Detection of an abnormal quantity of protein in urine is one of the most reliable signs of renal parenchymal disease. Urine from normal

persons contains less than 150 mg of protein per day. Any quantity above this amount should be investigated. Once proteinuria has been discovered by the dipstick or sulfosalicyclic acid method on a urine sample, the minimal workup should be undertaken as follows:

✓ **A. Complete physical examination and history.** A physical examination and history, especially in search of acquired or familial renal diseases and hypertension, are essential.

✓ **B. Twenty-four-hour urine collection for quantitative protein excretion.** This determination is absolutely mandatory to assess the degree of proteinuria, a quantitation that may convey prognostic and diagnostic information.

✓ **C. Repeat 24-hour protein measurement.** A repeat 24-hour protein measurement on three or four samples is necessary to ascertain the persistent or intermittent nature of the proteinuria. Intermittent proteinuria is usually associated with a benign course.

✓ **D. Exclusion of orthostatic proteinuria.** This simple test is done in the following manner. The patient voids in the evening (sample 1). The patient then retires immediately. Urine is collected the next morning while the patient is still supine (sample 2). The patient is then allowed to rise and ambulate. The next voiding is again collected (sample 3). All three samples are checked for protein. With orthostatic proteinuria the specimen should be negative or trace on sample 2 and positive on samples 1 and 3. If the proteinuria is orthostatic and less than 1 gm per day, without sediment abnormalities, serious renal disease is unlikely and the prognosis is benign.

E. Information on renal function. Information on renal function is obtained by measuring plasma creatinine and blood urea nitrogen (BUN). Creatinine clearance can be calculated if the sample for 24-hour protein is also used to determine 24-hour creatinine excretion.

F. Careful examination of the urinary sediment and urine culture

G. Routine hematologic and blood chemistry studies. These include complete blood count, electrolytes, and blood sugar tests.

These steps allow the proteinuria to be classified and at the same time provide a framework for a differential diagnosis.

II. Degrees of proteinuria: clinical characteristics and course

A. Low-grade proteinuria (less than 1 gm per day). This is a very common problem in medical practice. Low-grade proteinuria can be caused by a number of different renal afflictions (Table 8-3).

1. **Idiopathic low-grade proteinuria.** Idiopathic low-grade proteinuria is the diagnosis if the history and physical examination are normal, the renal function is normal, and no cells or casts are seen in the sediment. This proteinuria is usually due to minor abnormalities of the glomeruli or kidney vasculature. Long-term studies have demonstrated that the prognosis is benign. The proper approach, therefore, is to follow these patients carefully every 3 to 6 months with regular blood pressure measurements and determinations of plasma creatinine. Renal biopsy is not indicated if the renal function is stable and normal. The association of low-grade proteinuria and hematuria is a more serious matter and may indicate a progressive glomerular disease.
2. **Functional proteinuria.** Functional proteinuria is induced for unknown reasons by congestive heart failure, fever, or heavy exercise. The urine sediment is usually normal. Plasma creatinine can be somewhat elevated, secondary to a low renal perfusion with heart failure or dehydration in a febrile illness. The proteinuria should resolve with the treatment of the primary disease.
3. **Nephrosclerosis.** Nephrosclerosis is observed in patients with long-standing essential hypertension. Renal function is usually moderately decreased and the urine sediment is normal. Control of the blood pressure may decrease the proteinuria and ameliorate or stabilize the renal function.
4. **Polycystic kidney disease.** Polycystic kidney disease in its adult form may come to the attention of the physician initially because of low-grade proteinuria. A family history of death in the fourth and fifth decades due to renal failure, palpable kidneys, episodes of hematuria, and flank pain are characteristic. The excretory urogram and ultrasonogram usually confirm the diagnosis.

Fig. 8-1. White cells, red cells, and bacteria. The white cells are relatively uniform in size in contrast to tubule cells, which are not shown but which tend to vary in size, and have a granular cytoplasm such that their nuclei are not visible, but they are nevertheless identifiable as white cells by comparison of their size with the red cells and by their context, e.g., obvious urinary infection with pyuria as well as bacilluria. Only one of the red cells has obvious hemoglobin pigment but several other cells with homogenous cytoplasm are the same size and are, indeed, red cells. Bacilli are easily recognized in unstained preparations, as in this sediment, but cocci are indistinguishable from urinary granules without the use of Gram stain. (Provided courtesy of Ronald B. Miller, M.D.)

Fig. 8-2. Many polymorphonuclear leukocytes, approximately ten renal tubule cells, and a number of granules (which are not red blood cells). Cytoplasmic granules have been cleared by the addition of a few drops of dilute acetic acid to the sediment, which allows the nuclei of the cells to be seen. In contrast to the polymorphonuclear leukocytes, the renal tubule cells are larger, vary in size, and have single nuclei that are generally round, sometimes eccentric. (Provided courtesy of Ronald B. Miller, M.D.)

Fig. 8-3. Many red cells and a single, broad hyaline cast, which runs diagonally through the photograph. The hyaline cast, which is comprised of Tamm-Horsfall mucoprotein, is barely more refractive than the surrounding urinary water. With greater illumination, the hyaline cast might be invisible. (Provided courtesy of Jerome P. Kassirer, M.D.)

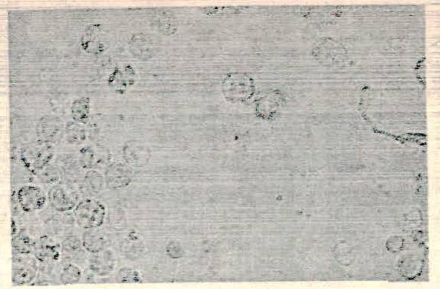
Fig. 8-4. A hyaline cylindroid (so-called because of its tail) with a number of granules at one end of the cast, presumably precipitated serum proteins in a hyaline matrix of Tamm-Horsfall protein. Note the mucous threads, which are thinner than all but the tail of the hyaline cast. (Provided courtesy of Ronald B. Miller, M.D.)

Fig. 8-5. A broad, finely granular cast, which presumably formed in either a collecting duct or a diseased, dilated tubule. The breadth of the cast can be appreciated by comparing it to the white cells and red cells free in the urine. (By definition, a broad cast is more than two or three cell diameters wide.) Broad casts do not invariably imply chronic renal failure, as was once believed; they may also occur in acute disease, particularly when there is oliguria. (Provided courtesy of Ronald B. Miller, M.D.)

Fig. 8-6. Another broad cast, somewhat more coarsely granular, surrounded by a number of squamous epithelial cells. (Provided courtesy of Ronald B. Miller, M.D.)

Fig. 8-7. A finely granular cast with a number of imbedded renal tubule cells (a so-called granulotubular cell cast). Rare hyalocellular or granulocellular casts may be seen in normal urine. If many such casts are present in a single urine specimen, particularly if they are as broad as this cast, it is reasonably certain that renal parenchymal disease is present although the nature of the disease is uncertain, since these casts are nonspecific. (Provided courtesy of Jerome P. Kassirer, M.D.)

Fig. 8-8. A degenerating cell cast with a few cell outlines evident and considerable granular material, presumably degenerating cell fragments rather than precipitated serum proteins. Under the microscope two individual cells in this cast had multilobed nuclei, identifying this cast as a leukocyte or pus cast. White cell casts are typical of pyelonephritis and other interstitial nephritides, but they also occur in exudative glomerulonephritis, sometimes in large numbers. (Provided courtesy of Ronald B. Miller, M.D.)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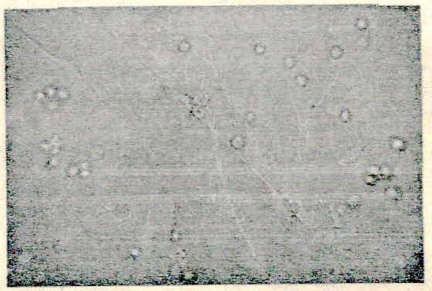
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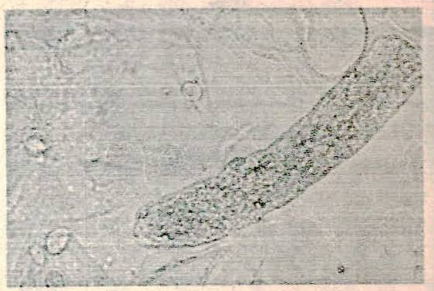
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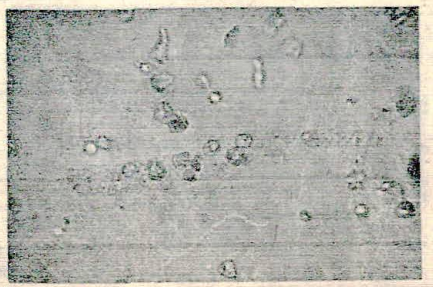
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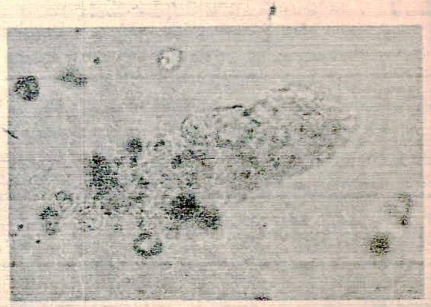
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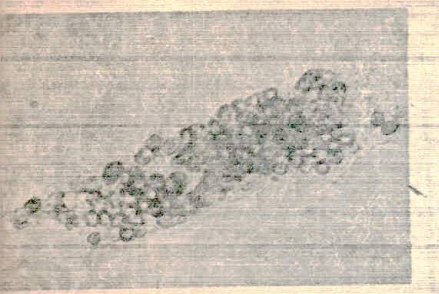

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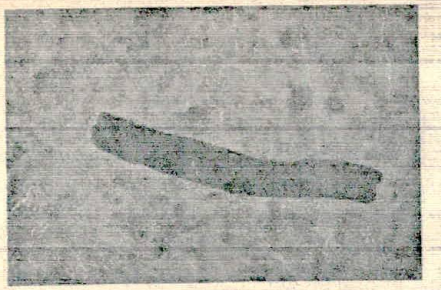

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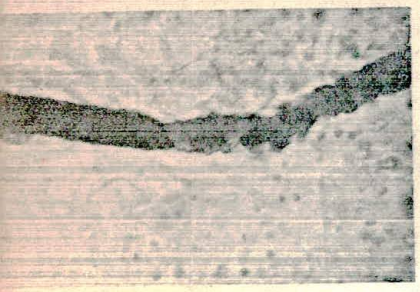

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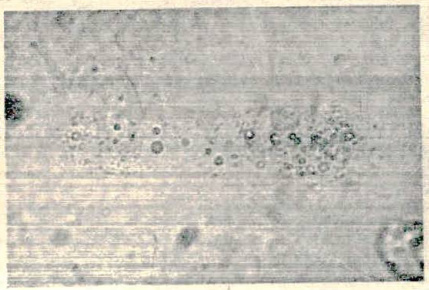

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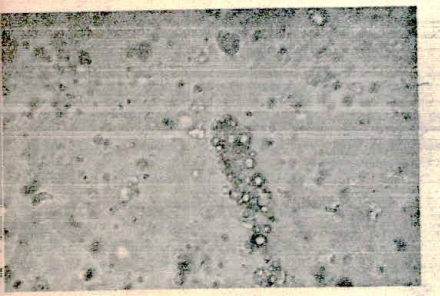

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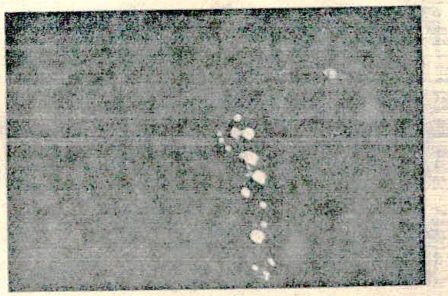

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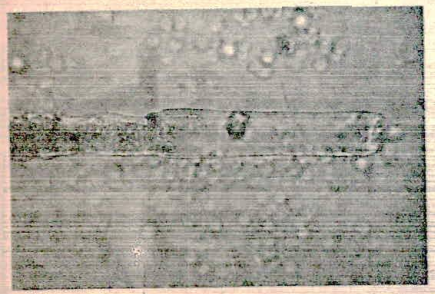

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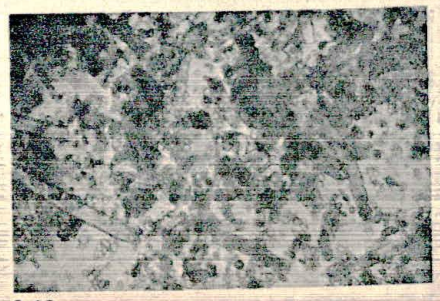


8-16

Fig. 8-9. A typical red cell cast with the hemoglobin pigment of the red cells clearly evident and cell outlines well preserved. Such a cast usually indicates glomerulonephritis, though red cell casts can also occur rarely with strenuous exercise or trauma to the kidney. (Provided courtesy of Ronald B. Miller, M.D.)

Fig. 8-10. Another red cell cast in which individual cell outlines are less evident. This cast is on its way to becoming a hemoglobin or blood cast (by breakdown of red cell walls). As is usually the case in acute nephritis, there are innumerable red cells free in the urine. (Provided courtesy of Ronald B. Miller, M.D.)

Fig. 8-11. A cast that at one end has discernible red cell outlines, at the other end a homogenous or slightly granular morphology with an unequivocal hemoglobin-tint. Thus, this cast is both a red cell cast and a hemoglobin or blood cast. The hemoglobin pigment is indistinguishable from myoglobin, but one would not expect red cell casts in a patient with myoglobinuria. (Provided courtesy of Ronald B. Miller, M.D.)

Fig. 8-12. A barely discernible hyaline matrix with many fat globules, as might be seen in a patient with the nephrotic syndrome. This is a hyalofatty cast. Were there more fat globules, it would be called a fatty cast. Note the variable size of the fat globules and their refractiveness with reduced illumination, characteristics that distinguish them from red blood cells. (Provided courtesy of Ronald B. Miller, M.D.)

Fig. 8-13. A fatty cast with sufficiently reduced illumination so that the fat globules are quite refractive. (Provided courtesy of Jerome P. Kassirer, M.D.)

Fig. 8-14. The same cast as in Figure 8-13 viewed with polarized light, which demonstrates the anisotropic nature of the fat (usually thought to be cholesterol ester). Although many are out of focus, several fat droplets can be seen to exhibit the maltese-cross phenomenon. (Provided courtesy of Jerome P. Kassirer, M.D.)

Fig. 8-15. A cast that is broad and waxy at one end and has red cells incorporated in its matrix at the other end. This unusual cast is from a patient with glomerulonephritis. The innumerable red cells free in the urine suggest the nephritis is acute or subacute. (Provided courtesy of Jerome P. Kassirer, M.D.)

Fig. 8-16. A busy or active sediment from a patient with acute tubular necrosis with many broad waxy casts, one of which is convoluted, and with a number of broad, brown, granular casts that are somewhat more typical of acute tubular necrosis than are the waxy casts. The pigment is not hemoglobin, but rather an unidentified brown pigment, particularly common in the casts of patients with acute tubular necrosis, but also occurring in casts of patients with chronic renal parenchymal disease. (Provided courtesy of Jerome P. Kassirer, M.D.)

Table 8-2. False-positive (+) and False-negative (−) Reactions With Dipstick or Sulfosalicylic Acid Test for Proteinuria

Clinical Setting	Dipstick	Sulfosalicylic Acid
X-ray contrast media	−	(+)
Tolbutamide	−	(+)
Penicillins	−	(+)
Sulfisoxazole (Gantrisin)	−	(+)
p-Aminosalicylic acid	−	(+)
Low molecular weight proteins, light chains	(−)	+
Dilute urine	(−)	+
Alkaline urine	(+)	±

Note: The absence of parenthesis indicates a correct finding.

5. **Medullary cystic disease.** Medullary cystic disease may be a cause of renal failure in adolescence. The disease is characterized by polyuria, nocturia, a severe anemia, and failure to thrive. A renal salt-wasting tendency is common. The sediment is unremarkable. The diagnosis is made mainly on clinical grounds and by a careful family history. The kidneys are small on excretory urogram and ultrasonogram, but these findings are nonspecific.
6. **Obstructive uropathy.** Chronic obstructive uropathy may present as nocturia, polyuria, or polydipsia. Pyuria and proteinuria may or may not be present.
7. **Chronic interstitial nephritis.** A nephropathy secondary to analgesic abuse, lead, cadmium, oxalate, uric acid, hypercalcemia, and hypokalemia may also present with mild proteinuria.

B. **Moderate proteinuria (1.0 to 3.5 gm per day).** With severe, advanced disease many of the disorders discussed above in association with low-grade proteinuria (sec. **II.A.**) can lead to moderate proteinuria. By far the most common causes of moderate proteinuria are glomerular diseases, however, interstitial diseases may also cause moderate proteinuria.

C. **Heavy proteinuria (greater than 3 to 5 gm per day): the nephrotic syndrome.** The nephrotic syndrome is not a disease itself; it may be caused by a variety of causative and pathogenetic mechanisms that result in a spectrum of pathologic lesions with vastly different prognoses.

1. **Clinical characteristics.** Proteinuria above 3 gm per day is usually classified as in the nephrotic range, but the symptom complex may vary widely from one patient to another. In addition to heavy proteinuria and lipiduria (oval fat bodies), the nephrotic syndrome is characterized by edema, varying from minimal degrees to frank anasarca, hypoalbuminemia, hypercholesterolemia, and hypertriglyceridemia. Even if all features of the syndrome are not present, proteinuria above 3 gm per day usually indicates a disease state that may lead with time to the complete nephrotic syndrome complex.
2. **Patient evaluation.** The nephrotic syndrome may be indicative of generalized disorders and should be approached as such. A narrow focusing on the kidney disease alone may be misleading. In addition to the steps listed previously (see **A.1.**), the evaluation of a nephrotic patient includes the following:
   a. **Renal biopsy.** Except with typical clinical pictures such as steroid-responsive nil disease (minimal change nephrotic syndrome), far-advanced diabetes mellitus, or constrictive pericarditis, a renal biopsy is usually indicated for the proper differential diagnosis of the cause of nephrotic syndrome.
   b. **Serologic tests.** Serologic tests should include those for streptozyme, antinuclear antibodies (ANA), total complement (CH_{50}), VDRL, hepatitis B–associated antigen, and cryoglobulins.

Table 8-3. Some Causes of Low-Grade Proteinuria

Cause	Clinical Clues	Critical Laboratory Findings
Idiopathic	No history of renal disease, normal blood pressure	Normal sediment, normal renal function
Functional proteinuria	Congestive heart failure, high fever, heavy exercise	Normal sediment, except sometimes white blood cells and an increase in hyaline casts
Nephrosclerosis	History of high blood pressure	Normal sediment
Chronic interstitial nephritis	Analgesic abuse, lead exposure, urinary tract infection	Pyuria
Glomerulonephritides	Streptococcal infection, symptoms of connective tissue disease (arthritis, skin rash, etc.)	Hematuria and red blood cell casts
Congenital diseases		
Polycystic kidney disease	Family history, palpable kidneys	Enlarged kidneys on excretory urogram, cysts on ultrasonogram
Medullary cystic disease (nephronophthisis)	Family history, short stature	Disproportionately severe anemia, salt wasting, renal tubular acidosis

c. **Heavy metal determination.** Heavy metal determination (e.g., gold, bismuth, mercury) should be made if the history is compatible.

3. **Differential diagnosis.** The diagnostic approach given above and the results of the renal biopsy usually allow the classifications shown in Table 8-4. Although the list is extensive, some diseases are very rare. In the Western world the most common causes of nephrotic syndrome are diabetes mellitus, nil disease, and the idiopathic glomerulonephritides, including idiopathic membranous nephropathy, focal glomerulosclerosis, and proliferative and membranoproliferative glomerulonephritis.

a. **Minimal change disease.** Minimal change disease (nil disease) is usually characterized by previous good health, normal renal function, absence of red blood cells or red blood cell casts in the sediment, and absence of hypertension. The patient is usually a child or young adult, and the disease is almost always steroid-sensitive. A disease that can be confused with nil disease is focal glomerulosclerosis, which is characterized by a much more frequent incidence of hypertension, hematuria, slightly decreased renal function, and, generally, steroid resistance. Since the disease seems to start in the deeper juxtamedullary nephrons, it is often missed on renal biopsy. The prognosis is much worse than that for nil disease: about 50 percent of patients require chronic maintenance dialysis or a kidney transplant, or are dead within 10 years after the diagnosis.

b. **Metabolic, systemic, and mechanical factors.** Metabolic, systemic, and mechanical factors provoking the nephrotic syndrome are usually recognized by associated clinical findings. In this category, diabetic nephropathy is probably the most common form of nephrotic syndrome in the temperate climates, and the prognosis is poor regarding preservation of useful renal function. However, meticulous control of blood sugar and blood pressure may improve the prognosis of the renal disease. Nephrotic syndrome due to poison and drugs is being recognized with increasing frequency. Nonsteroidal antiinflammatory agents, mercury, and gold therapy can cause nephrotic syndrome.

c. **Glomerulonephritis.** Nephrotic syndrome due to glomerulonephritis is suspected on clinical grounds by the associated red blood cells or red blood cell casts in the sediment and the frequent presence of hypertension. Any type of glomerulonephritis, of any histologic feature (segmental, focal, diffuse), idiopathic or associated with collagen vascular diseases or hypersensitivity reactions, can present with or be complicated by the nephrotic syndrome. Appropriate serologic tests, systemic manifestations, and a renal biopsy usually establish the diagnosis. In this group of diseases membranous nephropathy, secondary or idiopathic, is especially frequent.

III. Guidelines to therapy of nephrotic syndrome

A. Diuretics. Although extracellular fluid (ECF) volume is increased in patients with the nephrotic syndrome, circulating intravascular volume may be normal or decreased. Therefore, extreme caution should be exercised in the use of diuretics to avoid increased circulating volume depletion. A moderately potent diuretic, such as hydrochlorothiazide, is preferred to a more potent loop diuretic, such as furosemide. A weight loss of 0.5 kg per day is the maximum diuresis that is well tolerated. A low salt diet and the addition of spironolactone, an aldosterone antagonist, may be useful for refractory edema. Diuretics should be used only for symptomatic edema and not for marginal cosmetic benefit.

B. Corticosteroids. The only disease that will almost always respond to corticosteroid therapy is minimal change disease. Minimal change disease may remit spontaneously, but the more rapid beneficial effect of steroids on the proteinuria, hypoalbuminemia, and other features of the syndrome has led to the universal acceptance of steroid therapy for this entity. Physicians differ widely in their treatment schedules. A reasonable therapeutic approach is 1.0 to 1.5 mg/kg/day of prednisone until the urine is protein-free for about 7 days. The patient is then started on every-other-day therapy with twice the daily dosage of steroid, which is tapered over 2 to 3 months. More than 90 percent of patients with nil disease

Table 8-4. Differential Diagnosis of the Nephrotic Syndrome

Diagnosis	Clinical Clues	Critical Laboratory Findings
Minimal change disease	Young age, no manifestation of systemic disease, no hypertension	No hematuria, normal renal biopsy on light microscopy
Metabolic or systemic diseases		
Diabetes mellitus	History of diabetes, high blood pressure, retinopathy	Usually, decreased renal function, normal or large kidney size
Amyloidosis	Mediterranean origin, multiple myeloma	Usually decreased renal function, large kidneys, renal biopsy specific on electron microscopy
Neoplasia	Hodgkin's and non-Hodgkin's lymphoma, other carcinomas (e.g., renal cell, colonic)	Usually minimal change disease but membranous nephropathy may also be present on biopsy
Pregnancy with preeclampsia	High blood pressure, third trimester	Increased serum uric acid, glomerular endothelial cell swelling on renal biopsy
Malignant or accelerated hypertension	High blood pressure, target organ disease (cardiac, ophthalmologic)	Hematuria, decreased renal function
Sickle cell disease	Black race	Abnormal hemoglobin SS or SC
Mechanical factors		
Severe congestive heart failure	Evidence of heart failure on physical examination	Pulmonary congestion on chest x-ray
Constrictive pericarditis	Distended neck veins that distend more on inspiration (Kussmaul's sign)	Evidence of pericardial effusion on echocardiogram and cardiac catheterization, cardiac calcification on chest x-ray
Poisons, drugs, and allergens		
Mercury, bismuth, gold	History of exposure	Urinary determination of the metal
Penicillamine, trimethadione	History of treatment of rheumatoid arthritis, seizures	Membranous nephropathy on renal biopsy
Captopril, nonsteroidal antiinflammatory agents	History of exposure	Hematuria, positive serologic results according to cause
Allergens: poison ivy, insect bites	Skin rash, arthralgias, arthritis, photosensitivity, hair loss	
Glomerulonephritis of any kind (chronic or acute, primary or secondary to systemic collagen vascular disease)		

respond, but many (up to 50 percent) relapse and thus need another course of steroid therapy. After complete remission (proteinuria less than 200 mg per day), the patient should have 24-hour urine protein determinations and plasma creatinine determinations every 3 months. If the patient develops side effects from steroids (moon facies, hypertension, weight gain) because of frequent attempts at treating relapses, immunosuppressive agents, such as cyclophosphamide, should be considered after consultation with a nephrologist.

Other forms of the nephrotic syndrome may remit if the cause of the disease is reversible (e.g., discontinuation of the offending drug, control of accelerated hypertension, or termination of pregnancy in the toxemic patient).

When the nephrotic syndrome is caused by a form of glomerulonephritis, the prognosis is variable. The patient with systemic lupus erythematosus may have nephrotic syndrome in association with membranous nephropathy, diffuse proliferative glomerulonephritis, and, rarely, focal proliferative glomerulonephritis. Steroid therapy may produce a remission of the nephrotic syndrome in some of these patients with lupus nephritis. One study suggests that patients with idiopathic membranous nephropathy may respond to steroids. Except for some decrease in proteinuria, no beneficial effect of steroids was found in these patients compared to nontreated patients, until 2 years of follow-up. At that time, a significant deterioration in renal function was observed in the nontreated group compared to patients treated with steroids. The results of this study should, however, be considered preliminary. The recommended therapy is 2 mg per kilogram of prednisone every other day for 2 months followed by tapering of the dosage over a 2-month period.

C. **Diet.** If the renal function is normal, a high-quality protein diet is encouraged to offset the loss of large amounts of protein in the urine. Salt intake should be minimized to decrease the accumulation of edema.

D. **Additional comments.** Patients with the nephrotic syndrome seem to be more prone to infections than are normal persons. Thus, any complaint such as cough, abdominal pain, or fever should be carefully evaluated. Any rapid decrease in renal function in nephrotic patients should raise the suspicion of acute renal vein thrombosis. This complication may be asymptomatic or it may be accompanied by hematuria and costovertebral angle tenderness. The diagnosis should be pursued by renal venography. If venography documents the presence of renal vein thrombosis, the patient should be anticoagulated because pulmonary embolus is a feared complication. Chronic, asymptomatic renal vein thrombosis may also accompany proliferative or membranoproliferative glomerulonephritis. Acute deterioration in renal function in the nephrotic patient could also be due to volume depletion, treatment with nonsteroidal antiinflammatory agents, or drug-induced interstitial nephritis.

Hematuria

Aside from proteinuria, hematuria is the most important clue to the presence of kidney diseases or diseases of the urinary tract. A positive reaction with the Hemastix indicates the presence of hemoglobin in urine due to the presence of either red blood cells or free hemoglobin. More than three RBCs per HPF are required for a positive test. Myoglobin will also give a positive reaction. To document the presence of red blood cells, examination of the urine sediment is mandatory. Once true hematuria has been confirmed by sediment examination, its origin should be determined and the responsible lesion diagnosed. For practical purposes it is convenient to divide hematuria into two basic categories: group I—hematuria due to glomerular inflammation (i.e., all the glomerulonephritides) and group II—hematuria due to other causes.

I. **Hematuria due to glomerular inflammation—group I.** The distinction between groups I and II can be difficult. In group I diseases, hematuria is frequently accompanied by severe proteinuria, although some glomerular diseases may present with hematuria and minimal proteinuria. The presence of red blood cell casts provides absolute proof of the glomerular origin of the hematuria. Proteinuria, however, is a much more common indicator of the glomerular origin of the hematuria than is the presence of red blood cell casts. The combination of red blood cells, red blood cell casts, and proteinuria is commonly called a nephritic sediment. Recent studies suggest that abnormal red blood cell morphology on urinalysis also points to a glomerular site of origin.

II. **Hematuria due to nonglomerular causes—group II.** Since glomerular inflammation is absent in group II diseases, proteinuria is absent and red blood cell casts are not seen. However, a rare patient with red blood cell casts after trauma to the kidney has been described. Also, depending on the severity of the bleeding, actual blood clots may be seen with nonglomerular diseases; this never occurs with the glomerulonephritides.

III. **Approach to the patient with nephritic sediment—group I.** Since there is a total lack of specificity of a nephritic urinary sediment, a thorough clinical evaluation and additional laboratory tests are needed to make the diagnosis.

A. **Patient evaluation.** The minimum workup of a patient presenting with a nephritic urinary sediment includes the following:

1. **History and physical examination.** A complete history and physical examination should be made, with special emphasis on family history of renal diseases and antecedent streptococcal infections. Skin rashes, heart murmur, arthralgias, and other manifestations of systemic disease should be carefully sought.
2. **Serologic tests.** Serologic tests should include those for streptozyme, antinuclear antibody (ANA), total complement (CH_{50}), hepatitis B–associated antigen (HBAg), and VDRL.
3. **Evaluation of renal function.** This evaluation should include 24-hour protein excretion and 24-hour creatinine clearance.
4. **Routine laboratory tests.** Other routine tests include complete blood count with platelets and serum electrolytes.

B. **Clinical and laboratory characteristics.** Diseases that may present with a nephritic sediment and their associated clinical findings are given in Table 8-5. This classification is not based on pathogenic mechanisms but rather on clinical and laboratory characteristics that may lead to the correct diagnosis.

C. **Nephrologic consultation and renal biopsy.** It may not be possible for the complete evaluation of a patient presenting with a nephritic sediment to be completed by a primary care physician alone. He or she may need the assistance and expertise of a trained nephrologist and some sophisticated laboratory determinations. Nevertheless, with a careful clinical evaluation the primary physician will be able to focus on the most likely diagnosis. One specialized diagnostic test that may be necessary is the percutaneous renal biopsy. This diagnostic procedure is not without risk. The morbidity is 5 to 10 percent for benign complications and 0.5 to 1.0 percent for serious complications. Mortality is rare. Indications for renal biopsy vary widely among nephrologists. If the combination of a thorough history, physical examination, and appropriate laboratory tests does not allow a diagnosis with a reasonable degree of confidence, renal biopsy may be indicated. Nevertheless, few histologic or immunofluorescence studies of renal tissue can lead to diagnosis of one disease entity. Much more frequently, the findings are only compatible with a specific diagnosis. Thus, the synthesis of clinical, laboratory, and pathologic information may be necessary to establish the most likely diagnosis. The renal biopsy may also provide some indication of the prognosis of the renal disease. For instance, in a patient with glomerulonephritis, the finding of epithelial crescents in more than 80 percent of the glomeruli indicates a poor prognosis with respect to the potential reversibility and natural history of the renal disease. This is particularly true when there is no evidence of associated systemic disease, which indicates the diagnosis of idiopathic, rapidly progressive glomerulonephritis.

D. **Therapy.** Only a few therapeutic interventions are of proven benefit in the various forms of glomerulonephritis. In general terms, control of blood pressure and electrolyte balance is of utmost importance in all forms of glomerulonephritis, independent of any specific treatment.

Table 8-5. Causes of Nephritic Sediment

Glomerulonephritides	Clinical Clues	Confirmatory Laboratory Tests and Findings
Postinfectious		
Poststreptococcal	History of sore throat, impetigo, or skin infection	Positive streptozyme, low serum complement
Syphilis	History of syphilis with other physical findings	Positive VDRL, low complement
Malaria	History of exposure, fever, chills	Positive antimalarial antibodies, characteristic blood smear
Bacterial endocarditis	Heart murmur, fever, skin manifestations, splenomegaly	Positive blood cultures, low serum complement
Visceral abscesses	Fever, abdominal findings, postabdominal surgery	Low complement in one-third of patients
Viral hepatitis	Anorexia, jaundice, liver tenderness	Positive HBAg, membranous nephropathy on renal biopsy
Some other viral diseases (e.g., Guillain-Barré, infectious mononucleosis)	Ascending neuropathy, sore throat, splenomegaly	Albuminocytologic dissociation on spinal tap, positive "mono spot" test
Associated with multisystem diseases		
Systemic lupus erythematosus (SLE)	Arthralgias, skin rash, serositis, hair loss, photosensitivity	Positive ANA and DNA antibody, low serum complement
Progressive systemic sclerosis (PSS)	Skin changes, dysphagia, malabsorption	Positive Scl-1[a]
Wegener's granulomatosis	Associated sinusitis, abnormal chest x-ray	Nasal mucosa biopsy, lung and/or renal biopsy may be indicated
Mixed connective tissue disease	Features of SLE and PSS	Positive nuclear RNP[b]
Sjögren's syndrome	"Sicca" picture, rheumatoid arthritis (RA) associated	Positive SS-A or SS-B[c] in 60% of "sicca" cases, negative with associated RA
Leucocytoclastic vasculitis (hypersensitivity angiitis)	Palpable purpura, asthma	Skin biopsy, eosinophilia
Thrombotic thrombocytopenic purpura	Systemic manifestations with predominant neurologic symptoms	Microangiopathic hemolytic anemia, low platelet count, gingival biopsy
Adult hemolytic uremic syndrome	Abdominal pain, diarrhea, arthralgias	Microangiopathic hemolytic anemia
Polyarteritis nodosa	Systemic manifestations (lung, liver)	Muscle and/or testicular biopsy, arterial angiogram for splanchnic or renal microaneurysms
Essential cryoglobulinemia	Purpura, arthralgia, hepatosplenomegaly	Presence of cryoglobulins, low serum complement
Goodpasture's syndrome	Hemoptysis, abnormal chest x-ray	Renal biopsy (linear immunofluorescence staining), circulating antiglomerular basement membrane (anti-GBM) antibody
Familial nephropathy (Alport's syndrome)	Deafness, cataract (anterior or posterior), lenticonus, family history	Renal biopsy indicated (duplication of glomerular basement membrane by electron microscopy)
Idiopathic	None	None characteristic, renal biopsy indicated

[a] Scleroderma-1 (Scl-1): a soluble antigen present in rabbit thymus nuclei.
[b] Antiribonucleoprotein (RNP): complex of RNA and protein.
[c] Sjögren's syndrome A and B (SS-A, SS-B): extractable antigen from lymphoid cells.

Treatment of the underlying infection in the glomerulonephritis associated with bacterial endocarditis, malaria, syphilis, and visceral abscesses is of benefit. As already mentioned, the various forms of lupus nephritis are best controlled with steroids. The combination of steroids and immunosuppressive agents to treat diffuse proliferative lupus nephritis has not been shown to be better than steroids alone. In rapidly progressive glomerulonephritis due to systemic lupus erythematosus, plasmapheresis has been tried with some success. Steroidal and immunosuppressive therapy should accompany plasmapheresis to prevent immunologic rebound. Wegener's granulomatosis responds particularly well to cyclophosphamide. Leucocytoclastic vasculitis may respond to drug withdrawal if it is caused by a hypersensitivity reaction; a favorable response to steroid therapy may also be observed. Some cases of polyarteritis nodosa seem to benefit from prednisone and cyclophosphamide.

Pulmonary hemorrhages are the most life-threatening manifestations of Goodpasture's syndrome. With massive hemorrhage, short pulse therapy with methylprednisolone (1 gm per day intravenously in divided doses) has been used, with success in some isolated cases. Plasmapheresis accompanied by steroids and cytotoxic agents has been reported to be effective, but prospective controlled studies remain to be performed. Bilateral nephrectomy has been used as a last resort to control pulmonary hemorrhage; however, there have been well-documented cases of relapse after nephrectomy.

All of these therapeutic regimens involve dangerous medications (steroids, immunosuppressive agents) and/or elaborate technology (plasmapheresis). The primary care physician who decides to use these approaches must be fully aware of their complications and should work closely with a nephrologist.

IV. Approach to the patient with hematuria without proteinuria and red blood cell casts—group II. In this category of diseases an attempt should be made to localize the source of hemorrhage along the urinary tract.

A. Patient evaluation. Observation of the pattern of macroscopic hematuria is important. Total hematuria throughout urination is indicative of any lesion above the bladder neck; initial hematuria followed by clearing of the urine suggests a urethral lesion; and terminal hematuria usually originates in the prostatic urethra or the bladder neck. If the hematuria is microscopic, the three-glass maneuver with actual counting of the red blood cells in urine passed in each glass allows the same differentiation. With the three-glass maneuver, the patient initiates the urine stream into the first container (about 20 ml), continues voiding into the second container, and finishes into the third. Findings are shown in Table 8-6.

It cannot be overemphasized that the presence of hematuria may be indicative of a curable disease, including a renal carcinoma or renal tuberculosis. Therefore, every effort should be made to establish a diagnosis. The urologist and radiologist should be intimately involved in the evaluation of such patients. The minimal diagnostic evaluation of a patient presenting with hematuria without proteinuria or red blood cell casts should include the following:

1. **History.** A thorough history is necessary, with emphasis on factors such as a family history of renal diseases, anticoagulant ingestion, and history of exposure to tuberculosis. A careful physical examination for renal masses, for abnormal prostate enlargement or nodules, and of external genitalia (e.g., a right varicocele may accompany a renal tumor on the right) should be made.
2. **Assessment of the hematuria.** This assessment should be made by the three-glass maneuver, as described above.
3. **Routine laboratory tests.** Routine tests should include those for platelets, prothrombin time, partial thromboplastin time (PTT), sickle cell preparation, and skin test for tuberculosis (PPD).
4. **Straining of urine.** Straining of urine should be done for stone or tissue debris.
5. **Flat plate.** Flat plate of the abdomen and excretory urogram with nephrotomograms should be done in search of radiopaque stones and renal masses.
6. **Cystoscopy.** If a bladder origin of the hematuria cannot be excluded, cystoscopy should be performed.
7. **Urine culture**

Table 8-6. The Three-glass Maneuver

Glass	Initial Hematuria	Total Hematuria	Terminal Hematuria
1	+++	+++	0/+
2	+	+++	0/+
3	0/+	+++	+++

+ indicates the relative number of red blood cells.

B. Clinical characteristics. Causes of hematuria without proteinuria or red blood cell casts, along with some clinical clues and recommended diagnostic tests, are shown in Table 8-7. In 40 percent of patients with hematuria, a structural defect can be found, such as a bladder abnormality, a calculus, or a renal tumor. Another 40 percent have a renal parenchymal disease, and in 10 to 15 percent a cause cannot be determined.

A particularly important and frequent problem is the diagnosis of the patient with hematuria in whom a solitary renal mass is discovered on excretory urography. The patient presenting with hematuria, flank pain, and a palpable mass, although uncommon, is classic for the diagnosis of renal cell carcinoma, especially if the patient has associated signs of weight loss, fever or night sweats, and anemia or polycythemia. The main differential diagnosis is with a benign renal mass (e.g., solitary cyst, hematoma). Modern indirect techniques can make this differential diagnosis with near certainty and with less morbidity and mortality than a direct surgical approach. A recommended investigative sequence of events is shown in Figure 8-17. This diagnostic approach, if performed at an experienced institution, is 100 percent as sensitive and 97 percent as specific as direct surgical exploration. The mortality is also ten times less and the cost 50 percent less than exploratory surgery. More recently, many radiologists are recommending *only* CT scanning (with and without contrast) of renal masses. Such scans provide information on the nature of the mass (solid versus cystic), the extent of the mass, and the presence of nodal, renal venous, and hepatic involvement. Overall, this approach may prove more cost-effective and sensitive then that shown in Figure 8-17 (see Chap. 14).

C. Therapy. In most diseases in this category (neoplasms, impacted stones) the treatment is surgical. If acute interstitial nephritis is due to a drug hypersensitivity, withdrawal of the drug is essential. A short course of prednisone (1 mg/kg for 10 to 14 days) may hasten the recovery of renal function as well as the completeness of recovery with acute interstitial nephritis.

Pyuria

Pyuria may occur alone or associated with some degree of hematuria. Any acute or chronic inflammatory disease of the kidneys or urinary tract can result in pyuria.

I. Patient evaluation. The pyuria can be in the form of isolated pus cells, clumps, or, rarely, true white blood cell casts, which indicate the renal parenchymal origin of the disease process.

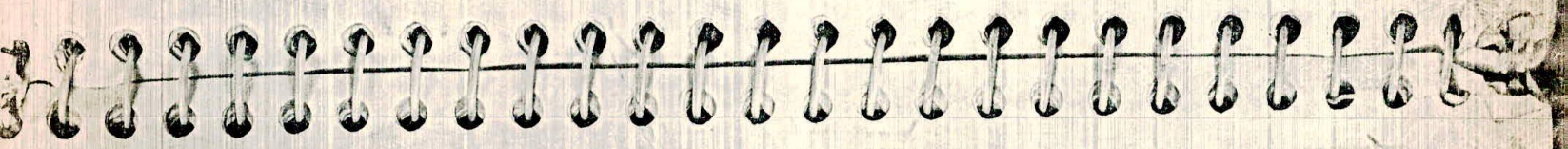
The minimal workup of a patient who presents predominantly with pyuria includes the following:

A. History and physical examination. A careful history includes episodes of fever, recent sexual contacts, drug ingestion (analgesics, antibiotics), and previous urinary tract infection or symptoms (dysuria, frequency, urgency).

B. Determination of plasma uric acid, calcium, electrolytes, and lead, if history indicates (e.g., drinking moonshine).

Table 8-7. Causes of Hematuria Without Proteinuria or Red Blood Cell Casts

Hematuria	Clinical Clues	Critical Tests and Findings
Hematuria of renal origin		
Neoplastic diseases		
Renal cell carcinoma	Renal mass, flank or abdominal pain, fever, weight loss, anemia	Excretory urogram (XU), ultrasound, angiogram (tortuous "tumor" vessels, arteriovenous fistulae), CT
Carcinoma of renal pelvis	History of analgesic abuse	XU, retrograde pyelography, CT
Other tumors of the renal parenchyma	Renal mass	XU, ultrasound, angiogram, CT
Papillary necrosis		
Diabetes mellitus	History, fever, bacteremia, flank or abdominal pain	Straining of urine for papillary debris in urine
Analgesic abuse	Middle-aged female, chronic pain, and several-kilogram analgesic ingestion	XU, positive Phenistix or ferric chloride reaction in urine (salicylates), papillary debris in urine
Sickle cell (SS) anemia	Flank or abdominal pain, history of SS crisis	XU, papillary debris in urine, SS hemoglobin on hemoglobin electrophoresis
Acute urinary tract obstruction	History, usually male (prostate)	XU, papillary debris in urine
Cystic diseases		
Polycystic kidney disease	Family history, hypertension, renal masses	XU, ultrasound, CT
Medullary sponge kidney	History of previous stones, renal tubular acidosis, nephrocalcinosis	XU
Solitary cyst	Generally no hematuria	XU, ultrasound, angiogram, CT
Medullary cystic disease	Rarely hematuria, salt losing nephritis, azotemia	
Vascular disorders		
Renal embolus (including atheromatous emboli)	Other embolic manifestations (e.g., abdominal pain, hemiparesis), cold, no pulse, painful extremity	Renal scan, angiogram, stool guaiac, ultrasound for mural thrombus



Stones	Previous history of renal calculi	XU, straining of urine
Trauma	History of trauma, blood clots in urine	XU, angiogram
Acute interstitial nephritis	History of drug intake (penicillins, allopurinol, cimetidine, furosemide, sulfonamides)	Peripheral eosinophilia, fever, rash, eosinophils in urine (possible proteinuria)
Hematuria of ureteral origin		XU, regrograde pyelogram, CT
Neoplasm		XU
Stone	Pain	XU, retrograde, pyelogram, CT
Trauma	History of trauma	
Hematuria of bladder origin		
Cystitis (viral or bacterial)	Dysuria, frequency, urgency	Associated pyuria, positive culture
Neoplasm		XU, cystoscopy, CT
Stone and foreign body	History	XU, cystoscopy
Runner's hematuria	Severe physical exercise, generally accompanied by proteinuria	
Trauma	History of trauma, fractured pelvis	XU, cystoscopy
Cyclophosphamide	History of drug treatment, dysuria	Cystoscopy
Hematuria related to the urethra or prostate		
Benign prostatic hypertrophy	History of nocturia, frequency, urgency, and dysuria	XU, cystoscopy
Acute urethritis	Dysuria	Cystoscopy
Trauma and foreign body	History	Cystoscopy

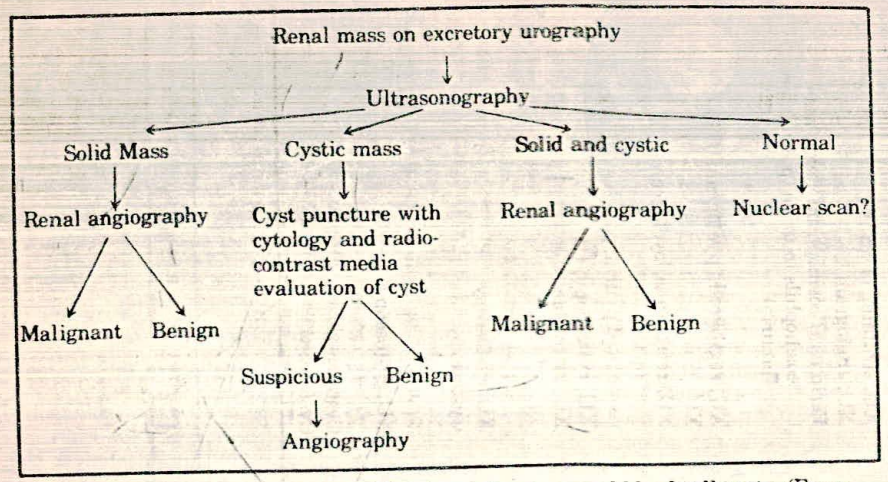


Fig. 8-17. Diagnosis of hematuria without proteinuria or red blood cell casts. (From R. V. Clayman, R. D. Williams, and E. E. Fraley, Current concepts in cancer: The pursuit of the renal mass. *N. Engl. J. Med.* 300:72, 1979.)

C. Urine culture, Gram stain of unspun urine for bacteria, dipstick for protein, examination of urine sediment.

D. Evaluation of renal function. The evaluation should be made with plasma creatinine, early morning urine specific gravity, or osmolality.

E. Skin test. This test should be made with intermediate-strength PPD.

F. Excretory urography. If pyuria is chronic or intermittently acute, excretory urography should be performed.

Frequent causes of pyuria, with some clinical clues and additional laboratory tests, are presented in Table 8-8.

II. **Clinical characteristics.** Pyuria related to bacterial infection is discussed in Chapter 7. The group of chronic interstitial nephritides is usually characterized by alterations in tubular function before any important decrease in glomerular function occurs. Polyuria and nocturia may be prominent clinical features, especially in nephropathy associated with nephrocalcinosis or potassium depletion. Hyperchloremic metabolic acidosis, with a decrease in plasma bicarbonate and a concomitant increase in plasma chloride, is common. Proteinuria is usually below 2 gm per day. Special mention should be made of the frequency of analgesic nephropathy, which is a frequently overlooked cause of unexplained chronic renal failure. The disease is especially common in middle-aged women with neurotic habits. Papillary necrosis is the predominant feature with either an acute presentation of pain, fever, and superimposed infection or a more chronic form discovered only on excretory urogram. The excretory urogram may be normal, however. Infection is present in approximately 40 percent of patients. Very often the diagnosis can be made only by finding on two or three occasions salicylate in urine (positive Phenistix) or acetaminophen in urine (measurement done by a drug assay laboratory). The history is often exceedingly difficult to obtain because the patient is reluctant to admit chronic drug abuse.

III. **Therapy.** The therapy of the various diseases manifested by pyuria is directed toward the cause. Renal infectious processes are discussed in Chapter 7. Renal stone disease is discussed in Chapter 6. In chronic interstitial nephritides special attention should be devoted to maintenance of an adequate extracellular fluid volume, since in some patients renal water and salt losses are an important part of the clinical picture. In the interstitial nephritides accompanied by hypertension (e.g., chronic urate nephropathy and nephrosclerosis), control of the blood pressure is essential.

Table 8-8. Causes of Pyuria

Cause	Clinical Clues	Confirmatory Laboratory Tests and Findings
Pyuria of renal origin		
Acute interstitial nephritis		
Bacterial—acute pyelonephritis	Fever, chills, flank pain	WBC casts, urine and blood cultures
Acute hypersensitivity nephritis	Hematuria frequent	Wright's stain of urine for eosinophils renal biopsy is most definitive
Chronic interstitial nephritis		
Chronic bacterial pyelonephritis	History of previous acute episodes	Excretory urogram (XU) reveals cortical scars, blunted calyces, and small kidneys
Analgesic abuse	Sterile pyuria (60%), middle-aged female	XU may reveal papillary necrosis (e.g., ring sign), positive Phenistix
Potassium depletion	Polydipsia, polyuria	Hypokalemia
Nephrocalcinosis	Polydipsia, polyuria	Hypercalcemia
Lead poisoning	Children, moonshine drinkers, professional history (battery workers)	Elevated uric acid, anemia, basophilic stippling of erythrocytes
Radiation nephritis	History of exposure	
Tuberculosis	History of exposure, positive PPD	XU, may reveal strictures of ureters and/or renal infundibulum, frequently associated hematuria
Nephrosclerosis	Long-standing high blood pressure	Anemia, XU reveals small kidneys bilaterally
Nephronophthisis (medullary cystic disease)	Family history, polyuria, nocturia, renal failure in second decade	
Pyuria originating from the excretory system		
Pyelitis associated with stone	Pain	XU reveals calculi, positive urine culture
Cystitis, acute	Frequency, urgency, pain	Positive urine culture
Urethritis		
Gonococcal	History of sexual contact	Positive urine culture
Nongonococcal	History of sexual contact	Negative urine culture

Suggested Reading

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9

The Patient With Acute Azotemia

Robert E. Cronin

A variety of disorders in both hospitalized and nonhospitalized patients may lead to acute azotemia. The term *azotemia* implies a retention in body fluids of nitrogenous wastes normally excreted by the kidney. However, the presence of azotemia does not necessarily imply a malfunctioning kidney. A healthy kidney in a person depleted of salt and water may quite appropriately reduce excretion of all solutes and fluids to maintain an adequate blood volume. Conversely, an obstructed or otherwise acutely injured kidney may result in acute azotemia in the absence of volume depletion. The following example may serve to illustrate the often complex circumstances that surround acute azotemia.

Example (Figure 9-1): A 41-year-old white man was admitted to the hospital on July 16, 1977, with leg pain. He had a history of severe bilateral atherosclerotic disease of the peripheral vasculature and 2 years earlier had undergone a left above-the-knee amputation. On this admission an arteriogram demonstrated complete occlusion of the aorta below the renal arteries. An unsuccessful revascularization procedure under general anesthesia was followed in 3 days by a right below-the-knee amputation. Several revisions of the stump were required over the next 2 months. Because of a persistent purulent drainage from the stump following the initial operation, parenteral and oral antibiotics were begun. Despite a combination of cephalothin and gentamicin, a fever of 100° to 103° F persisted. Seven weeks after admission a wound culture grew *Acinetobacter* resistant to gentamicin, ampicillin, and cephalothin, but sensitive to colistin and carbenicillin. The patient was begun on a 14-day course of colistin. On the ninth day of colistin therapy, nonoliguric acute renal failure was noted for the first time. Five weeks following discontinuation of all antibiotics, the patient's renal function returned to baseline values.

This patient, like many hospitalized patients, was exposed to a variety of insults capable of causing acute azotemia, including high-dose intravenous x-ray contrast, surgery, general anesthesia, gram-negative infection, and three potentially nephrotoxic antibiotics.

I. Clinical setting and characteristic features. An elevated blood urea nitrogen (BUN) and serum creatinine and a reduced urine volume are compatible with a variety of disturbances that may be of renal or nonrenal origin. The mere documentation of azotemia offers little guidance to the physician in choosing the proper diagnosis or therapy. Acute azotemia can usually be attributed to one of the causes described below.

A. Prerenal azotemia. Prerenal azotemia represents a decrease in glomerular filtration rate resulting from a decrease in renal perfusion pressure and/or intense renal vasoconstriction, such as ocurs with:

1. Volume depletion, secondary to:
   - **a.** Excessive diuresis
   - **b.** Hemorrhage
   - **c.** Gastrointestinal losses
   - **d.** Third space losses
     - **(1)** Burns
     - **(2)** Traumatized tissue
     - **(3)** Peritonitis
     - **(4)** Pancreatitis

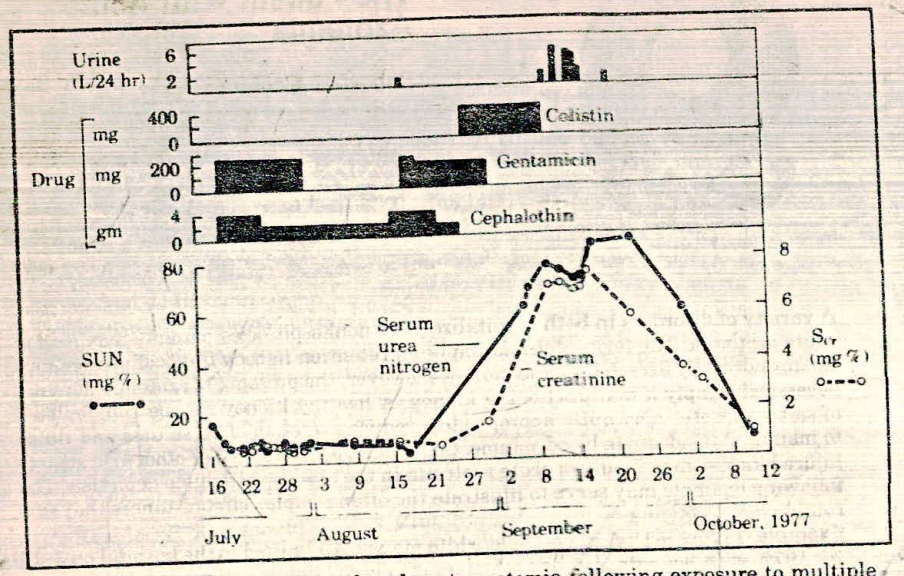

Fig. 9-1. A 41-year-old male developed acute azotemia following exposure to multiple operations, infections, and potentially nephrotoxic drugs.

2. Cardiac and vascular disorders
   - a. Congestive heart failure
   - b. Acute myocardial infarction
   - c. Pericardial effusion with tamponade
   - d. Acute pulmonary embolism
   - e. Renal artery emboli, thrombosis, or stenosis
3. Peripheral vasodilatation
   - a. Gram-negative sepsis
   - b. Antihypertensive medications
4. Increased renal vascular resistance
   - a. Surgery
   - b. Anesthesia
   - c. Hepatorenal syndrome
   - d. Prostaglandin inhibitors (aspirin, indomethacin, ibuprofen)

Many disturbances developing in both hospitalized and nonhospitalized patients may seriously alter extracellular fluid (ECF) volume. Thus volume depletion must always be excluded as a cause of prerenal azotemia. Prerenal azotemia accounts for the vast majority of patients with acute azotemia, and it must be considered in every patient in whom the diagnosis of acute azotemia is in doubt. Moreover, it often precedes and predisposes to the development of acute renal failure and as such is a risk factor for the more serious forms of acute azotemia. Since the causative factors for prerenal azotemia and acute renal failure overlap, distinguishing between these two disease states may become possible only by the outcome of therapy (e.g., if volume repletion or improved cardiac function rapidly reverses the azotemia, then prerenal azotemia was present).

B. Postrenal azotemia. The common causes of postrenal azotemia include:

1. Urethral obstruction
   - a. Urethral valves
   - b. Urethral strictures
2. Bladder neck obstruction
   - a. Prostatic hypertrophy
   - b. Prostatic and bladder carcinoma
   - c. Autonomic neuropathy or ganglionic blocking agents

3. Ureteral obstruction—bilateral
   - a. Intraureteral
     - (1) Stones
     - (2) Blood clots
     - (3) Pyogenic debris or sloughed papillae
     - (4) Edema following retrograde pyelography
   - b. Extraureteral
     - (1) Prostatic, bladder, or cervical cancer
     - (2) Retroperitoneal fibrosis
     - (3) Accidental ureteral ligation or trauma during pelvic surgery

The common denominator of acute azotemia in this set of disorders is obstruction to the flow of urine. The patient most at risk for acute postrenal azotemia is the elderly man in whom prostatic hypertrophy may lead to complete or partial obstruction to urine flow. Young boys with congenital urethral valves may also have acute obstruction. In women, complete urinary tract obstruction is relatively uncommon in the absence of pelvic surgery or pelvic malignancy. However, transient, unilateral, partial ureteral obstruction is not uncommon in the course of acute bacterial pyelonephritis (pyogenic debris) or fungal (fungal ball) urinary tract infection.

C. Acute renal failure. In contrast to the two preceding categories, the disorders listed here and in the next two sections represent primary renal disturbances. The course of acute azotemia in these situations cannot be changed by manipulating factors outside the kidney (e.g., volume repletion, improving cardiac function, correcting hypotension, removing obstruction). The term *acute tubular necrosis* (ATN) is often used interchangeably with the term *acute renal failure*. However, proximal tubular necrosis, although present in many of these cases, does not always occur in a patient who otherwise fits the description of acute renal failure.

1. **Ischemic disorders.** Ischemic disorders predisposing to the development of acute renal failure include:
   - a. Complications of surgery
   - b. Hemorrhage
   - c. Trauma
   - d. Rhabdomyolysis with myoglobinuria
   - e. Gram-negative sepsis
   - f. Postpartum hemorrhage
   - g. Pancreatitis

With the ischemic disorders, reduced blood flow to the kidneys results from either a decreased total blood volume or a redistribution of blood away from the kidney. It is seen most commonly following surgery and trauma. Rhabdomyolysis with myoglobinuria is being recognized with greater frequency and may account for many of the cases of acute renal failure previously classified as "etiology unknown."

2. **Nephrotoxic disorders.** Nephrotoxic disorders include those caused by:
   - a. Antibiotics
     - (1) Aminoglycosides
     - (2) Cephalosporins
     - (3) Colistin
   - b. Iodine-containing x-ray contrast
   - c. Heavy metals (arsenic, lead, cadmium, mercury, bismuth, uranium)
   - d. Organic solvents (carbon tetrachloride)
   - e. Ethylene glycol (antifreeze)
   - f. Anesthetics (methoxyflurane, enflurane)
   - g. Cyclosporin

In hospitalized patients nephrotoxins have become a major cause of acute renal failure. Antibiotics, particularly those of the aminoglycoside class, are the most important contributors. Even with careful dosing and measurement of blood levels, nephrotoxicity occurs in 15–25 percent of all patients treated with aminoglycosides. Intravenous x-ray contrast administration is also a major cause of acute renal failure, especially in patients with multiple myeloma and diabetes mellitus. The increased susceptibility of diabetic patients has been appreciated only during the

past 10 years. The factors that put these patients at risk appear to be preexisting renal insufficiency, volume depletion, hypertension, vascular disease, and proteinuria. It is also likely that administration of unrelated nephrotoxins may have an additive nephrotoxic effect on the kidney. For example, in experimental animals, aminoglycoside antibiotics are more nephrotoxic if given after the fluoride-containing anesthetic methoxyflurane. X-ray contrast media and aminoglycoside antibiotics may also have additive nephrotoxicities, since both agents are normally concentrated in proximal tubular cells.

D. Acute interstitial nephritis. The following therapeutic agents represent the primary causes of acute interstitial nephritis:

1. Antibiotics
   - **a.** Penicillins
   - **b.** Cephalosporins
   - **c.** Rifampin
   - **d.** Sulfonamides
2. Miscellaneous drugs
   - **a.** Diuretics (furosemide, thiazides, chlorthalidone)
   - **b.** Allopurinol
   - **c.** Phenytoin
   - **d.** Phenindione
   - **e.** Phenylbutazone
   - **f.** Nonsteroidal antiinflammatory drugs

Although any member of the penicillin group of drugs may cause such a reaction, methicillin is the agent most frequently described. In contrast to the proximal tubular necrosis seen commonly with acute renal failure, the primary histologic lesion of acute interstitial nephritis is marked edema of the interstitial space and a focal or diffuse infiltration of the renal interstitium with lymphocytes, macrophages, plasma cells, and polymorphonuclear leukocytes. Loss of renal function from drug hypersensitivity tends to be less abrupt and severe than with classic acute renal failure; nevertheless, dialysis therapy may be required. Recovery of renal function following withdrawal of the drug may be slow and incomplete.

E. Primary renal, systemic, and vascular diseases. Diseases in these categories associated with acute azotemia include:

1. Acute poststreptococcal glomerulonephritis
2. Rapidly progressive glomerulonephritis
3. Goodpasture's syndrome
4. Systemic lupus erythematosus
5. Subacute bacterial endocarditis
6. Necrotizing vasculitis
7. Malignant hypertension
8. Postpartum renal failure

When acute azotemia develops in association with these disorders, it often represents only one of many serious complications of an underlying disease. Moreover, histologically, the primary site of injury is the glomerulus or the vascular supply of the glomerulus, with the proximal tubule and the interstitial areas relatively uninvolved. Azotemia during the course of acute glomerulonephritis is rare, but the glomerular filtration rate is nearly always reduced. Anuric or severe oliguric acute renal failure complicating acute glomerulonephritis appears to be more frequent in adults. Characteristically, acute azotemia developing in the course of systemic vasculitis is an ominous sign, and recovery of renal function, if any, is often delayed and usually incomplete.

II. Differential diagnosis

A. Evaluation of the acutely azotemic patient. Whether the patient is seen for the first time in the office, in the emergency room, or in the hospital, careful tabulation and recording of data is the first step in diagnosis and treatment. Vital signs, daily weights, records of intake and output, past and current laboratory data, and the fluid and medication list should be recorded on a flow sheet and included in the patient's chart. In situations in which the patient has been hospitalized for several days or weeks with a complicated course before developing acute azotemia, a carefully prepared flow sheet may often be the only way to comprehend the problem and guide the way to proper therapy.

B. History. In evaluating a hospitalized patient with acute azotemia it is helpful to determine whether the azotemia developed outside or inside the hospital.

1. **Azotemia developed outside the hospital**
   - **a. Chronic systemic illness.** Azotemia first discovered in the office or emergency room may be chronic or acute in origin. A previous systemic disease (e.g., diabetes mellitus, hypertension, systemic lupus erythematosus) or a history of kidney disease (e.g., kidney infection, abnormal urinalysis on a previous physical examination) suggests that the azotemia may be chronic.
   - **b. Acute systemic illness.** Alternatively, an acute systemic illness (e.g., viral influenza, gastroenteritis) may lead to acute azotemia through a variety of mechanisms (e.g., volume depletion, rhabdomyolysis with myoglobinuria). Acute poststreptococcal glomerulonephritis is usually preceded by streptococcal pharyngitis or pyoderma. Pyoderma may occur in children and adults of any age and is characterized by vesicular lesions, usually on the extremities, which become pustular and then crust.
   - **c. Trauma.** Trauma as the cause of acute azotemia is usually apparent at the time of admission to the hospital, but the unconscious or comatose patient may harbor internal injuries, extensive muscle damage, or acute urinary retention that are not discovered initially.
   - **d. Obstructive uropathy.** Male patients with acute azotemia should be screened carefully for symptoms of prostatism.
   - **e. Adverse drug reaction.** Antiinflammatory compounds that work by inhibiting prostaglandin synthesis (e.g., aspirin, indomethacin, ibuprofen) cause prerenal azotemia by removing important intrarenal vasodilating prostaglandins. Steroids and tetracycline compounds cause an elevation of blood urea nitrogen, presumably through enhanced protein breakdown and urea production, but there is usually no effect on glomerular filtration rate, and thus in a strict sense this does not represent a renal disorder. Demeclocycline, however, may be nephrotoxic in the patient with liver disease. Diuretic agents with a structural similarity to sulfa compounds (thiazides, furosemide, chlorthalidone), antibiotics (penicillins, cephalosporins, rifampin), and a variety of miscellaneous drugs may cause a hypersensitivity reaction in the renal interstitium, leading to acute azotemia.
   - **f. Intoxication.** Accidental or intentional intoxication with heavy metal compounds, solvents, ethylene glycol, salicylates, or sedatives, especially in a patient presenting with disordered mentation, may explain an otherwise unexpected episode of acute azotemia.
2. **Azotemia developed inside the hospital.** When azotemia develops in the hospital setting, the list of possible causes narrows.
   - **a. Fluid and electrolyte depletion.** Fluid and electrolyte depletion usually results from a failure to appreciate and replace fluid losses (e.g., excessive diuresis, nasogastric suction, surgical drains, diarrhea) in patients who are too ill to control their own solute and water intake.
   - **b. Surgery and anesthesia.** Both surgery and anesthesia cause a vasoconstriction of the renal artery and release of antidiuretic hormone; both of these effects may persist for 12 to 24 hours into the postoperative period. As a result, reduced volumes of concentrated urine in the early postoperative period tend to be the rule rather than the exception. If postoperative infection or unexpectedly large wound or drain losses occur, negative fluid balance may supervene, leading to prerenal azotemia.
   - **c. Nephrotoxic drugs and diagnostic agents.** Although there seems to be little justification for continued use of methoxyflurane (Penthrane), an occasional case of acute renal failure from its use still occurs. Enflurane, a related agent, may also cause acute renal failure, but the risk seems to be much less. Prolonged administration of methoxyflurane (greater than 4 to 5 hours) or repeated administration appears to predispose to nephrotoxicity.

     Nephrotoxic drugs and diagnostic agents represent a major and serious

cause of acute azotemia. Since the kidney is the primary organ of excretion for many antibiotics and x-ray contrast agents, the renal tubular epithelium is exposed to very high concentrations and not infrequently sustains damage. Nonoliguric acute renal failure (greater than 500 ml of urine per day despite a rising BUN and serum creatinine) is characteristic of azotemia that develops following aminoglycoside nephrotoxicity. Frank azotemia secondary to aminoglycosides may develop for the first time after the drug has been discontinued; conversely, recovery of renal function following discontinuation of the nephrotoxic aminoglycoside is often delayed and may require weeks to months to be complete. In contrast, acute renal failure following intravenous or intraarterial administration of x-ray contrast agents is characteristically abrupt in onset and usually oliguric. Recovery tends to begin within 2 to 3 days. However, patients with advanced renal failure, particularly diabetic patients, may never recover function following x-ray contrast–induced acute renal failure and may require chronic hemodialysis therapy.

C. Physical examination. Since prerenal azotemia is the most common cause of acute azotemia, the adequacy of extracellular fluid volume must be carefully determined.

1. **Adequacy of effective blood volume.** Physical findings useful in assessing the status of the extracellular fluid compartment include:
   a. Body weight
   b. Postural blood pressure and pulse changes
   c. Skin turgor
   d. Mucous membrane moisture
   e. Intraocular pressure

   Reduced body weight, a fall in systolic blood pressure of greater than 10 mm Hg or a rise in pulse of greater than 10 bpm when assuming the upright posture, "tenting" of upper thorax skin when pinched with the fingers, dry mucous membranes, and reduced fullnes of the eyeballs on light palpation, all suggest a reduction in extracellular fluid volume. Prerenal azotemia may also develop in states in which extracellular fluid is expanded (e.g., cardiac failure, cirrhosis, nephrotic syndrome). Although the ECF may be expanded as judged by bedside criteria (e.g., elevated jugular venous pressure, pulmonary rales, ventricular gallop rhythm, ascites, peripheral edema), the effective blood volume, or that portion within the arterial circulation, may be decreased, thus leading to prerenal azotemia.
2. **Urinary tract obstruction.** The physical examination is also important in diagnosing postrenal azotemia, especially in the unconscious patient or in the confused patient in whom otherwise unexplainable agitation may be the only clue to acute urinary retention. Careful abdominal examination may uncover a distended, tender bladder or bilaterally hydronephrotic kidneys. A digital examination of the prostate should be performed routinely in any azotemic male patient, and pelvic masses should be sought in female patients through a bimanual pelvic examination. In any patient in whom lower tract obstruction is suspected as the cause of acute azotemia, a sterile "in-and-out" diagnostic postvoid bladder catheterization should be performed as a routine part of the physical examination. The urine volume should be recorded and the specimen saved for the studies described in section **II.D.1.a.**
3. **Hypersensitivity reaction.** Physical findings with acute drug-induced interstitial nephritis may be lacking, although fever and a maculopapular or petechial skin eruption may occur with any of the agents, particularly the penicillin derivatives and allopurinol. Ordinarily, however, laboratory findings are more helpful in making this diagnosis.
4. **Toxins or muscle damage.** The physical abnormalities in these forms of acute renal failure may vary from none to many, depending on the circumstances. When the cause is unclear, particular attention should be directed toward uncovering evidence of intoxication (e.g., altered mental status, odors on the breath or clothing) and muscle tenderness or edema.

5. **Systemic diseases.** The physical examination in primary renal, systemic, and vascular disorders is variable and is usually remarkable for the absence of gross urinary tract findings, but the mucous membranes, eyes, joints, and skin often demonstrate abnormalities.

D. Testing procedures

1. **Laboratory studies.** Although physical findings are the best guide to the adequacy of the extracellular fluid volume, several laboratory tests point to the presence of prerenal azotemia.
   a. **Urinary diagnostic indices.** With prerenal azotemia the specific gravity of the first voided urine is often high (greater than 1.020), whereas patients with postrenal failure and acute renal failure tend to have a urinary specific gravity similar to that of plasma (approximately 1.010). The ratio of BUN to serum creatinine in health and in established acute or chronic renal failure is ordinarily 10 : 1. In the presence of prerenal azotemia, this ratio tends to rise, reaching levels as high as 60 : 1. The first specimen of urine obtained from a patient with newly discovered acute azotemia may be particularly helpful in differentiating prerenal azotemia from other causes of renal failure (Table 9-1). The first voided or catheterized specimen of urine of such a patient should be analyzed for the concentrations of sodium, creatinine, and urea nitrogen, and for osmolality. Determination of the various ratios and indices listed in Table 9-1 may help differentiate between prerenal and acute renal failure. Intermediate values may occur in patients with postrenal failure or in those in transition from prerenal to acute renal failure. Values with postrenal failure can also mimic exactly those in acute renal failure. However, it is important to bear in mind that previous use of a potent diuretic agent (furosemide or mannitol) in an attempt to prevent or reverse acute renal failure may totally invalidate the use of these diagnostic indices for up to 24 hours. Acute renal failure occurring after x-ray contrast may be associated with a low urinary sodium concentration (<10 mEq/L), and thus represents an exception to these guidelines. When time is a critical factor in determining the cause of acute azotemia, or not all the tests are immediately available, prerenal azotemia may be suspected strongly if the urinary specific gravity is greater than 1.016, the urinary sodium concentration is less than 20 mEq per liter, and the BUN to creatinine ratio is greater than 20 : 1.
   b. **Examination of urinary sediment.** Examination of the urinary sediment may also be helpful. Hyaline casts in large numbers may be seen in prerenal azotemia, whereas granular casts, white cells, and tubular cells are char-

Table 9-1. Urinary Diagnostic Indices

Index	Prerenal Azotemia	Oliguric ARF
Urine sodium (U_{Na}), mEq/L	<20	>40
Urine osmolality, mOsm/kg H_2O	>500	<350
Urine to plasma urea nitrogen	>8	<3
Urine (U_{Cr}) to Plasma (P_{Cr}) creatinine	>40	<20
Renal failure index $RFI = \frac{U_{Na}}{U_{Cr}/P_{Cr}}$	<1	>1
Fractional excretion of filtered sodium $FE_{Na} = \frac{U_{Na} \cdot P_{Cr} \times 100}{P_{Na} \cdot U_{Cr}}$	<1	>1

ARF = acute renal failure.

acteristic of acute renal failure. Red cells and red cell casts suggest acute glomerulonephritis or vasculitis. Heavy oxalate (envelope-shaped) or hippurate (needle-shaped) crystalluria may be seen with ethylene glycol ingestion. Trace to 1+ proteinuria on dipstick of the urine may be compatible with prerenal azotemia or acute renal failure, but higher grades of proteinuria suggest acute interstitial nephritis or glomerulonephritis.

Rhabdomyolysis should be suspected when acute azotemia is associated with frank muscle injury, a prolonged period of unconsciousness, alcohol or drug abuse, seizures, Parkinson's disease, hypokalemia, hypophosphatemia, or heat stress. Since the urinary dipstick does not distinguish between hemoglobin and myoglobin, a strong presumptive diagnosis of rhabdomyolysis with myoglobinuria can be made by demonstrating hemepositive urine in the absence of red cells or on the supernatant of the urine, an elevated creatinine phosphokinase (CPK) and aldolase in the serum, and a normal color to the serum (i.e., absence of hemolysis).

In instances of acute drug-induced interstitial nephritis (e.g., after methicillin), fever, maculopapular skin rash, 10 to 60 percent eosinophilia in peripheral blood, proteinuria, and urinary sediment abnormalities (gross or microscopic hematuria, pyuria, eosinophiluria, and casts) are common. A Wright's stain preparation on a freshly voided and sedimented urine specimen may demonstrate that eosinophils account for 33 percent of the urinary white cells. The urinary sediment is air-dried on a slide and Wright's stain is applied for 1 minute, followed by Wright's buffer for 2 minutes. The specimen is then observed under the microscope using an oil immersion objective lens. Eosinophils in the urine appear as granulated binucleated cells. Because of varying urinary pH, the granules may or may not take up the eosin.

If with these laboratory tests the cause of acute azotemia is still in doubt, a blood screen for toxic chemicals and drugs may be warranted.

2. **Radiographic studies**
   a. **Plain film of abdomen.** Several radiographic procedures to assess acute azotemia are available, the simplest of which is the plain film of the abdomen. Often this procedure can document the size of the kidneys, thus giving information regarding the duration of the azotemia (e.g., small kidneys suggest chronic renal disease, and normal or large kidneys suggest an acute process).
   b. **Excretory urography.** Excretory urography may give additional information regarding renal anatomy, chronicity of the disease, and presence of urinary tract obstruction. However, a combination of the noninvasive procedures described below often give equally valid information without the risk inherent in contrast administration.
   c. **Renal angiography and renal scan.** Patients with a history of hypertension, type IV hyperlipidemia, or atherosclerotic disease of the large vessels and/or renal artery, because of cholesterol emboli, may experience chronic prerenal azotemia or acute oliguria and azotemia may develop, sometimes associated with flank pain and hematuria. Also, renal embolization of a mural thrombus following a myocardial infarction may lead to acute azotemia; however, such an event may be overshadowed in importance by a concomitant, devastating central nervous system embolic stroke. When acute oliguria develops as a consequence of acute renal embolization, renal angiography is usually warranted, since acute surgical intervention in selected cases may restore renal function. In less critical situations a renal scan is often useful in determining whether renal blood flow to one or both kidneys is impaired.
3. **Renal ultrasonography.** This procedure may be useful in assessing kidney and bladder size. Also, a normal renal pelvis and calyceal system on ultrasonography virtually excludes important urinary tract obstruction. Thus, a combination of flat abdominal film, renal scanning, and renal ultrasonography in most instances of acute azotemia can supply as much pertinent information as excretory urography at virtually no risk to the patient.
4. **Urologic studies.** In instances of acute azotemia with a high suspicion of urinary tract obstruction (e.g., calculi, pyogenic debris, blood clots), cystoscopy and retrograde pyelography should be performed, even if ultrasonography is negative for obstruction. Ureteral calculi extraction or placement of ureteral catheters or stints may relieve the obstruction and allow urinary drainage. It is particularly important to consider this diagnostic course in patients with superimposition of acute azotemia on a background of chronic stable azotemia.
5. **Renal biopsy.** In patients in whom the cause of acute azotemia is unknown and a systemic disease (e.g., vasculitis) or acute interstitial nephritis is suspected but not proved, percutaneous or open renal biopsy may be warranted. A renal biopsy in such circumstances may form the basis and justification for aggressive therapy (e.g., high-dose steroids, cytotoxic agents, plasmapheresis). In patients in whom the oliguric phase of acute renal failure extends beyond 4 to 5 weeks, a renal biopsy may be warranted to determine whether another, less favorable diagnosis, such as cortical necrosis, should be entertained.

III. Treatment

A. Prerenal azotemia

1. Correction of underlying disorder

a. **Pure volume depletion.** When prerenal azotemia is due to deficits in extracellular fluid volume, therapy is geared to restoring fluids to the body similar to those lost. In gastrointestinal and other types of acute hemorrhage packed red cells in saline are indicated. When blood has not been lost from the body, but plasma moves out of the intravascular compartment to a third space (e.g., crush injury with extensive edema formation in devitalized muscle, burns), isotonic saline approximates extracellular fluid tonicity and will restore blood volume and blood pressure. Gastrointestinal fluid losses vary widely in electrolyte content and tonicity, and laboratory analysis for sodium, potassium, and chloride concentrations is the most precise way to determine the type of replacement fluid. Ordinarily, gastric juices will require replacement liter for liter with one-quarter to one-half normal saline containing 10 to 20 mEq per liter of potassium chloride. Pancreatic, biliary, and small bowel losses will require replacement with isotonic saline. Diarrheal losses can be restored with 5% dextrose and water to which has been added one ampule of 7.5% sodium bicarbonate (45 mEq sodium bicarbonate) plus 20 to 30 mEq of potassium chloride.

b. **Ineffective arterial blood volume with edema.** Prerenal azotemia occurring in this setting usually represents a secondary problem overshadowed by a primary cardiac, hepatic, or renal disease.

(1) **Cardiac failure.** In cardiac failure, diuretic agents in combination with digitalis therapy may increase the cardiac output and improve renal perfusion, and thus lessen the azotemia. Vasodilator drugs, such as hydralazine, may also improve cardiac function. However, with advanced heart failure refractory or only partially responsive to these agents, the physician may be forced to accept mild-to-moderate prerenal azotemia as a trade-off. Such azotemia rarely leads to acute renal failure or symptomatic uremia.

(2) **Hepatic disease.** Prerenal azotemia associated with advanced hepatic cirrhosis, with or without the hepatorenal syndrome, is often refractory to attempts to improve intravascular volume. However, despite the presence of peripheral edema and ascites, some of these patients may improve renal function and renal excretion in response to a saline challenge. Ordinarily, however, such patients are best treated with sodium-restricted diet (1 to 2 gm salt), modest water restriction (1500 to 2000 ml per day), and an aldosterone antagonist (spironolactone 50 mg four times daily), while the usually mild prerenal state is ignored. A potent diuretic agent such as furosemide (40 to 80 mg twice daily)

is sometimes successful in causing a diuresis and improving renal function, but this therapy carries the risk of precipitating severe hypokalemia, increased ECF volume contraction, hepatic coma, or the hepatorenal syndrome. Paracentesis and reinfusion of the ascitic fluid into a peripheral vein may temporarily increase intravascular volume and improve urine flow, but these benefits are of such short duration that this cumbersome therapy is of little long-term practical value. Moreover, infection and disseminated intravascular coagulation are definite risks. For selected, compliant patients with intractable symptomatic ascites who have relatively good liver function, a peritoneovenous shunt (LeVeen shunt) may reduce ascites and improve renal function (see Chap. 1). Major complications of the peritoneovenous shunt are infections, disseminated intravascular coagulation, pulmonary edema, and variceal bleeding.

(3) **Nephrotic syndrome.** Prerenal azotemia often occurs with nephrotic syndrome from any cause, particularly when it is accompanied by severe hypoalbuminemia (serum albumin less than 2.5 gm/L) and heavy proteinuria (10 to 20 gm/day). As in the other states of prerenal azotemia associated with an expanded ECF but reduced effective arterial blood volume, success in reversing the prerenal state depends on correcting the primary disease state. Idiopathic nephrotic syndrome, especially in children, usually responds to short-term, high-dose prednisone (1 to 2 mg/kg/day), but steroid resistance or frequent relapse may require the addition of cyclophosphamide (1 to 3 mg/kg/day). When nephrotic syndrome occurs as a complication of a primary renal disease (e.g., membranous nephropathy) or as a complication of a systemic disease (e.g., diabetic nephropathy), the level of proteinuria and thus the level of prerenal azotemia may wax and wane spontaneously, and no drug therapy has been found to be especially useful in altering this pattern. However, a recent multicenter cooperative study shows that patients with membranous nephropathy treated with an 8-week course of prednisone (100 to 150 mg every other day) with subsequent tapering of the dosage over 2 months appear to have better long-term renal function than untreated controls.

2. **Monitoring therapy.** In most instances of prerenal azotemia secondary to volume depletion, the volume of fluid required to replace the deficit can be estimated from actual quantitation of fluid or blood losses or from changes in body weight. A useful rule is to replace no more than one-half to two-thirds of the total calculated deficit in the first 24 hours, especially in elderly patients or in patients with a compromised cardiovascular system. The simplest way to follow the patient's response to replacement therapy is by bedside evaluation, with frequent monitoring of orthostatic changes in blood pressure and pulse. The jugular venous pulsation is a gross indicator of pressure in the central venous area of the right heart. In a normovolemic patient, jugular venous pulsations are visible when the patient is supine, but disappear when the patient assumes the sitting position. Jugular venous pulsations are not visible in the volume-depleted patient; thus, their reappearance following fluid administration suggests that the central venous pressure has returned to normal. The heart and lungs should also be monitored regularly. The presence of basilar rales or a third heart sound implies too vigorous fluid replacement, with resultant cardiopulmonary congestion.

In patients in whom vigorous resuscitation efforts are required and there is doubt regarding cardiovascular tolerance to sudden fluid challenges, some form of indwelling monitoring system is desirable.

a. **Central venous catheter.** In most instances in which rapid fluid administration is required and severe heart and or lung disease is absent, a catheter positioned in the central venous area of the right heart is a satisfactory guide to the speed of fluid administration. Long polyethylene catheters are placed in the antecubital vein and advanced into the central venous area. A shorter polyethylene catheter may be placed in the central venous area via the subclavian vein, but this procedure presents more risks (pneumothorax, hemothorax, air embolism). Fluctuation of the pressure with respiration suggests successful placement of the catheter in the area of the right atrium, but the exact location of the catheter should be ascertained with an x-ray of the chest. This precaution will also serve to detect those instances in which catheter placement has caused pneumothorax. The central venous pressure (CVP) normally ranges between 2 and 12 cm of water. In volume-depleted states, values of zero or below can be expected. Before vigorous volume repletion is begun, a fluid challenge of 200 to 300 ml of normal saline should be attempted over a 10- to 20-minute period. In an otherwise uncomplicated volume-depleted patient, this amount of saline will have little effect on the CVP reading. A CVP rise greater than 5 cm of water suggests cardiac failure, and the infusion should be immediately discontinued. Venous thrombophlebitis, a major late complication of central venous catheterization, can be avoided in large part by removing the central line after resuscitation is complete or after a maximum of 36 hours.

b. **Balloon-tipped catheter.** When a volume deficit must be repaired in the presence of tricuspid stenosis, acute or chronic pulmonary disease, or an unstable cardiovascular system, the central venous pressure does not give a reliable index of left ventricular performance. In this situation, a balloon-tipped catheter (Swan-Ganz) can be wedged in a pulmonary artery. This gives an indirect measurement of left ventricular end-diastolic pressure and thus is a better guide to the adequacy and speed of fluid replacement. Because of the complications of infection, pulmonary infarction, and hemopneumothorax, this device should be inserted and placed only by trained professionals.

B. **Acute renal failure**

1. **Diagnostic and therapeutic use of diuretic agents.** Osmotic diuresis with mannitol and, in more recent years, the potent loop diuretics (furosemide and ethacrynic acid) has been used almost routinely to prevent or reduce the severity of acute renal failure (Table 9-2). However, no human studies clearly document that this therapy is effective. Available evidence suggests that these agents are effective only if given early in the initiation phase of acute renal failure (e.g., immediately after a mismatched blood transfusion or crush injury with rhabdomyolysis). There are no data to support their use in established acute renal failure.

In patients in whom volume deficits have been repaired with isotonic saline or its equivalent and oliguria persists, 50 ml of 25% mannitol (12.5 gm) is generally given and repeated after 30 minutes if a diuresis of 40 ml per hour does not ensue. If a diuresis does not occur, no more mannitol should be given since the hypertonic mannitol will increase the plasma volume and may precipitate pulmonary congestion. If a diuresis occurs, it should be sustained with repeated boluses of mannitol or an infusion of 5% mannitol until the patient

Table 9-2. Diuretic Agents in Acute Renal Failure

Rationale for use
Convert oliguric to nonoliguric acute renal failure
Prevent acute renal failure (unproven)
Dosages
Mannitol
Initial 12.5 gm (50 ml of 25% solution)
Repeat 12.5 gm
Maintain with 5% mannitol solution
Furosemide intravenous bolus 80–400 mg

can maintain an adequate urine flow spontaneously. If mannitol fails to produce a diuresis, furosemide may be used. Furosemide has the advantage of not causing volume expansion. It is given intravenously in a dose of 80 to 400 mg. Doses higher than this are rarely effective and add the risk of ototoxicity. The chance of having a satisfactory diuretic response is small if (a) acute renal failure is more than 36 hours old, (b) the 24-hour urine output is less than 200 ml per day, and (c) the serum creatinine is greater than 5 to 6 mg per deciliter.

2. **Fluid therapy**
   a. **Oliguric acute renal failure (ARF).** The use of dialysis therapy for oliguric ARF may permit fluid intakes of 1.5 to 2 liters per day, depending on the status of the cardiovascular system. If hemodialysis or peritoneal dialysis is not immediately available, fluid balance usually can be maintained by replacing insensible losses (400 to 600 ml/day) with 10% dextrose in water and measured losses (e.g., urine, gastric drainage, diarrhea) liter for liter with 0.45% saline. If the plasma bicarbonate level falls below 20 mEq per liter, one or two ampules of 7.5% sodium bicarbonate (45 mEq of bicarbonate per ampule) should replace an equivalent quantity of sodium chloride in these fluids. The best monitor of adequacy of fluid therapy is an estimate of the ECF volume status and daily weights. A serum sodium determination every other day is helpful in deciding whether water intake is appropriate to solute intake (hyponatremia indicates excessive water intake and hypernatremia indicates too little water intake). Since hypokalemia is rarely a problem with ARF, and because of the danger of cardiac arrhythmias from hyperkalemia, potassium chloride is not added to intravenous fluids.
   b. **Nonoliguric ARF.** In general, nonoliguric ARF represents a milder renal injury and requires dialysis less frequently. As a result, fluid management tends to be easier. These patients ordinarily should receive a volume of water per day that equals their urine output plus insensible losses. The salt content of their diets should be approximately equal to what is excreted in the urine and lost in other measurable bodily fluids.
3. **Parenteral hyperalimentation.** This form of therapy may be effective in decreasing mortality in ARF occurring in hypercatabolic surgical and trauma patients, especially when complications have developed. The so-called renal failure fluids consist of 50% dextrose as the source of carbohydrates and essential l-amino acids as the nitrogen source. When ARF occurs in the absence of the hypercatabolic state, parenteral hyperalimentation is not recommended.
4. **Dialysis therapy.** Indications for dialysis therapy are as follows:
   a. Absolute indications
      (1) Central nervous system dysfunction
         (a) Asterixis
         (b) Neuromuscular irritability
         (c) Somnolence
         (d) Coma
         (e) Seizures
      (2) Gastrointestinal complications
         (a) Nausea and vomiting
         (b) Hemorrhage
      (3) Pericarditis
   b. Relative indications
      (1) Cardiovascular complications
         (a) Pulmonary edema
         (b) Hypertension
         (c) Arrhythmias
      (2) Metabolic complications
         (a) Hyperkalemia
         (b) Hyperuricemia
         (c) Hyponatremia (< 125 mEq/L or symptomatic)

It is now generally accepted that in the patient with acute renal failure, dialysis therapy should be used as often as necessary to maintain the BUN below 100 mg per deciliter. Dialysis should also be used to prevent symptoms of uremia (irritability, insomnia, failure to concentrate, anorexia, vomiting). Thus, if a 65-year-old patient has uremic symptoms with a BUN of 70 mg per deciliter, dialysis should be begun. In severely catabolic patients (e.g., crush injury, burns) daily dialysis may be required. The type of dialysis therapy for a particular patient—hemodialysis versus peritoneal dialysis—depends on the clinical situation. Patients with severe tissue breakdown (e.g., rhabdomyolysis, trauma, burns, sepsis, postoperative) have enhanced urea production and usually require hemodialysis. Hemodialysis may also be indicated in methanol or ethylene glycol poisoning to remove the toxin and control the accompanying metabolic acidosis. In other types of ARF in which the catabolic component is less prominent, such as when renal failure occurs secondary to antibiotics or x-ray contrast, peritoneal dialysis may be adequate. However, these patients often can be managed successfully without dialysis, using the conservative measures described above.

C. **Postrenal failure.** In large part, the therapy of urinary tract obstruction is surgical and requires early urologic consultation. Foley catheter drainage is usually successful for acute obstruction secondary to prostatic hypertrophy and may be followed in several weeks by prostatic resection. With ureteral obstruction, cystoscopy and placement of ureteral drainage catheters may allow passage of obstructing stones, sludge, or pus, but if this fails operative intervention will be required.

D. **Acute interstitial nephritis.** When a therapeutic agent is identified as the cause of acute interstitial nephritis, removal of the agent is the obvious first step in therapy. When renal impairment is minor, nothing more need be done. In more severe cases, high-dose, short-term prednisone therapy (60 mg/day for 1 to 2 weeks) may speed recovery of renal function and normalize urinary sediment. The extent

Table 9-3. Therapy of Acute Azotemia in Primary Renal, Systemic, and Vascular Diseases

Disease	Therapy
Acute poststreptococcal glomerulonephritis	No specific therapy
Rapidly progressive glomerulonephritis and Goodpasture's syndrome	Pulse methylprednisolone 1 gm IV over 20 minutes for 3 days and/or prednisone 1–2 mg/kg/day
	Cyclophosphamide 1–3 mg/kg/day
	Plasmapheresis 4 L/day for 1–3 weeks
Systemic lupus erythematosus	Prednisone 1–2 mg/kg/day
	Cyclophosphamide 1–3 mg/kg/day
Subacute bacterial endocarditis	Antibiotics
Necrotizing vasculitis	
Large vessel polyarteritis	Prednisone 1–2 mg/kg/day and/or cyclophosphamide 1–3 mg/kg/day
Small vessel polyarteritis (leukocytoclastic vasculitis, hypersensitivity vasculitis)	Prednisone 1–2 mg/kg/day and/or cyclophosphamide 1–3 mg/kg/day
Henoch-Schönlein purpura	No specific therapy
Wegener's granulomatosis	Cyclophosphamide 1–3 mg/kg/day
Malignant hypertension	Antihypertensives
	Dialysis, if required
Postpartum ARF	No specific therapy

ARF = acute renal failure.

and severity of the nonrenal manifestations (e.g., fever, dermal eruption) will also be a consideration in the decision to use corticosteroids.

E. **Primary renal disease, systemic diseases, and vascular diseases.** There is no particularly effective therapy for acute glomerulonephritis, including prolonged bed rest or immunosuppressives. Prophylactic antibiotics to prevent future attacks are not recommended. When renal failure develops in the course of a systemic or vascular disorder, it is usually a grave sign. However, experience with several of these disorders suggests that aggressive therapy may be warranted and considerable recovery of renal function may occur in some patients. A comprehensive discussion of the treatment of these systemic and vascular disorders is beyond the scope of this chapter, but Table 9-3 outlines the diseases and usually recommended therapies. Management of such patients is often multidisciplinary and includes the joint participation of a rheumatologist or immunologist and a nephrologist. In all of these disorders, the drugs and their dosages represent usual starting therapy. Certain patients may require higher doses, some will require less. Response to therapy usually dictates how long high-dose therapy should be continued and how rapidly the drugs should be tapered. Ordinarily, a positive response to therapy will be apparent within 3 to 4 weeks. Although there is not complete agreement in the medical community regarding the usefulness of each of these agents or protocols, the poor prognosis and relentless, progressive nature of these diseases when untreated usually dictate a trial with some form of aggressive treatment. At present, cytotoxic agents, particularly cyclophosphamide, are gaining favor as a primary drug in necrotizing vasculitis; and in Wegener's granulomatosis, cyclophosphamide is the agent of choice.

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10 The Patient With Chronic Azotemia, With Emphasis on Chronic Renal Failure

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Azotemia literally means an increase in the concentration of nitrogenous compounds in the blood. These include proteins, peptides, amino acids, creatinine, urea, uric acid, and ammonia. In common usage, however, the term *chronic azotemia* implies prolonged (months to years) retention of waste products of protein metabolism that would normally be excreted in the urine, particularly urea and creatinine. Thus, the term may be used simply as a synonym for chronic renal insufficiency or it may be used to imply an abnormal concentration of urea in the blood without an equivalent elevation of serum creatinine. The latter circumstance obtains when there is an inordinate generation of urea, as in patients with massive protein intake or significant catabolism, or when there is inordinate renal tubular reabsorption of urea, as in partial urinary tract obstruction or in cardiac failure. Severe azotemia (blood urea nitrogen concentration above 50 to 75 mg/dl) rarely occurs without retention of creatinine as well as urea, and is due to either renal failure or obstructive uropathy.

1. **Clinical setting**
   A. **Causes of chronic azotemia.** The causes of chronic azotemia are chronic renal failure, obstructive uropathy, cardiac failure, massive protein intake, and catabolic states.
      1. **Chronic renal failure.** The common causes of chronic renal failure (Table 10-1) in both children and adults are glomerulonephritis (including hereditary nephritis), polycystic kidney disease, and interstitial nephritis (including pyelonephritis). In adults additional common causes are diabetes and hypertension (nephrosclerosis). In children additional common causes are renal hypoplasia, obstruction, and a variety of hereditary disorders, each of which is itself uncommon or even rare, such as medullary cystic disease, cystinosis, and oxalosis. Some infrequent causes of severe renal failure are amyloidosis, sickle cell anemia, tuberculosis, hemolytic uremic syndrome, and renal artery or vein occlusion; there are many others.
      2. **Obstructive uropathy.** Urinary tract obstruction is common, particularly at the extremes of life. A variety of congenital obstructive disorders (frequently with associated vesicoureteral reflux) occur in infants and young children and, unfortunately, often result in chronic azotemia, because either the diagnosis of obstruction is not made for a long period of time or there are complications (surgical or infectious). Renal damage may result from prolonged unrelieved obstruction, recurrent (or even aggravated) obstruction following surgery, or complicating infection. Obstructive nephropathy (i.e., obstruction resulting in severe renal dysfunction) may progress over a period of months to years to end-stage renal disease (ESRD) in children and occasionally in adults. At the other extreme of life, the commonest obstructive nephropathy in the aged is that due to benign prostatic hypertrophy. Fortunately, surgery for this disorder is usually successful and sustained renal failure is rare, even in patients with chronic infection. There are, of course, several other causes of obstruction in both children and adults (such as urinary stones, tumors, surgical misadventure, and retroperitoneal fibrosis or tumor), and the prognosis of these disorders is variable.
      3. **Cardiac failure.** Cardiac failure causes edema (which is of paramount importance) and also azotemia (which is usually mild and thus relatively unim-

Table 10-1. Relative Frequency of Causes of Chronic Renal Failure in Adults and Children

Cause	Adults	Children
Glomerulonephritis	3+	4+
Polycystic kidney disease	2+	1+
Interstitial nephritis	2+	2+
Diabetes	4+	Rare
Hypertension (nephrosclerosis)	2+	Rare
Obstructive uropathy	1+	3+
Renal hypoplasia	Rare	2+
Hereditary disorders*	Rare	1+

*Excludes Alport's syndrome (hereditary nephritis with nerve deafness), which is included in the glomerulonephritis category, and polycystic disease, both of which are listed above.

portant, except that its cause must be distinguished from other causes of azotemia). To the extent that edema is associated with a decrease in glomerular filtration rate, there is a proportionate rise in blood urea nitrogen (BUN) and serum creatinine. Salt and water retention in congestive heart failure may also be due to secondary aldosteronism and increased fractional proximal renal tubular reabsorption of salt and water, and these disturbances may account for sufficiently slow flow of filtrate down the nephron that there is enhanced renal tubular reabsorption of urea as well. This presumably accounts for the disproportionate rise of BUN compared with serum creatinine in most patients with heart failure such that many patients with chronic congestive failure have a BUN in the range of 30 to 60 mg per deciliter but a serum creatinine concentration usually less than 2.5 mg per deciliter and not infrequently within the normal range.

4. **Massive protein intake.** Dietary protein is an uncommon cause of azotemia in an otherwise healthy person. When protein intake is massive there may be a rise in BUN without a proportionate rise in serum creatinine, but the rise in BUN is relatively mild. This phenomenon is seen in obese persons with extreme dietary restriction of carbohydrate and fat, but either no restriction or, more commonly, supplementation of protein intake. Occasionally the phenomenon is seen in persons who are not restricting calories, carbohydrate, and fat but are simply ingesting inordinate amounts of protein. More common than these voluntary causes of chronic azotemia are iatrogenic causes of acute azotemia. One iatrogenic cause of azotemia is parenteral hyperalimentation (the intravenous infusion of amino acids as well as carbohydrate in a patient unable to assimilate them from the gastrointestinal tract), and this results in a disproportionate rise in BUN, particularly in patients who already have renal insufficiency. Another iatrogenic cause of azotemia (in which BUN may be disproportionately elevated to creatinine) is the use of high-protein tube feedings in a patient who is comatose or otherwise unable to communicate thirst and who is given insufficient water and solute to offset the urea diuresis that occurs from administration of inordinate amounts of protein. These iatrogenic disorders are usually of short duration and, except in very unusual circumstances, do not result in chronic azotemia.
5. **Catabolic states.** Catabolism (with increased endogenous protein breakdown) is a more frequent cause of azotemia than is increased protein intake. Most catabolic states, however, are not of sufficiently long duration to cause chronic azotemia, although in exceptional circumstances they may. The increased urea generation due to catabolism may result from an underlying illness or from the administration of a catabolic drug such as tetracyline or adrenal corticosteroids.

B. Presentation of the patient with chronic azotemia. Most patients with chronic azotemia (except when due to heart failure) are asymptomatic. A patient may nevertheless know of his or her chronic azotemia from previous evaluation and may present with a request for additional evaluation or management. Other patients may present with unrelated intercurrent illness or for routine periodic examination, and their azotemia may be discovered by chance, a circumstance increasingly common because of the use of screening panels of laboratory tests. The minority of patients with chronic azotemia present because they have symptoms of uremia, and even then the presentation may be nonspecific (e.g., failure to grow in children, failure to thrive in children or adults) or even misleading (e.g., profound anemia). Whatever the presentation, additional evaluation is in order.

II. Clinical features

A. Obstructive uropathy. The clinical features of obstruction of the urinary tract depend on the cause of the obstruction, the level of the urinary tract obstructed (and whether it affects one or both kidneys), the rate and degree of obstruction, and the existence of complications.

1. **Features related to the cause of the obstruction.** If obstruction is due to a renal tumor, the patient may have local symptoms such as pain, mass, or hematuria, or systemic symptoms such as fever and anemia. If obstruction is due to stones, the patient may have a family or personal history of stones or renal colic, hematuria, complicating or causative infection, or manifestations of other causative disorders such as hyperparathyroidism, gout, or renal tubular acidosis. If obstruction is due to retroperitoneal fibrosis, it may be occult, as in idiopathic cases, or there may be a history of headache and methysergide use, or there may be manifestations of a causative lymphoma. If obstruction is due to pelvic surgery (with inadvertent ligation of a ureter) or pelvic irradiation for tumor, these historical features are obvious. If the cause of obstruction is intrarenal uric acid deposition, there is often a history of neoplasia that may have been treated with radiation or chemotherapy.
2. **Features related to the level of obstruction.** Obstruction at the bladder neck is commonly accompanied by symptoms of bladder dysfunction (such as hesitancy, intermittency, sensation of incomplete emptying, and nocturia) and, occasionally, by complicating urinary infection. Higher levels of obstruction, particularly when chronic, are often asymptomatic, although there may be pain and/or a palpable mass.
3. **Features related to unilateral versus bilateral obstruction.** Complete bilateral obstruction (or unilateral obstruction in a patient with a solitary kidney) of course produces anuria. Unilateral obstruction in a patient with two kidneys, however, is often silent unless the rate of obstruction is sufficient to produce pain or severe enough to produce a hydronephrotic mass, or the obstruction is complicated by infection, which may cause bacteremia.
4. **Features related to the rate and degree of obstruction.** Pain is much more common when obstruction occurs suddenly than when it occurs slowly; thus, pain is not a usual manifestation of chronic obstruction. Complete obstruction causes anuria, but partial obstruction may also cause abnormalities of urinary volume. Renal tubular dysfunction from partial obstruction may result in polyuria. Varying degrees of partial obstruction may cause a fluctuating urine volume, a nearly diagnostic sign.
5. **Features related to complications of obstruction.** Infection is probably the most common complication and may occur spontaneously or after diagnostic or therapeutic manipulation. Hypertension and polycythemia are less common manifestations of obstruction but may be striking in individual patients. Uremia (i.e., symptomatic renal failure) is the ultimate manifestation of obstruction and may occur with severe and prolonged partial obstruction as well as with complete obstruction.

B. Clinical features of chronic renal insufficiency

1. **History of patients with chronic renal insufficiency.** The constellation of symptoms that eventually develops in patients with severe renal insufficiency is called *uremia* (Table 10-2). Initially the symptoms are subtle, and their onset may be so insidious that the patient is aware of them only in retrospect. Most patients have generalized symptoms such as fatigue (particularly late in the day), weakness, malaise, and a feeling of being cold. Symptoms derive from malfunction of most organ systems, and those related to specific organ systems vary from patient to patient. However, most patients have gastrointestinal symptoms, many have itching, some have neuromuscular symptoms, and others have cardiovascular symptoms.
   In addition to the symptoms that are nonspecific, a history of a relatively specific nature may provide a clue to the cause of the renal insufficiency (Table 10-3). Such important information as previous elevation of blood pressure, proteinuria, or hematuria may not be recalled, but if the patient is asked about the results of examinations for school, life insurance, or the military service, he or she may at least recall that an abnormality was detected. When renal insufficiency has reached end-stage, even renal biopsy may fail to differentiate the nature of the disease. Thus, obtaining data from previous examinations or other physicians or hospitals may be the only way to reconstruct the natural history of the disease.
2. **Physical signs of patients with chronic azotemia.** Physical examination of patients with chronic azotemia often reveals only nonspecific signs (see Table 10-2). However, occasionally there are specific physical signs that suggest the cause of the patient's disease (Table 10-3).
3. **Laboratory features of patients with chronic azotemia.** When azotemia is relatively mild, laboratory tests other than BUN and creatinine are often normal (except for the presence of proteinuria and cylindruria in patients whose azotemia is due to renal parenchymal disease). As indicated above, an elevation of BUN disproportionate to serum creatinine suggests obstruction, cardiac failure, high protein intake, or catabolism, whereas proportionate elevations of urea and creatinine suggest renal parenchymal disease.
   When azotemia is severe, whether due to obstructive nephropathy or renal parenchymal disease, there usually are many abnormalities of laboratory tests, although they may be nonspecific (see Table 10-2). There may also be more specific laboratory findings (Table 10-3) that provide etiologic information. For example, a strongly positive antinuclear antibody (ANA) test is diagnostic of systemic lupus erythematosus (SLE) and severe carbohydrate intolerance of diabetes mellitus. It must be remembered that mild carbohydrate intolerance is common in patients with renal insufficiency of any cause, but also that diabetic nephropathy can occur in patients who have sufficiently mild carbohydrate intolerance not to require insulin. Other clinical laboratory findings, such as a nephritic or nephrotic urinary sediment, are somewhat less specific (e.g., a nephritic sediment may occur in subacute bacterial endocarditis ([SBE]), SLE, and malignant hypertension as well as chronic glomerulonephritis, and a nephrotic sediment may occur in congestive heart failure, malignant hypertension, preeclampsia, sickle cell anemia, myeloma, and other malignancies as well as in chronic glomerulonephritis), but at least they place the patient within a category of diseases and exclude other types of diseases.
   Often the most specific laboratory features in the patient with chronic azotemia are radiographic. Although there is a risk of precipitating acute renal failure by intravenous urography (particularly in patients with diabetes or multiple myeloma), it may not be possible to make a specific diagnosis of the renal disease without radiographic study, although one may exclude obstruction and detect cysts with ultrasonography. One might think that renal biopsy would be invariably definitive; although it may be in early stages of chronic renal parenchymal disease, it usually is not in end-stage disease in which the histologic damage may be so severe that it is nonspecific.

Table 10-2. Nonspecific Clinical Features of Patients with Chronic Azotemia (Uremic Manifestations)

Symptoms
General: fatigue, weakness
Gastrointestinal: anorexia, nausea, vomiting, abnormal taste, hiccoughs
Skin: itching, bruising
Neuromuscular: restless legs, numb feet, muscle cramps or twitching, inability to concentrate, insomnia, irritability
Genitourinary: loss of libido or potency, nocturia
Cardiovascular: dyspnea, edema, pericardial pain
Signs
General: ill appearance, wasting
Skin: pallor, hyperpigmentation, ecchymoses, excoriations
Head, eyes, ears, nose, and throat: retinopathy, uriniferous breath
Cardiovascular. hypertension, cardiomegaly, murmur, friction rub, edema
Neuromuscular: peripheral neuropathy, drowsiness, asterixis, myoclonus
Laboratory Findings
Azotemia
Acidosis, metabolic
Anemia, usually normochromic, normocytic
Leukopenia and occasionally thrombocytopenia
Hyperuricemia
Hyperphosphatemia, at times hypocalcemia and hyperphosphatasia
Radiographic osteomalacia or osteitis fibrosa
Proteinuria
Cylindruria

Table 10-3. Specific Clinical Features that Suggest the Cause of Chronic Azotemia

History
Chronic glomerulonephritis: history of acute nephritis or nephrotic syndrome, symptoms of systemic lupus erythematosus (SLE), deafness (Alport's syndrome)
Diabetes: polyuria, polydipsia, family history
Polycystic disease: family history
Nephrosclerosis: hypertension before proteinuria or renal failure
Interstitial nephritis: recurrent urinary infection, analgesic abuse
Obstruction: symptoms of bladder dysfunction, stones
Physical examination
Diabetes: retinopathy, neuropathy
Polycystic disease: palpable kidneys, hematuria
SLE: facial rash, arthritis
Alport's syndrome: deafness, ocular abnormalities
Obstruction: large prostate, palpable kidneys
Gout: tophi
Laboratory tests
Chronic glomerulonephritis: nephritic or nephrotic sediment
Diabetes: hyperglycemia
Polycystic disease: diagnostic intravenous pyelography (IVP) or ultrasonography
Interstitial nephritis: diagnostic IVP if pyelonephritis
Obstruction: diagnostic IVP or ultrasound study
SLE: positive antinuclear antibody, nephritic or nephrotic sediment

III. Diagnostic approach to patients with chronic renal failure

A. An overview. The first step in evaluating a patient with renal failure, aside from assessing its severity and initiating appropriate therapy if the patient is critically ill, is to determine whether the renal failure is chronic or acute. Chronic disorders are more likely to be stable and thus less of an immediate threat to the patient than acute renal failure, but, unfortunately, chronicity often implies irreversibility. Irreversibility is not, however, invariable, and the second question to be asked is, even if the basic disease is chronic, is it remediable? Even if it is irreversible, can its progress at least be slowed? The third question to be asked is, even if the basic disorder is not remediable, are there remediable complications (i.e., factors that contribute to, or aggravate, the azotemia)?

Only when there are reasonably certain answers to these questions can the physician comfortably embark on therapy. Conservative management often suffices for months or years and includes the prevention of complications, measures to slow the progression of renal failure, and therapy to prevent or relieve the symptoms of uremia. In progressive disorders conservative management eventually fails, and the physician must proceed with radical management (i.e., treatment of end-stage renal failure by chronic dialysis or renal transplantation).

B. Evidence that renal failure is chronic. The most reliable evidence that renal failure is chronic is documentation of previous sustained elevation of BUN and/or serum creatinine. Such data should be sought in every patient, however inconvenient, even if the expeditious approach of radiographic determination of renal size demonstrates kidneys smaller than normal. The reason it is necessary to obtain previous laboratory data even in patients with small kidneys is that the relation between structure and function is variable; patients may have had surprisingly good renal function despite substantial reduction in renal mass. The converse (i.e., poor function despite normal-sized or even large kidneys) may also be true with polycystic kidney disease, diabetic nephropathy, malignant nephrosclerosis, multiple myeloma, rapidly progressive glomerulonephritis, and, occasionally, chronic glomerulonephritis. Particularly in patients who have normal-sized kidneys despite renal failure, renal biopsy may be necessary to demonstrate the nature of the disease and whether or not it is chronic. Yet another diagnostic approach that may yield reasonably certain evidence of chronicity is x-ray of the bone, demonstrating renal osteodystrophy, particularly osteitis fibrosa. Even this, however, may be unreliable in the rare patient who has a parathyroid adenoma and deterioration of renal function due to previous hypercalcemia.

There are other data that may suggest chronicity, but they are less reliable than documentation of previous azotemia, renal x-ray, renal biopsy, and bone x-ray. A patient with a family history of an inheritable renal disorder such as adult polycystic kidney disease or Alport's syndrome is likely to have the same disorder. A history of prolonged nocturia, polyuria, itching, or neuropathy is suggestive of chronic renal insufficiency, but at times is misleading. The same is true of a history of hypertension, since chronic hypertension does not invariably result in renal insufficiency. Stigmata of uremia, hypertension, or hypercalcemia on physical examination (e.g., pigmentation, neuropathy, retinopathy, and band keratopathy) are reasonably convincing evidence of chronicity. So, too, is the presence of severe azotemia without uremic symptoms. Stability of azotemia is suggestive of chronicity since the BUN and creatinine usually rise when the disorder is acute and progressive, but with chronicity the converse is of relevance. Elevation of urea disproportionate to creatinine has been previously discussed. Except in patients with acute disease who are capable of, and forced to have, a water diuresis, a serum creatinine disproportionately elevated to urea almost invariably indicates chronic renal insufficiency with reduced urea generation due to either anorexia and impaired protein intake in the absence of significant catabolism or dietary preferences such as those of a vegetarian. The patient with acute renal failure secondary to rhabdomyolysis and myoglobinuria also may have a disproportionate rise in serum creatinine. The presence of severe acidosis, with tolerance for it, is often evidence of chronicity. Hyperphosphatemia may imply chronicity, but it is common in acute renal insufficiency when there is hypercatabolism. Hypocalcemia is a somewhat more reliable indicator of chronic renal insufficiency, but it may occur in acute renal failure, particularly in association with rhabdomyolysis. Anemia can occur with acute renal insufficiency but is more typical of chronic renal insufficiency. Patients with severe chronic renal insufficiency, however, may not have profound anemia until they become frankly uremic.

C. Screen for remediable causes of chronic renal failure. Table 10-4 lists a number of chronic but remediable causes of renal failure as well as suggestive or diagnostic features of these disorders. There are also some acute disorders that can lead to permanent renal failure, including rapidly progressive glomerulonephritis (e.g., antiglomerular basement membrane nephritis or Goodpasture's syndrome) and, rarely, antibiotic nephrotoxicity (particularly that caused by cephaloridine and amphotericin).

Table 10-4. Remediable Causes of Chronic Renal Failure

Causes	Diagnostic Features and Tests
Obstruction	
Bladder neck or prostate	Nocturia, hesitancy, intermittency, decreased caliber or force of urinary stream, postvoiding residual
Therapeutic misadventure	History of pelvic surgery or radiation
Retroperitoneal fibrosis or tumor	Intravenous pyelography (IVP), use of methysergide (Sansert), lymphoma, myeloma
Calculi	Colic, hematuria, passage of stone, plain x-ray of abdomen, IVP
Stone formation	Stone passage
	KUB for radiopaque calcium or magnesium stone in kidney or ureter
	IVP for nonopaque uric acid stone
Stones and/or nephrocalcinosis	Renal tubular acidosis, hyperparathyroidism
Hypercalcemic nephropathy	Hyperparathyroidism, milk alkali syndrome, other causes of high serum calcium
Pyelonephritis with active infection or papillary necrosis	IVP, urine sediment, culture
Interstitial nephritis	History of analgesic abuse, other drugs or toxins (lead, cadmium)
Multiple myeloma	Serum and urine electrophoresis or light-chain testing, bone marrow
Bilateral renal artery stenosis	Angiography, bruits, rise in serum creatinine if captopril is administered
Malignant nephrosclerosis	Hypertension, retinopathy, renin
Lupus nephritis	Extrarenal manifestations of lupus (skin rash, hair loss, arthritis)
Wegener's granulomatosis	Upper and lower respiratory tract manifestations of Wegener's, e.g., sinusitis, pulmonary infiltrates
Gouty nephropathy	Elevated serum uric acid, history of podagra
Potassium depletion	Low serum potassium, history of diuretic or laxative use

KUB = Kidney, ureter, and bladder x-ray.

It would be far better to prevent chronic renal insufficiency than to treat it, but, unfortunately, many of the most common causes of end-stage renal failure either go undetected for such long periods of time that irreversible damage results or are not amenable to prevention. At our present stage of knowledge the latter is true of most forms of chronic glomerulonephritis, diabetic nephropathy (although the vascular complications of diabetes may be less when blood sugar is tightly controlled), polycystic kidney disease, and many other inherited or idiopathic disorders. Even interstitial nephritis due to chronic pyelonephritis (particularly when it occurs in a child with vesicoureteral reflux) may not be preventable, and certainly chronic pyelonephritis can progress long after bacteriuria is eradicated. Nevertheless, there are several common causes of chronic renal failure that should be preventable. These include hypertensive nephrosclerosis, obstructive nephropathies of most types, and nephropathy due to analgesic abuse.

It should be evident that it is mandatory for a physician seeing a patient with chronic renal insufficiency to make a specific diagnosis if it is possible to do so without unreasonable risk to the patient. Many diagnostic features and approaches are suggested in Table 10-4, but diagnostic approaches for disorders that are not remediable are not listed. Those approaches for polycystic kidney disease, diabetic nephropathy, and renal hypoplasia are relatively self-evident. Details of the patient's history, meticulous examination of the urinary sediment, excretory urography, and percutaneous renal biopsy are the mainstays of differential diagnosis of parenchymal renal disease. Occasionally, immunologic, bacteriolgic, or blood chemistry determinations allow a specific diagnosis to be made.

It is well known that the majority of patients with acute renal failure will recover essentially normal renal function if they can be sustained through their acute illness by dialysis and by appropriate medical and surgical therapy of the condition that caused the acute renal failure. This is true even when acute renal failure is prolonged. It is less well known that there are several causes of chronic renal failure that, even if severe enough to require dialysis for a substantial period of time (even many months), occasionally improve sufficiently that dialysis is not required for a period of months (or even years). Such disorders include malignant nephrosclerosis, lupus nephritis, Wegener's granulomatosis, multiple myeloma, and disorders in which a reversible complication is discovered.

D. **Screen for remediable complications or contributors to azotemia in patients with chronic renal failure.** Although the principle of parsimony (reluctance to make more than one diagnosis in a young person) may be helpful in arriving at a correct unifying diagnosis in a patient with multiple symptoms, the principle is dangerous when applied to patients with chronic azotemia. Chronic renal failure not only does not protect against other disorders, such as prostatism, but it makes the patient susceptible to a number of complications that may worsen the disease. Table 10-5 lists remediable contributors to azotemia.

1. **Erroneous laboratory data.** Erroneous laboratory data not only may cause undue concern to the physician and patient, but also may elicit inappropriate therapeutic responses. The physician must not only be alert to the possibility of erroneous data, but also must appreciate that a number of substances, particularly drugs, may interfere with various chemical methods. For example, an artifactually elevated serum creatinine may result from hyperglycemia, ketonemia, albumin infusion, or ingestion of arginine, ascorbic acid, cefoxitin, levodopa, and methyldopa. Some drugs may increase serum creatinine, not by decreasing glomerular filtration rate but by interfering with the tubular secretion of creatinine. Examples are trimethoprim and cimetidine. An artifactually elevated blood urea may result from infusion of dextran or ingestion of acetohexamide, ammonium salts, aspirin, chloral hydrate, chloramphenicol, hydantoins, and sulfonamides.
2. **Congestive heart failure and pericardial disease.** Heart failure may cause a decrease in creatinine clearance of approximately 50 percent in a patient with chronic renal insufficiency, just as it may in patients with normal renal function. Renal failure may cause pericarditis, which may be complicated by tamponade, and tamponade may in turn additionally impair renal function and precipitate flagrant uremia. If pericarditis is complicated by defective blood coagulation, life-threatening intrapericardial hemorrhage may result.
3. **Hypertension.** Hypertension must be severe, often accelerated or malignant, to impair renal function acutely and reversibly. Another cause of worsening renal function in a hypertensive patient with chronic renal insufficiency is overtreatment of the hypertension. Reversible renal failure may also occur when patients with bilateral renal artery stenosis are treated with captopril.
4. **Urinary tract infection, obstruction, and catabolism.** Kidney infection without obstruction rarely causes a profound disturbance of renal function unless it is so fulminant as to produce microabscesses throughout the kindeys, or papillary necrosis. The latter is particularly common in diabetics, especially when there is coexisting obstruction. Extrarenal infection with septicemia and/or catabolism is as frequent a cause of progressive azotemia in patients with chronic renal insufficiency as infection of the kidney itself. Innumerable other causes of catabolism, including infection, surgery, gastrointestinal bleeding, steroids, and tetracycline, may similarly complicate chronic renal insufficiency.
5. **Drugs.** Drugs may cause azotemia in a variety of ways, including direct nephrotoxicity, catabolism with increased urea generation, diuretic loss of salt and water with consequent volume depletion, reduction of blood pressure even in the absence of volume depletion, prostaglandin inhibition, and interference with the excretion of other substances or drugs that are nephrotoxic. Drugs may also complicate chronic renal insufficiency by causing complications other than azotemia (e.g., hyperkalemia). Drugs that cause hyperkalemia include salt substitutes (which may provide a dietary load greater than the patient can excrete), spironolactone, amiloride and triamterene (which interfere with potassium excretion), and succinylcholine (which causes release of potassium from muscle).
6. **Electrolyte imbalance.** Numerous electrolyte disturbances, either known or suspected to impair glomerular filtration rate are listed in Table 10-5. Most ominous, because it is frequently insidious and unrecognized, is salt depletion. It is instinctive to treat the patient with hypertension or congestive failure with salt restriction and/or diuretics, but this can be dangerous in the patient

Table 10-5. Remediable Contributors to Azotemia in Patients with Chronic Renal Failure

Laboratory error or chemical interference with laboratory determination
Heart failure: congestive, low-output, pericarditis with tamponade or constriction
Hypertension: severe, especially malignant; overtreatment of hypertension
Urinary obstruction:
Intrarenal: uric acid, papillary necrosis
Ureteral: bilateral, unless patient has only one kidney
Bladder outlet
Vascular obstruction: arterial or venous
Infection: renal or extrarenal
Catabolism: infection, surgery, gastrointestinal bleeding, steroid, tetracycline
Drugs: diuretics, antibiotics, radiographic dyes, anesthetics, analgesics, vitamin D, alkali, phenazopyridine (Pyridium), magnesium antacids, prostaglandin inhibitors, captopril
Salt depletion: restriction, diuretics, anorexia and nausea, vomiting, diarrhea, laxatives
Electrolytes: salt, water, or potassium depletion; hypercalcemia, hypermagnesemia, hyperphosphatemia, hyperuricemia, acidosis
Hypoproteinemia: nephrotic syndrome, cirrhosis, peritoneal dialysis, plasmapheresis
Uncontrolled diabetic glucose diuresis
Pregnancy: especially toxemia, preeclampsia
Acute renal failure of any cause

who also has chronic renal insufficiency. Although most patients with renal insufficiency do not have manifest salt wasting (inability to sustain salt balance on a normal intake), most are unable to elaborate a sodium-free urine and thus are at risk of volume depletion whenever salt intake is reduced below their obligatory excretion. This is often more than half a gram of salt per day. The volume depletion may be subclinical yet sufficient to impair glomerular filtration seriously.

E. Assessment of severity of chronic renal failure. For many patients, once the renal failure is substantial, the cause of the underlying renal disease is less important than its severity with regard to manifestations, complications, and therapy. Thus, when the physician has excluded remediable causes of chronic renal failure and remediable aggravating factors, he or she must shift attention to assessment of the severity of the renal failure and, thus, to its proper management.

1. **Symptoms.** The symptoms of renal insufficiency depend not only on its severity but also on the rate at which it develops. If uremic symptoms are present, the physician can be reasonably certain that renal insufficiency is severe. However, if symptoms are absent, the renal insufficiency may nevertheless be equally severe and on occasion even life-threatening. Thus, the physician must not rely on symptoms alone but must repeatedly obtain extensive laboratory data to follow a patient with chronic renal insufficiency.
2. **Physical findings.** The physical examination of patients with renal insufficiency may also reveal evidence of severe renal disease. If there is uremic frost, pericarditis (particularly with tamponade), neuropathy (particularly motor rather than simply sensory), or evidence of bone disease (deformities in children, tenderness or pathologic fractures in adults), the renal insufficiency is severe. Other stigmata, such as hypertension, hyperpigmentation, retinopathy, and even ecchymoses, do not necessarily correlate with the severity of the renal insufficiency and may correlate better with its duration.
3. **Laboratory data.** Aside from the history, physical examination, and observation of urine volume (oliguria invariably represents severe and potentially life-threatening disease), definitive assessment of the severity of renal insufficiency is dependent on laboratory findings. Anemia, acidosis, hyperphosphatemia, hypocalcemia, and hyperuricemia are all important but less useful in assessing severity than are measurement of BUN, creatinine, and creatinine clearance. Creatinine clearance is the most important clinical test. However, it overestimates glomerular filtration rate (GFR) when GFR is reduced below 5 to 10 percent of normal, and in this circumstance a mean value of creatinine and urea clearances (since the latter underestimates the extremely low GFR) gives a more accurate value. Despite the overestimation of the very low GFR by creatinine clearance, it is adequate for all clinical purposes. Except for errors related to improper timing and collection (e.g., a patient with variable emptying of the bladder or who is confused may be unable to collect a timed sample reliably), creatinine clearance is superior to measurement of serum creatinine alone. This is particularly true of malnourished and elderly patients whose muscle mass may be difficult to estimate to interpret the clinical implication of their serum creatinine level. Furthermore, if the patient is not severely catabolic or anabolic (e.g., a growing child), once an accurate urinary creatinine excretion has been obtained, creatinine clearance can ever after be calculated from that value together with serial serum creatinine determinations.
Creatinine clearance is not always necessary for clinical purposes if it is appreciated that a large, muscular, young man should have a significantly higher serum creatinine than a small, elderly woman. Furthermore, any change in serum creatinine concentration reasonably reflects a change in glomerular filtration rate, since renal tubular secretion of creatinine is a relatively stable and minor factor (except in advanced renal failure), and since the other dependent variable is the production of creatinine, which varies less than 10 percent unless there is a change in muscle mass.
The BUN is a less accurate measure of GFR because the production of urea is much more variable than the production of creatinine and because renal tubular reabsorption of urea is more variable than is the secretion of creatinine. Nevertheless, particularly when it is obtained in conjunction with a serum creatinine, the BUN provides additional information about the patient that may be even more important than knowledge of the GFR itself. For example, altered production of urea (decreased with inadequate protein intake or very severe liver dysfunction, increased with catabolism or gastrointestinal bleeding) or increased reabsorption of urea (with decreased fluid intake, hypovolemia, impaired cardiac function, or urinary obstruction) changes the BUN relative to the serum creatinine. Thus, a serum creatinine disproportionately elevated to urea (normal ratio 1 : 10) suggests inadequate protein intake, water diuresis, or advanced liver disease, and a BUN disproportionately elevated to creatinine suggests prerenal or postrenal failure.
4. **Radiography, ultrasonography, and other studies.** Although clinical laboratory parameters provide critical quantitative information, additional studies are often useful. Chest x-ray may reveal cardiomegaly, an increase in cardiac silhouette due to pericardial effusion, or uremic pneumonitis (which has never been convincingly demonstrated to be more than a hilar pattern of pulmonary edema). Renal x-ray (with or without radiographic contrast), renal scintiscans, and ultrasound may all assess the severity of renal disease by indicating renal size and may also detect obstruction. Bone x-ray, particularly of hands and feet to look for subperiosteal resorption or vascular calcification, are the most practical tests of renal osteodystrophy, although bone densitometry allows quantification of osteodystrophy and may be helpful, particularly when osteopenia is the major bony abnormality. Nerve conduction velocity is quantifiable but somewhat variable, and may add relatively little to clinical assessment of peripheral neuropathy as an index of the severity of renal insufficiency.

F. Varying natural history of different causes of chronic renal failure. The rate of progression of renal insufficiency expected for a given patient is of obvious importance. If serial determinations of serum creatinine are not available, the rate of progression may be predicted from the diagnosis. If the rate of expected progression is fulminant (as might be true of rapidly progressive glomerulonephritis, scleroderma, or malignant nephrosclerosis), the physician will probably want to have the patient in the hospital not only to follow the progress of the renal insufficiency but also to assess the efficacy of whatever therapy is employed and to detect complications of the disease or of therapy. If the rate of expected progression is rapid but not fulminant (late-stage juvenile diabetes), the patient should be seen in the office more frequently than if the rate of expected progression is intermediate (glomerulonephritis, lupus nephritis, pyelonephritis) or slow (polycystic disease, benign nephrosclerosis, nephrocalcinosis, partial obstruction, IgA nephropathy, adult diabetes).
This information regarding expected rate of progression is particularly useful when a patient is seen for only a second or third time. An abrupt change in function unexpected for the underlying disorder dictates a search for remediable complications. After the physician has followed a patient for a period of time, however, the patient should serve as his or her own control. That is, after serum creatinine has been measured on several occasions, the rate of progression can be estimated. A semilogarithmic plot of the serum creatinine against time should yield a roughly linear slope, and any abrupt change in rate demands an explanation.

G. Parameters to monitor in patients with chronic renal failure. The symptoms and signs of renal insufficiency and its complications are particularly useful in conjunction with laboratory parameters in following patients with chronic renal disease. Both clinical and chemical features should be used to guide conservative and eventually radical management of renal insufficiency.
These parameters are categorized in Table 10-6 by history, physical examination, laboratory tests, x-ray, and neurologic tests. Here we consider the parameters from another point of view. The signs, symptoms, and laboratory derangements of uremia should be followed to know when dietary protein restriction must be

Table 10-6. Parameters to Follow in Patients with Renal Failure

History
Symptoms of uremia
Physical examination
Weight, supine and standing blood pressure, retinopathy, skin turgor, cardiac size, prostate, edema, reflexes, sensation
Laboratory tests
Blood urea nitrogen, creatinine, potassium, HCO_3^-, uric acid, phosphate, calcium, albumin, hematocrit, platelets, serum iron or ferritin, alkaline phosphatase, parathyroid hormone, urine sediment and culture; 24-hour urine volume, creatinine, protein, sodium
X-ray tests
Chest, bone, kidney size
Neurologic tests
Physical examination *or* nerve conduction velocity, electroencephalogram, psychometrics

initiated and, after it has failed, when dialysis and/or transplantation should be initiated. The signs, symptoms, and radiographic manifestations of hypertension and cardiac dysfunction should be followed to assess the need for antihypertensive, diuretic, antiarrhythmic, and cardiotonic drugs and also eventually to appreciate when dialytic therapy may be required to control circulatory overload that may aggravate hypertension and/or cardiac dysfunction. Laboratory parameters such as potassium and bicarbonate should be followed to know when dietary therapy or other drugs are required, and parameters such as calcium, phosphorus, parathyroid hormone, and bone x-ray or densitometry to know when to modify the diet and to use medications such as phosphate binders and vitamin D analogues. Other tests, such as serial determination of body weight, urine sediment and culture, and serum iron or ferritin, are important to detect complications such as salt depletion, urinary infection, and iron deficiency, to make therapeutic maneuvers to prevent rapid deterioration of function or to treat complicating illness.

IV. Treatment of patients with chronic renal failure

A. Conservative management

1. Measures to prevent aggravating renal failure and complications

a. Careful drug usage. As in all medicine, primum non nocere. Renal failure may be aggravated or complicated, particularly by the injudicious use of medications or inappropriate manipulation of the diet. Many drugs depend on renal excretion and have excessive or toxic effects if employed in normal dosage in patients with renal disease. Other medications must be used cautiously because of the impaired homeostatic mechanisms in patients with renal failure. Nonsteroidal antiinflammatory agents are prostaglandin synthesis inhibitors that may cause serious renal insufficiency, presumably by decreasing renal blood flow. At times they may cause even more serious and less rapidly reversible renal insufficiency by causing interstitial nephritis, with or without nephrotic syndrome. Other drugs which may cause interstitial nephritics include phenylhydantoin, cimetidine, captopril, methicillin, allopurinol, and furosemide. Such agents may be more likely to cause interstitial nephritis in patients who already have some degree of renal insufficiency. A detailed discussion of drug use in renal failure is beyond the scope of this chapter, but tables for modification of drug dosage are readily available in the current literature and in Chapter 11. To summarize briefly, a few medications are so toxic or dangerous that they should be avoided altogether; these include nitrofurantoin (which may cause peripheral neuropathy); spironolactone, amiloride, and triamterene (which may cause lethal hyperkalemia); cephaloridine (which may cause severe renal failure); phenformin (which may cause severe lactic acidosis); and sulfonylureas (which may cause severe hypoglycemia).

Many medications must be used in decreased dosage, with monitoring of blood levels whenever possible; these include digoxin, many antibiotics, cytotoxic medications, cimetidine, clofibrate, long-acting barbiturates, and insulin. The physician must be particularly cautious in using drugs that are potentially nephrotoxic and ototoxic, such as gentamicin, kanamycin, and vancomycin. A few medications require increased dosage in patients with renal insufficiency to be effective; these include diuretics and some antibiotics when used to treat urinary infection.

b. Avoid volume depletion and hypotension. In patients with renal insufficiency, it is particularly important to avoid excessive treatment of hypertension and edema. Thus, special care is necessary in the use of antihypertensive medications and diuretics. Upright as well as supine blood pressure should be monitored to detect postural hypotension, whether due to an antihypertensive drug or to volume depletion. Even restriction of dietary sodium is potentially dangerous and generally should be avoided. Vomiting and diarrhea are particularly hazardous to the patient with renal insufficiency because the renal ability to reabsorb sodium and bicarbonate is limited; these symptoms are danger signals requiring prompt diagnostic and therapeutic intervention, at times including intravenous fluid therapy.

c. Avoid electrolyte imbalance. Although the ability to excrete potassium is sufficient to handle the potassium in a normal diet until chronic renal disease has progressed to an oliguric stage, the ability to excrete extra potassium loads is not. Thus, supplemental medicinal potassium is rarely required, and salt substitutes (KCl) as well as potassium-sparing diuretics should be avoided in patients with chronic renal disease. Patients with hyporeninemic hypoaldosteronism may require potassium restriction or 9α-fluorohydrocortisone. In diabetic patients with renal insufficiency, care must be taken to avoid extreme hyperglycemia as well as acidosis to avoid shifts of potassium out of cells and dangerous hyperkalemia.

d. Avoid indiscriminate protein restriction. Dietary protein restriction is highly effective in ameliorating early uremic symptoms, but indiscriminate protein restriction may result in malnutrition. Thus, when the quantity of dietary protein is restricted, the remaining protein should be of high biologic value (i.e., rich in essential amino acids).

e. Avoid pregnancy in high-risk patients. Although many patients with renal insufficiency are infertile, some are not, and these women should be advised against pregnancy (which may accelerate renal failure, at times irreversibly) or at least cautioned of the high risk to the mother as well as fetus. Risks are greatest in patients with hypertension, serum creatinine greater than 3.0 mg per deciliter, or both. If pregnancy is not interrupted, extremely close observation is mandatory.

f. Avoid instrumentation and radiographic contrast studies. Some diagnostic maneuvers are potentially hazardous in patients with renal insufficiency. Catheters and other urinary tract instrumentation should be avoided if at all possible because of the risk of urinary infection. Radiographic contrast studies are potentially dangerous to all patients with renal insufficiency, particularly to patients with multiple myeloma, diabetes mellitus, hyperuricemia, or dehydration. Serum uric acid as well as BUN and serum creatinine should be measured before any contrast study; if the serum uric acid is elevated, the patient should be pretreated with allopurinol unless the x-ray study is urgent. Fluid intake should not be restricted before urographic or angiographic studies, and at times additional fluid should be administered. Patients with cholecystitis are frequently dehydrated, and volume repletion is indicated before cholecystography or cholangiography. A cholecystogram should not be repeated in a patient with renal insufficiency without a substantial interval of time between studies.

2. Approaches to slow the progression of renal failure

a. Control hypertension. Control of hypertension, most particularly of malignant hypertension, may slow the progression of renal insufficiency whether the hypertension is primary or secondary. With initial therapy

there may be transient worsening of renal function, but this should not dissuade the physician from achieving control of the hypertension, even if the patient is on the borderline of uremia and might require temporary dialysis. On the other hand, as previously mentioned, overtreatment of hypertension is to be avoided since it is as dangerous as inadequate treatment: syncopal episodes, aggravation of azotemia, and even modest reduction of blood pressure with captopril may cause reversible renal insufficiency in patients with bilateral renal artery stenosis.

b. **Treat urinary tract infection.** Treatment of urinary infection is less frequently effective in slowing the progression of renal insufficiency. Some patients with severe renal infection have substantial improvement in function with effective therapy, but treatment of patients whose infection is restricted to the lower tract is unlikely to have a beneficial effect on renal function. Nevertheless, since there are other reasons to treat infection and since there is no sure way to tell which patients have only lower tract infection, all patients should be treated unless the treatment is judged to be more dangerous than the infection.

c. **Limit dietary protein.** Protein ingestion or amino acid infusion increases renal blood flow and GFR and may increase renal size. A substantial body of evidence—albeit much of it indirect or in experimental animals—suggests that the rate of progression of renal insufficiency of any cause, even ageing, may be greater when protein intake is high. Conversely, protein restriction may slow the progression of renal disease. Whether considerable slowing can be achieved by modest reduction of dietary protein remains to be seen, but presently it seems reasonable to limit dietary protein to 1 gm per kg body weight per day in patients whose creatinine clearance is less than 30 ml per minute. Some advocate more stringent restriction even earlier in the course of renal disease.

d. **Control hyperphosphatemia.** It is now well known that hyperphosphatemia sufficient to initiate parathyroid hyperplasia and hyperparathyroidism occurs relatively early in renal insufficiency (when glomerular filtration is reduced by only approximately 30 percent); thus, to protect the skeleton and to prevent other potential hazards of hyperparathyroidism, use of phosphate-binding medication and avoidance of excessive phosphate intake (primarily, dairy products) are appropriate. It is also likely that hyperphosphatemia mediates renal damage by enhancing calcium-phosphorous deposition and hastens the progression of renal insufficiency; it should be treated for this reason as well.

e. **Treat severe hyperuricemia (> 10 mg/dl).** Although not as well demonstrated a pathogenetic factor in progressive renal insufficiency as hyperphosphatemia, hyperuricemia also causes renal parenchymal damage by interstitial inflammation and scarring. Thus, its treatment may also slow the progression of renal insufficiency even in patients who do not have gouty nephropathy.

f. **Treat severe metabolic acidosis.** Metabolic acidosis should be treated, at least when serum bicarbonate falls below 17 mEq per liter, not only to provide a buffer reserve against acidogenic insults, but also to protect the skeleton from demineralization. It seems possible that acidosis may impair renal function as well as cardiovascular function. If edema or aggravation of hypertension results from sodium bicarbonate therapy, dietary sodium restriction or diuretics may be required to allow continued alkali therapy.

g. **Control blood sugar in diabetic patients.** Just as high protein intake may cause glomerular hyperfiltration, so may hyperglycemia. Early in the course of diabetes mellitus creatinine clearance is often high, and renal size, large. Long-standing hyperfiltration may be associated with proteinuria and glomerular damage. Conversely, rigid control of blood sugar may lessen renal damage in diabetics or at least slow the progression of renal insufficiency. Tight control with twice-daily long-acting insulin and supplemental regular insulin before meals or with an insulin pump should be advised, particularly in young diabetic patients.

Table 10-7. Therapy to Alleviate Uremic Symptoms

Itching	Restrict phosphorous and protein; treat with ultraviolet irradiation, diphenhydramine
Gastrointestinal symptoms	Restrict protein; correct acidosis; treat with frequent small meals, prochlorperazine
Neuromuscular symptoms	Restrict protein; treat with diazepam, sedatives, anticonvulsants
Bone disease	Treat acidosis; restrict and bind phosphate; treat with calcium supplementation, vitamin D, or $1,25(OH)_2D_3$
Neuropathy	Treat with vitamins
Anemia	Treat with iron, anabolic steroids, and, if severe, with transfusions
Malnutrition	High-quality protein when quantity of protein is restricted
Arthritis	Restrict and bind phosphate; treat with allopurinol, phenylbutazone

3. **Therapy to alleviate uremic symptoms**

a. **Dietary protein restriction.** When renal function fails and symptoms develop, dietary protein restriction is indicated because uremia is largely due to the production of protein catabolites whose excretion is impaired, and because a low-quantity, high-quality protein diet decreases the production of protein catabolites. It is important to appreciate, however, that a high-quality protein diet (one rich in essential amino acids) is necessary to maintain nutrition. Furthermore, as described above, such a diet may slow the progression of renal failure and even, perhaps, improve renal function.

Dietary protein restriction should not be severe (i.e., should not be less than 0.5 gm protein/kg body weight/day) until uremic symptoms develop, since the beneficial effect in slowing progression of disease seems less than the risk of malnutrition. Furthermore, reserving marked protein restriction to the uremic stage of renal insufficiency generally allows the physician to know that there is still time to prepare for end-stage renal disease management without undue haste or alarm, since marked protein restriction usually allows one to several months of sufficient amelioration of symptoms before dialysis or transplantation is required. To initiate marked protein restriction before the onset of symptoms, and thereby to delay their appearance until very late in renal failure, obliterates this important signal to the physician that referral for end-stage renal disease care is indicated, thereby exposing the patient to greater risk of life-threatening complications such as hyperkalemia and pericarditis.

b. **Treatment of pruritus.** In addition to dietary protein restriction, a variety of medications is usually required to prevent or alleviate symptoms once uremia has supervened. Itching is a common and particularly unpleasant problem that is not always amenable to conservative therapy. Restriction of dietary protein and restriction or binding of dietary phosphate may suffice. If dryness of the skin contributes, avoidance of frequent or prolonged bathing, use of mild soaps, and application of skin creams may be helpful. Ultraviolet irradiation has occasionally been highly effective. Other antipruritic medication may be helpful in selected patients, but diphenhydramine is usually the drug of choice both because it often decreases itching and because it is sedative. Itching is particularly bothersome to the uremic patient at night when activities of the day no longer distract attention from what is often relatively mild pruritus.

c. **Treatment of gastrointestinal symptoms.** Gastrointestinal symptoms are almost universal in uremia. They include anorexia; a musty, metallic, or otherwise abnormal taste; nausea; vomiting, particularly in the morning; early satiety; and, occasionally, diarrhea. These symptoms are usually relieved by dietary protein restriction, even though the foods allowed may be less appealing than the patient's customary diet. As renal failure advances, however, symptoms recur, and additional measures may be indicated. The abnormal taste may be abolished by decreasing oral bacteria (which convert urea to ammonia) with half-strength hydrogen peroxide mouthwash or by neutralization of ammonia with small amounts of lemon juice. Nutrition may be sustained despite anorexia and early satiety by the use of frequent small meals. Nausea may respond to correction of metabolic acidosis with sodium bicarbonate or to the use of prochlorperazine or trimethobenzamide.

d. **Treatment of neuromuscular symptoms.** Neuromuscular symptoms are perhaps the next most common in uremia. They include restless legs, paresthesias and dysesthesias as well as other symptoms of peripheral neuropathy, muscle cramps and myoclonic jerks, fatigue (particularly later in the day), insomnia, and even convulsions. These symptoms also may be ameliorated by restriction of dietary protein, and vitamins should be provided to the patient with neuropathy even though vitamin deficiency is an infrequent cause of it. Diazepam, sedatives, and—when indicated—anticonvulsants may also be helpful.

e. **Treatment of bone and joint disease.** Renal osteodystrophy is frequently present, although rarely symptomatic. Even if asymptomatic, it should be treated by restriction and binding of dietary phosphate and by correction of metabolic acidosis. Since dairy product restriction is necessary, the renal diet is usually deficient in calcium. It is, however, not yet established that dietary calcium supplementation or vitamin D should be given prophylactically. On the other hand, if bone disease is symptomatic or evident on radiographic survey, calcium carbonate (0.5 to 1.0 gm calcium daily) and 1,25 dihydroxy-vitamin D_3 (0.25μg daily) are appropriate, provided that serum phosphorus is controlled and that serum calcium is followed regularly. If aluminum-induced osteomalacia is demonstrated by an aluminum stain on bone biopsy, the renal osteodystrophy may respond to aluminum removal by desferroxamine. Arthritis is fortunately infrequent in uremia, but several forms may occur. Periarticular hydroxyapatite deposition and inflammation may be prevented by dietary restriction and binding of phosphate or, if present, pain may respond to phenylbutazone. Gout may be treated prophylactically with allopurinol and acutely with colchicine or phenylbutazone. Pseudogout may also be treated with phenylbutazone or indomethacin. All forms of arthritis should be treated initially with immobilization as well.

f. **Treatment of anemia.** The anemia of renal insufficiency is a particularly vexing problem. It is presumably due, at least in part, to erythropoietin deficiency. Unfortunately, erythropoietin has not been synthesized and is not available for treatment of patients clinically. Patients should be screened for other forms of anemia, particularly iron deficiency with serum iron or ferritin, but if no remediable form of anemia is found the only practical therapy is the parenteral administration of anabolic steroids, whose efficacy is, unfortunately, not great. Because of risk and short-lived benefit, transfusions should generally be avoided except in patients with symptomatic coronary artery disease, cerebrovascular disease, or cardiac failure, whose symptoms relating to these cardiovascular diseases improve with transfusion.

g. **Treatment of intercurrent illness.** Finally, it should be noted that the symptoms of uremia are so protean as to simulate many other disorders. Thus, the physician must be alert to intercurrent illness with uremic symptoms, such as gastroenteritis, since such illness may be amenable to therapy and, if not treated, may aggravate uremia.

B. **When to refer the patient with renal failure to a nephrologist**

1. **In renal insufficiency of any stage (early to advanced) when there are concerns regarding the evaluation or management of the patient.** When no longer comfortable in caring for the patient, the primary physician should seek nephrologic consultation. This may be because he is not confident of the evaluation of the underlying disease or of possible superimposed complications, or the primary physician may not be confident that he is providing optimal conservative management. Such confidence is understandably shaken when there is unexpected, unexplained progression of renal insufficiency, when complications develop, or when manifestations are not controlled by therapy.

2. **When temporary dialysis may be required.** Dialysis for a relatively short period of time may be indicated in a patient with moderate, suburemic renal insufficiency who develops an intercurrent illness or catabolic stress that precipitates symptomatic uremia. Preoperative preparatory dialysis may be indicated in patients who require elective surgery that might cause uremia. Temporary dialysis may also be required in a patient with moderate renal insufficiency who has had surgery, complicating intraabdominal infection, or intestinal fistula necessitating parenteral alimentation, any of which may precipitate symptomatic uremia. In these situations the need for temporary dialysis can be predicted, and it can be applied prophylactically before the development of uremic symptoms. In other circumstances the need for temporary dialysis may not be anticipated, such as in the patient who requires emergency surgery or who, for whatever reason, develops an abrupt and severe deterioration of renal function that results in uremia.

   Temporary dialysis may also be required for a patient who presents already uremic but who has not been adequately evaluated for the duration, cause, reversibility, or complications of renal failure. Similarly, a patient may present with uremia, with known, chronic, irreversible renal disease, who has not been adequately evaluated for the appropriateness of chronic dialysis or transplantation. Specifically, the patient may not have been evaluated for such problems as metastatic disease, end-stage heart failure, intractable pain, and psychosocial misery, any of which might contraindicate definitive ESRD care. Such a patient should be dialyzed until the evaluation is complete.

3. **To consider, plan, and prepare for definitive ESRD therapy**

   a. Indications for initiating chronic dialysis or transplantation for a patient with otherwise suburemic severe renal failure include:
      (1) Circulatory overload, congestive heart failure or hypertension that fails to improve with medication
      (2) Severe, progressive peripheral neuropathy, especially motor neuropathy
      (3) Pericarditis
      (4) Severe renal osteodystrophy
      (5) Progressive physical debility or malnutrition
      (6) Progressive emotional discouragement or psychosis
      (7) Early, but progressive, diabetic retinopathy
      (8) Severe diabetic neuropathy, gastroenteropathy, or vascular disease
      (9) Creatinine clearance less than 4 ml per minute
      (10) Irresponsible or noncompliant patient and danger of death from hyperkalemia or other complication
      (11) Bleeding diathesis

   b. Indications for initiating chronic dialysis or transplantation for a patient with uremic ESRD include:
      (1) Conservative management fails to sustain quality of life or productivity
      (2) Patient emotionally as well as intellectually prepared

   c. Patients should be referred to a nephrologist when any of these indications exists. Preferably, to allow for a smooth transition so that the patient has adequate time to become acquainted with the new physician and to adjust to the frightening and awesome transition from conservative to radical management of renal failure, the patient should be referred before the development of these indications. A signal that the time for referral is auspicious is the onset of symptoms in a patient before the initiation of

marked dietary protein restriction. Creatinine clearance may also serve as a guide; referral is generally indicated when the clearance has fallen to 10 ml per minute or in the diabetic patient when it has fallen to 15 ml per minute. Early referral is desirable not only for the reasons just mentioned, but also to allow time for maturation of an arteriovenous fistula for vascular access for hemodialysis or for preparation of the patient for transplantation. If there are willing related donors, time for their evaluation and preparation is also necessary.

C. Definitive ESRD therapy (chronic dialysis and transplantation)

1. **Indications to initiate chronic dialysis or transplantation.** Indications that the time has arrived or passed for proper initiation of ESRD therapy are listed above and are for the most part self-explanatory. A few, however, deserve comment.
   a. **Neuropathy.** Sensory neuropathy is common, frequently only mildly distressing to the patient, and not a cause for undue alarm. However, even early motor neuropathy is an indication that dialysis or transplantation should be initiated without delay, especially since dialysis rarely reverses peripheral neuropathy but may halt its progress. In fact, if motor neuropathy has progressed considerably, transplantation may be preferable to dialysis because it may allow regeneration of peripheral nerves.
   b. **Uremic pericarditis.** Uremic pericarditis is often mild and as such does not cause tamponade. However, there are occasional patients in whom pericarditis is fulminant, particularly those whose uremia is also complicated by a hemorrhagic diathesis. Hemorrhage into the pericardium may precipitate tamponade, and a fibrinous, hemorrhagic pericardial exudate may not be easily drained by pericardiocentesis. Thoracotomy with drainage, at times pericardiectomy, may be required. Indomethacin frequently ameliorates the pain of uremic pericarditis, and if initiated early it may possibly lessen the risk of tamponade and hemorrhage.
   c. **Malnutrition and physical debility.** Malnutrition and physical debility often develop insidiously in uremic patients, and the conscientious physician who sees patients at short intervals may be at a disadvantage in appreciating these afflictions. Malnutrition and debility predispose patients to intercurrent illness and impair their ability to recover from such illness.
   d. **Emotional considerations.** The various complications of uremia were common in the early days of dialysis when it was less available and when conservative therapy was prolonged beyond what we now know to be a reasonable time. Thereafter, the pendulum swung to early initiation of dialysis, even at the inception of uremic symptoms, and nephrologists took pride in the fact that they were able to initiate definitive therapy with minimal uremic symptoms. It is now apparent, however, that dialysis can be initiated too early as well as too late, and that the patient who has not had to endure unpleasant uremic symptoms finds it extremely difficult to accept emotionally the time-consuming, expensive, and at times unpleasant demands of chronic dialysis or transplantation.
   The patient must be emotionally as well as intellectually prepared for ESRD therapy and thus probably should be allowed to experience early uremic symptoms to accept dialysis or transplantation and thereby, in the long run, to suffer less. The physician should, nevertheless, initiate dialysis or transplantation when conservative management fails to sustain a reasonable quality of life and health or fails to sustain productivity. The inability of a person to continue work or school activities or to enjoy retired life is an important signal that dialysis or transplantation should be deferred no longer.
2. **Contraindications to initiating chronic dialysis or transplantation or to continuing chronic dialysis.** An absolute contraindication to initiation of dialysis or transplantation is the patient's decision against such action, if the patient is mentally competent and well informed. Specifically, the patient should be given an opportunity to consider the pros and cons of prolongation of life by dialysis or transplantation when neither depressed nor under the stress of acute illness or life situations. Another absolute contraindication is extrarenal illness that, in the patient's and physician's opinions, has so destroyed the quality of life that dialysis or transplantation would simply postpone death and prolong suffering.
   A relative contraindication to dialysis and transplantation is disability or severe handicap in an infant who, in the parents' and physician's opinions, would have severe difficulty adjusting even to a sheltered existence. Another relative contraindication to initiating or continuing dialysis is the existence or development of serious illness that, in the opinion of the family and physician, would cause severe and prolonged suffering of an incompetent patient.
3. **Use of hemodialysis**
   a. **Ancillary therapy and technical aspects.** Although the adequacy of dialysis is difficult to measure or even define, most patients require 4 hours of hemodialysis three times weekly to sustain reasonable health. Dietary and fluid restrictions are mandatory, and ancillary therapy is almost invariably required. For nearly all patients such therapy includes supplemental water-soluble vitamins (B and C), folic acid, and phosphate binders (aluminum hydroxide or carbonate). For many patients therapy also includes antihypertensive medications, supplemental calcium and/or active vitamin D, iron, and periodic transfusion of blood. Occasional patients require subtotal parathyroidectomy because of bone disease, and rare patients require nephrectomy for treatment of hypertension. Although there are fewer problems with arteriovenous fistulae than with external shunts, vascular access fails periodically in most patients. The forearm veins of many patients are inadequate to create adequate fistulae, and interposition segments of bovine carotid artery, microporous Teflon (Impra or Goretex), or umbilical vein are often required.
   Perhaps the most important decision in chronic hemodialysis is whether to perform it in the home or in a center. Some centers are within hospitals, others in free-standing units, and a few offer limited-care dialysis at lower cost by virtue of greater patient and/or assistant participation. The advantages of home dialysis are a sense of independence, ability to schedule dialysis to meet personal or business needs thus allowing better rehabilitation, less exposure to hepatitis, less expense than center dialysis and, for the child, a more natural setting. The disadvantages of home dialysis are the added psychological stress for the patient and assistant, the disruption of family or marital life that the stresses may occasion, the lack of expertise and equipment for cardiorespiratory resuscitation should it be required by illness or technical misadventure, and the lesser frequency of evaluation of the patient by nurses and physician.
   b. **Efficacy of chronic dialysis.** Uremic manifestations and how they are controlled by dialysis are listed in Table 10-8. The net effect of these variables is a patient whose life is clearly prolonged, whose health is variably but usually reasonably restored, and who has to expend considerable time and effort, if not money, to achieve these ends. A minority of patients, perhaps 10 percent, feel entirely well, and their lives are primarily disrupted by the time required for treatment and for medical evaluation and supervision. The vast majority of patients are well enough to enjoy reasonably normal lives, and half of them can continue full-time work, school, or retirement activities. A minority of patients, generally 10 to 20 percent depending on acceptance criteria of the individual center, remain seriously ill and have a questionable quality of life. Nearly all such patients have serious extrarenal disease that is primarily responsible for their failure to be restored to reasonable health or to be rehabilitated.
   As might be anticipated, elderly and retired patients tend to adjust better to the demands of chronic hemodialysis than do younger patients. Surprisingly, many elderly patients have fewer medical problems than their younger counterparts.

Table 10-8. Efficacy of Chronic Dialysis in Controlling Uremic Symptoms

Well Controlled	Variably Controlled	Poorly Controlled
Neurologic symptoms	Sodium, water, potassium balance*	Cardiovascular disease
Gastrointestinal symptoms	Hypertension*	Growth
Bleeding	Circulatory overload*	Development
	Acidosis	Maturation
	Hyperuricemia	Sexual interest and function
	Arthropathy	Muscle cramps
	Osteodystrophy	Anephric anemia
	Anemia*	
	Neuropathy	
	Pericarditis	
	Hyperlipidemia	
	Carbohydrate intolerance	
	Pruritis	
	Amenorrhea	
	Strength and endurance	

*Better controlled by continuous peritoneal dialysis than by hemodialysis.

c. **Complications of hemodialysis.** Complications of chronic hemodialysis are listed in Table 10-9. Only a few require additional comment.

(1) **Vascular access.** With the exception of patients with large-caliber, superficial forearm cephalic veins that allow an optimal radial artery–cephalic vein internal fistula for dialysis access, fistula or shunt surgery is a periodic requirement for patients undergoing hemodialysis on a long-term basis. Surgical ingenuity and the relatively long life of bovine carotid arteries and of microporous Teflon tubes as interposition grafts have made it rare that a patient cannot continue long-term hemodialysis for lack of vascular access. External arteriovenous shunts are often required on a temporary basis but are rarely employed as the primary access on a long-term basis because their additional complications of dislodgment and more frequent hemorrhage, infection, and thrombosis than an internal arteriovenous fistula make them a poor second choice.

When shunts were the only available vascular access, and warfarin compounds were employed to prevent thrombosis in many patients, hemorrhagic complications were frequent. When dialyzers (artificial kidneys) required large amounts of heparin, hemorrhage was often feared but rarely occurred except in patients with gastrointestinal ulceration. Under such circumstances it was routine to employ regional anticoagulation—that is, to neutralize the heparin in blood returning to the patient with protamine. This technique, however, has been largely abandoned in favor of tight-systemic anticoagulation with the use of relatively low-dose heparin; perhaps surprisingly, hemorrhagic complications are now a rare event.

(2) **Complications related to the dialysis procedure.** More patients are made ill by dialysis than we like to think. Fortunately, serious illness, such as septicemia, endocarditis, or air embolism, is rare; however, unpleasant symptoms, such as muscle cramps (related in part to the ultrafiltration required by excessive fluid intake between dialyses), headache, nausea, and vomiting during dialysis, or a "washed out" syndrome following dialysis, are common. Symptomatic hypotension is also common during dialysis, particularly now that high-performance dialyzers are commonly used to remove the accumulated solute waste in short periods of time (4 hours or even less). This necessitates the removal of fluid gained between dialyses in the same short period of time. Transfer of fluid from interstitial and cellular spaces to the intravascular compartment may not proceed at a rate sufficient to prevent hypotension.

Table 10-9. Complications of Hemodialysis

Vascular access: hemorrhage, thrombosis, embolus, infection, aneurysm, arterial steal, venous congestion, high flow (strain on heart)
Technical misadventure: impure water, improper dialysate, air embolism, ruptured dialyzer, excessive anticoagulation, excessive ultrafiltration
Hepatitis and carrier state
Removal of nutrients, medications, other solutes
Anemia and impaired oxygen delivery
Neutropenia and eosinophilia
Bleeding and clotting tendencies
Cardiovascular: cardiac stress, hypotension, hypertension, arrhythmias, endocarditis
Gastrointestinal: phosphate depletion, obstipation, ascites
Genitourinary: sexual dysfunction, oliguria, stones, papillary calcification, acquired cystic disease (often with tumor)
Neuromuscular: muscle cramps, seizures, disequilibrium, dementia, carpal tunnel syndrome, intradialysis headaches, nausea, vomiting, hypotension, muscle cramps
Postdialysis hypotension or "washed out" feeling

(3) **Disequilibrium syndrome.** The disequilibrium syndrome consists of headache, nausea, vomiting, and even convulsions, with or without increased intracranial pressure. It has been thought, although not demonstrated, that a blood-brain barrier to urea transfer results in greater removal of urea from blood than from cerebral tissues during dialysis and that the resulting osmotic gradient causes an influx of water to the brain (i.e., cerebral edema). Thus disequilibrium is more likely to occur when BUN is very high (e.g., when hemodialysis is initiated or when a patient has gastrointestinal bleeding or has missed dialyses). Symptoms of disequilibrium may be prevented by infusion of mannitol during dialysis. Fortunately, severe disequilibrium is infrequent despite the short, 4-hour dialyses that patients prefer.

(4) **Dialysis dementia.** A much more serious and lasting disturbance of the brain, so-called dialysis dementia, has become a major problem in many dialysis centers. After the patient has been undergoing dialysis for a period of time, often several years, this syndrome may begin insidiously, usually with minor disturbances of speech. Thereafter, the disturbance progresses to incomprehensible speech or even mutism, an apraxia of gait as well as speech, epileptiform and slow-wave abnormalities on EEG, and at times, convulsions. There is a tendency for all manifestations to be aggravated by dialyses. At times the development of flagrant psychosis or progressive and disabling dementia occurs with dialysis. The cause of this disorder is not known, although excessive aluminum in the grey matter of the brain has been implicated in some patients. Unfortunately there is no effective remedy, apparently not even transplantation, although there is hope that removal of aluminum through chelation with desferrioxamine may be therapeutic and has been reported to be effective in some patients.

Table 10-10. Causes of Death of 557 Chronic Hemodialysis Patients

Cause	Percentage*
Sepsis	22
Cardiac	21
Myocardial infarction	18
Cerebrovascular	10
Miscellaneous	10
Withdrawal or suicide	8
Dialysis-related	5
Pericarditis	3
Gastrointestinal bleeding	3

*Thirty percent of deaths occurred in the first month of dialysis.

d. Morbidity and mortality from chronic hemodialysis. Most patients undergoing chronic hemodialysis require periodic hospitalization for vascular access surgery; some require hospitalization for intercurrent illness, but few are hospitalized for problems directly related to dialysis. A study of 1800 patients in California and Minnesota several years ago revealed that following their initial stabilization on dialysis, patients spent a mean of 2 to 3 days per month (median of 1 day per month) in the hospital. In the same study, the causes of death of 557 patients were carefully reviewed (Table 10-10). It should be emphasized that 30 percent of the deaths occurred in the first month of dialysis. Other studies indicate that the annual mortality of chronic hemodialysis patients is 10 to 15 percent in the first year and 5 to 10 percent annually thereafter. Only a minority of deaths relates directly to renal failure or dialysis. This is especially true now that patients with serious extrarenal disease are commonly (and appropriately) accepted for chronic dialysis therapy.

4. Chronic peritoneal dialysis. In the past several years chronic intermittent peritoneal dialysis has become an acceptable alternative to chronic hemodialysis for many patients, and continuous ambulatory peritoneal dialysis (CAPD) or continuous cycling peritoneal dialysis (CCPD) may conceivably revolutionize the treatment of end-stage renal disease and become the treatment of choice for the majority of patients.

a. Indications for, and contraindications to, chronic peritoneal dialysis

(1) Indications. Even though peritoneal dialysis became firmly established in the treatment of acute renal failure years before hemodialysis was used, the reverse was true for treatment of chronic renal failure. Thus, the indications for chronic peritoneal dialysis remain for the most part, even today, contraindications to hemodialysis. In the next several years development of more positive indications for chronic peritoneal dialysis can be anticipated, especially if CAPD and CCPD find widespread applicability because of the development of technologic means to decrease the frequency of complicating infections. Currently, indications for peritoneal dialysis as opposed to chronic hemodialysis include:

(a) Home dialysis. Peritoneal dialysis may be preferable for a patient who desires to undergo dialysis at home but who has no available assistant for home hemodialysis. Although assistance is desirable, it is unneccessary for home peritoneal dialysis.

(b) Severe cardiac arrhythmia, angina, intravascular volume instability, or autonomic neuropathy. Each of these conditions may make hemodialysis technically dangerous or difficult.

(c) Refusal of blood transfusion. This tenet of Jehovah's Witnesses makes hemodialysis potentially dangerous.

(d) Inability to construct vascular access. This may occur in a patient who has had failed vascular accesses as in all extremities, or there may be a temporary unavailability of functional vascular access.

(e) Infants. Peritoneal dialysis is preferable to hemodialysis for infants in whom problems of vascular access and circulatory instability complicate hemodialysis. Infants also have a high ratio of peritoneal surface area to body mass, which makes peritoneal dialysis relatively more effective for infants than for older patients.

(f) Diabetes. Peritoneal dialysis may also be preferable for diabetics, because the progression of retinopathy may be less, the risk of limb ischemia reduced (vascular access not required), and hyperglycemia better controlled by intraperitoneal insulin.

(g) Cost. The cost of peritoneal dialysis is less than that of hemodialysis, an important consideration for patients who do not have Medicare entitlement and also a favorable factor for the national health economy.

(2) Contraindications. The risk of peritonitis is unacceptable if a patient has a fecal fistula, colostomy, or abdominal wall infection. Peritoneal dialysis is theoretically contraindicated if the patient has a synthetic aortic prosthesis, because peritonitis could cause infection and anastomotic rupture. Communication between peritoneal and pleural spaces is rare, but when it is present, peritoneal dialysis may cause massive hydrothorax and atelectasis. Even the mild elevation of the diaphragm from peritoneal dialysis makes it hazardous for patients with severe pulmonary dysfunction. Patients with cirrhosis and ascites may lose unacceptably large amounts of protein if peritoneally dialyzed. Patients with massive polycystic kidneys or extensive peritoneal adhesions may not tolerate the instillation of the 1.5 to 2.0 liters of peritoneal dialysate necessary for effective dialysis.

b. Technical aspects of chronic peritoneal dialysis. For peritoneal dialysis to be carried out for an extended period of time, safe peritoneal access is mandatory. The entry of bacteria from the skin to the peritoneum can be impeded by two Dacron felt cuffs bonded to the catheter and located in properitoneal subcutaneous tunnel. The cuffs allow ingrowth of tissue to prevent a fistulous tract from skin to peritoneum. The patient must practice meticulous aseptic technique in making connections between the peritoneal catheter and the closed dialysate delivery and drainage system. For unattended, overnight, intermittent peritoneal dialysis (IPD), an automated, monitored delivery-drainage system (which produces pure water by reverse osmosis and mixes it with dialysate concentrate) was developed. This allowed dialysis to be performed while the patient slept for 10 to 12 hours, 3 to 4 nights each week. The machines for intermittent, overnight dialysis proportion 100 ml of dialysate concentrate from a single 2-liter bottle with 1900 ml of purified water for each of 20 exchanges and require connections and disconnections only at the beginning and end of a 40-liter dialysis. Continuous ambulatory peritoneal dialysis (CAPD) is a promising technique in which 3 to 5 dialysis exchanges are performed each day, continuously for 24 hours. Presently it is too often complicated by peritonitis because of the greater number of tubing connections and disconnections required than for IPD. For CAPD, dialysate is supplied in 1-,1½-, or 2-liter bags that require a connection at the beginning and a disconnection at the end of each exchange. The average patient carries out three 5-hour, 2-liter exchanges during the day (with the empty dialysate bag and tubing rolled up and worn under the clothing while the dialysate is in the peritoneum) and one 9-hour, 2-liter exchange while sleeping at night. This provides excellent chemical and fluid control with slow but truly continuous dialysis. It requires no additional equipment, no assistant, and only a short training

period; also, it entails less expense than other forms of dialysis and provides considerable mobility for the patient.

A modification of CAPD called continuous cycling peritoneal dialysis (CCPD) has been developed using a cycling device for automatic delivery of a number of exchanges of dialysate during the night. These cyclers are easier to set up and use than the machines for IPD, and in addition patients leave an exchange of dialysate in the abdomen each morning so that dialysis and ultrafiltration can continue (albeit slowly) during the day. CCPD is preferred to CAPD by patients who want to avoid the inconvenience or time necessary to do exchanges during the day or who wish to cap off their peritoneal catheter rather than wear the rolled-up dialysate bag and tubing during the day. Even using 2-liter bags of dialysate and thus the same or greater number of connections and disconnections than with CAPD, CCPD is reported to have decreased the incidence of peritonitis, perhaps because aseptic technique is more strictly adhered to when almost all the connections and disconnections are done at a single time. The incidence of peritonitis may be additionally reduced with larger (3- or 5-liter) bags of dialysate for the cycler and with semiautomated connections made under ultrviolet light. Such large bags of dialysate could not be used for the CAPD technique because the volume is too great to infuse into the abdomen for a single dialysis exchange (a large bag of dialysate is used for more than one of the nighttime exchanges using the CCPD technique), and thus the patient would have to carry about a partially filled bag of dialysate rather than an empty bag that can be rolled up along with the tubing and carried conveniently on the body.

c. **Complications of chronic peritoneal dialysis.**

(1) **Infection.** The most serious complication of chronic peritoneal dialysis is infection, either of the skin exit site, of the subcutaneous catheter tunnel, or of the peritoneum itself. In several series, CAPD patients averaged two episodes of peritonitis annually. Although these patients usually can be treated on an outpatient basis, sometimes they require hospitalization. Sometimes peritonitis does not clear without removing the catheter, and of course patients then have to be hemodialyzed for a month or more.

(2) **Inadequate peritoneal clearance and ultrafiltration.** Repeated episodes of peritonitis can so diminish peritoneal surface area and clearance of solute that peritoneal dialysis becomes ineffective. With prompt recognition and treatment of peritonitis, however, it is now rare for a patient to return to hemodialysis for this reason. Occasional patients inexplicably lose the ability to ultrafilter and to maintain fluid balance even though solute clearance is not diminished.

(3) **Catheter failure.** Catheter failure in peritoneal dialysis is a problem comparable to failure of vascular access in hemodialysis, although less frequent. It usually is due to infection, but occasionally to spontaneous repositioning of the end of the catheter to a nondependent area in the peritoneal space, fibrin clotting of the catheter, or omental encasement of the catheter.

(4) **Excessive removal of fluid or electrolytes.** As with hemodialysis, the goal to control fluid and electrolyte balance may be exceeded to the point of depletion. Therefore, the physician may need to liberalize dietary or fluid intake, alter dialysate concentration of glucose or potassium, decrease the duration or frequency of dialysis with IPD, or decrease the number of exchanges with CAPD.

(5) **Malnutrition.** Malnutrition (due to loss of protein in peritoneal dialysis effluent) can develop if the patient fails to ingest an adequate quantity of protein, especially if he has frequent bouts of peritonitis, which greatly increase the peritoneal loss of protein.

(6) **Hypernutrition.** Conversely, some patients become hypernourished, even obese, from absorption of dialysate glucose. Glucose is present in peritoneal dialysate to effect osmotic removal of fluid (ultrafiltration), since the patient ingests more fluid than can be excreted in urine, stool, sweat, and insensible losses.

(7) **Hypernatremia.** When a patient's fluid intake and thus ultrafiltration requirement is large, he or she must employ a high dialysate glucose concentration (2.5% or 4.25% glucose rather than the customary 1.5% glucose dialysate). The absorbed glucose may provide excessive calories, and the unabsorbed glucose may remove so much water that hypernatremia develops. If substantial, the hypernatremia may in turn require the use of low-sodium dialysate or the provision of solute-free water, which attenuates the effectiveness of the intended ultrafiltration.

(8) **Hyperglycemia.** In the diabetic patient, the absorbed glucose may result in hyperglycemia, which may require additional insulin during each dialysis with IPD or each day with CAPD. Many CAPD patients add some or all of their daily insulin to their dialysate.

(9) **Insomnia.** Occasionally insomnia complicates overnight, unattended peritoneal dialysis.

5. **Renal transplantation**

a. **Indications for transplantation.** It has long been hoped that a scientific breakthrough in immunologic matching, manipulation, or suppression would allow the uniform success of transplantation so that the indication for renal transplantation would become end-stage renal disease itself (i.e., tansplantation would be preferable to dialysis for all patients). Major advances in transplantation in the past decade have decreased mortality and increased graft retention, but transplantation is still not preferable even for the majority of patients. These advances include restraint in immunosuppressive therapy, especially of acute rejection episodes; preparation of cadaver-transplant recipients with multiple, random, third-party transfusions; preparation of living-related donor transplant recipients with donor-specific transfusions; DR histocompatibility matching; and introduction of cyclosporine, a semiselective immunosuppressive agent. Prevention or treatment of rejection might be equally or more effective, yet less toxic, if nonimmunogenic human monoclonal antibody to selected T-lymphocyte subsets (helper, suppressor, cytotoxic) were developed. Tissue typing for the endothelial-monocyte antigen system as well as HLA antigens may prevent hyperacute rejection not prevented by present crossmatch techniques.

(1) **Absolute indication.** The only nearly absolute indication for transplantation of a patient with end-stage renal failure is the existence of either a healthy identical twin or an HLA-identical sibling willing to donate a kidney. HLA-identical sibling transplantation, although requiring prednisone and azathioprine, has nearly the success of identical-twin transplantation.

(2) **Relative indications.** Transplantation should be seriously considered for the following:

(a) A recipient who has a willing and healthy sibling, parent, or child donor, who is ABO-compatible and shares an HLA haplotype and to whom the recipient does not develop antibodies after three blood transfusions from the prospective donor

(b) A recipient who does not have a relative to donate a kidney but who:

(i) Prefers a cadaveric transplant to dialysis and is well informed, and/or

(ii) Has adapted poorly to dialysis, and/or

(iii) Is a child (because dialysis interferes with the active life of youngsters) and/or

(iv) Is an insulin-dependent diabetic.

What is an acceptable risk to one person, may not be to another, and patient and physician may not always agree; nevertheless, a reasonable and informed patient's preference should be a major factor in the decision whether to transplant or dialyze the patient.

To oversimplify perhaps, the patient must decide whether he prefers dialysis, which offers a slightly greater chance of survival but a lesser chance of full restoration of health, or transplantation, which involves a slightly greater chance of death or of requiring prolonged hospitalization but—if successful—a greater chance of excellent health.

b. Contraindications to transplantation. Contraindications to transplantation are listed below. For the most part they are either self-explanatory or sufficiently technical to require the nephrologist rather than the family physician to explain them to the patient considering transplantation.

(1) Absolute contraindications

(a) ABO incompatibility
(b) Positive crossmatch, except B-cell or D-locus crossmatch (i.e., recipient serum is cytotoxic to donor T-lymphocytes)
(c) Previous cytotoxic antibody in recipient to an HLA antigen of donor
(d) Active infection: disseminated histoplasmosis or coccidioidomycosis, active tuberculosis, active urinary infection, recent hepatitis or recent development of HB_sAg
(e) Active peptic ulcer disease
(f) Oxalosis
(g) Malignancy

(2) Relative contraindications

(a) HLA antigen in donor for subsequent transplant also present in donor of a previously rejected transplant
(b) Antiglomerular basement membrane antibody
(c) Malignancy in recipient within 2 years
(d) Debilitation and malnutrition
(e) Cytotoxic antibodies over 50 percent
(f) Unsuitable bladder and/or urethra
(g) Diverticulosis
(h) Recurrent peptic ulcer disease
(i) Antibody to cytomegalovirus (CMV) in donor if not present in recipient

c. Recipient evaluation and preparation

(1) Evaluation. Recipient evaluation includes testing for the various absolute and relative contraindications to transplantation, particularly to exclude patients (at least temporarily) who have active infection, peptic ulcer, malignancy, debilitation, or an unsuitable lower urinary tract (although transplantation is technically possible with an ileal conduit or other diversion).

(2) Preparation. Preparation of the transplant recipient may require any of several additional surgical procedures before or at the time of transplantation. These procedures include:

(a) Bilateral nephrectomy, if malignancy is the primary renal disease and is bilateral, if malignant hypertension cannot be controlled, or if there is persistent infection with reflux or polycystic disease, or if the renal disease is tuberculosis
(b) Splenectomy if marked leukopenia or thrombocytopenia is present
(c) Urologic surgery (e.g., prostatectomy, ileal conduit)
(d) Vagotomy and pyloroplasty if previous peptic ulcer disease, or colon resection if there is severe diverticulitis
(e) Parathyroidectomy if calciphylaxis, or if hyperparathyroidism is very severe, since it will not regress even after successful transplantation.
(f) Transfusion. A surprising finding verified in centers throughout the world is that blood transfusion with packed cells or whole blood improves the success of cadaveric transplantation. Since blood transfusion can presensitize a patient to transplant antigens and thereby cause rejection and failure of a transplant, at first it was thought that the improved graft survival of transfused patients was simply a matter of patient selection. Specifically, patients presensitized by blood transfusion were excluded from consideration for transplantation at the time a donor kidney became available, either because of high levels of cytotoxic antibodies or because of specific antibodies to the donor kidney with a positive crossmatch. This is not the entire explanation, however. It appears that transfusion actually has a positive effect, although the mechanism is unknown, in decreasing the chance of rejection of a transplant. Thus, patients who do not have a living related donor are currently prepared in most institutions for cadaveric transplantation by the transfusion of one to ten or even more units of nonfrozen, nonsaline, washed red blood cells over weeks to months preceding transplantation.

(g) Donor-specific transfusions. Just as random, third-party transfusions have improved the success rate of cadaveric transplantation, so have donor-specific transfusions for living-related donor transplants. If a parent, child, or sibling donor causes high mixed lymphocyte culture (MLC) reactivity with the potential recipient, the Salvatierra protocol is to give a total of three transfusions at two weekly intervals from the donor to the recipient. Transplantation is carried out a month later if crossmatch is negative, but if it is positive (as it becomes in one-third of patients) the recipient is advised to seek cadaveric transplantation. In the future the percentage of recipients who are sensitized by transfusion from their donors might be decreased by using smaller transfusions of stored donor blood and/or giving azathioprine concurrent with transfusions.

d. Donor evaluation and preparation

(1) Living related donor. Criteria for an acceptable living related renal transplant donor include:

(a) Willingness to donate to a close relative; psychological motivation is important because of an 8 to 15 percent operative morbidity and the risk of having only a single kidney
(b) Two kidneys, both healthy (preferably with single renal artery)
(c) No disease that might be adversely affected (e.g., nephrolithiasis or hypertension)
(d) No active urinary infection
(e) ABO blood group compatibility
(f) Negative crossmatch
(g) HLA typing to identify double or single haplotype matches, then MLC to select among relatives who are single haplotype matches

Many centers have an additional criterion: the recipient's health must be sufficiently good to justify removal of a kidney from a healthy donor, no matter how willing or anxious the relative is to donate.

There appears to be no greater success of renal transplantation from a living unrelated donor than from a cadaver, and such transplants are rarely performed.

(2) Cadaver donor. The mechanically ventilated cadaver with beating heart is thought to be the optimal cadaveric organ donor since good renal perfusion reduces the probability of acute renal failure in the early post-transplant period. Such cadavers are those with brain death (usually due to vehicular accidents or gunshot). Criteria for brain death are, in the absence of hypothermia or central nervous system depressant drugs, (a) no response to external stimuli, (b) no spontaneous muscle movement or respiration, (c) no elicitable brain reflexes, and (d) flat EEG. These observations must be made twice, 24 or more hours apart, by two physicians, neither of whom is a member of the transplant team.

Other criteria for cadaveric donors include:

(a) The deceased and/or next of kin has given permission for organ donation

(b) Age of 10 to 65 years, preferably
(c) No potentially transferable disease such as malignancy (except central nervous system), sepsis, hepatitis, or urinary tract infection
(d) Healthy kidneys: no previous renal disease or severe hypertension, no prolonged ischemia, blood urea nitrogen less than 30 mg per deciliter, creatinine less than 2 mg per deciliter, urine volume more than 20 ml per hour, urinalysis near normal
(e) ABO blood-group compatibility
(f) Negative crossmatch
(g) HLA typing with matching desirable (especially at B locus) but not necessary; serologic DR typing, which allows rapid determination of similar compatibility factors to those tested by the much more time-consuming MLC technique for living-related donors, also desirable
(h) Experimental: pretreatment of donor with 5 gm of cyclophosphamide and 4 gm of methylprednisolone, intravenously

These criteria are also self-explanatory, except for the pretreatment of donors with cyclophosphamide and methylprednisolone. The theoretical rationale for this experimental pretreatment is the destruction of passenger leukocytes (i.e., lymphocytes [and perhaps other cells] in the donor organ that might mediate or augment sensitization to donor antigens, thereby increasing the risk of rejection).

e. **Management and follow-up of transplant recipient.** Two agents have been used for 2 decades to prevent transplant rejection: prednisone and azathioprine. Prednisone may be initiated at 200 mg daily, tapered to 40 mg per day over 2 weeks, and thereafter to 15 mg per day or 30 mg on alternate days (occasionally to even lower dosages, particularly in HLA-identical sibling transplant recipients). Azathioprine is generally employed in a dosage of 2 to 3 mg/kg/day, which is usually continued unless there are complications. If hepatic toxicity develops, cyclophosphamide may be substituted for azathioprine, usually in a dosage two-thirds that of azathioprine.
Cyclosporine, a fungal peptide formerly called cyclosporin A, is a more "selective" immunosuppressant than prednisone (which affects monocytes and blocks interleuken I) or azathioprine (which blocks proliferation of rapidly dividing cells such as immunologically competent cells). Cyclosporine inhibits interleuken II (T-cell growth factor), a mediator required for differentiation and proliferation of cytotoxic and helper T cells (but spares suppressor T cells). Thus, cyclosporine suppresses both cellular and humoral (antibody) immunity. This drug is best used without azathioprine, and although some use it without prednisone, probably it is wise to use prednisone in reduced dosage. Although serum creatinine may be higher than in patients treated with prednisone and azathioprine, the percentage of patients with adequate graft function is higher, and patient survival is superior, with cyclosporine. There is also much less marrow suppression with cyclosporine, but there are a variety of adverse effects including nephrotoxicity and hepatotoxicity (both of which are dose-related), development of lymphomas (especially if azathioprine is given concurrently), and infections, hypertension, hirsutism, gum hyperplasia, and tremor. Cyclosporine (Sandimmune) may be given orally or intravenously, and the dosage should be adjusted according to blood levels.
All other therapies to prevent transplant rejection, such as the administration of antilymphocyte serum and thoracic lymph duct drainage, must be considered experimental because they are not unquestionably efficacious. Such therapies are listed in Table 10-11.
The mainstay of treatment of acute transplant rejection is an increase in adrenal corticosteroid dosage for 3 to 5 days, usually oral prednisone (100 mg/day) or intravenous methylprednisolone (1 gm/day). An experimental therapy of acute steroid-resistant rejection is plasmapheresis (or lymphoplasmapheresis). The theoretical rationale is the removal of cytotoxic antibodies to transplant antigens (and/or the removal of lymphocytes), but preliminary results with this therapy are equivocal. Other experimental therapies for acute rejection include the use of cyclosporine, antilymphocyte globulin, and anticoagulants.

Table 10-11. Immunosuppression for Renal Transplant Recipients

Standard
Prednisone 200 mg/24 hr tapered to 40 mg per day over 2 weeks and thereafter to 15 mg per day or 30 mg q.o.d.
Azathioprine 2 to 3 mg/kg/day
Cyclophosphamide, especially if recipient is intolerant of azathioprine
Cyclosporine
Experimental
Extracorporeal irradiation of recipient blood
Thoracic duct drainage to deplete lymphocytes
Total lymphoid irradiation
Antilymphocyte serum or globulin, antithymocyte globulin
Local x-irradiation of kidney (150 rads for three doses)
Heparin, sodium warfarin, dipyridamole
Solu-Medrol 1 gm per day for 3 to 5 days
Lymphoplasmapheresis
Monoclonal antibody

The transplant recipient is generally followed in the hospital with daily laboratory tests for 2 or 3 weeks. Acute tubular necrosis or other complications may require longer hospitalization. Thereafter, the patient is followed as an outpatient, initially with laboratory tests every 2 to 3 days. The most crucial parameters to follow are urinary volume, BUN and serum creatinine, urinary protein excretion, weight and blood pressure, and—to detect excessive dosage of azathioprine—white blood count, platelets, and hematocrit. Other parameters, such as serum potassium, bicarbonate, calcium, and phosphate, and urine culture and sediment, are also followed. Fever is an ominous sign that requires prompt evaluation for infection and/or rejection, the former sometimes triggering the latter.

f. **Efficacy of transplantation.** Uremia is "cured" with successful renal transplantation, but preexistent disease (e.g., diabetes) and preexistent complications of uremia (e.g., hypertension, cardiovascular disease, hyperparathyroidism) may be aggravated. Furthermore, the original renal disease may recur in the transplant. Diseases that may recur include oxalosis, glomerulonephritis (particularly antiglomerular basement membrane nephritis, rapidly progressive glomerulonephritis, mesangiocapillary glomerulonephritis, and focal glomerular sclerosis), diabetes, and cystinosis.

g. **Complications of transplantation**

(1) **Technical complications. Early** technical complications of renal transplantation include:
(a) Acute tubular necrosis
(b) Wound infection
(c) Vascular anastomotic leak or occlusion
(d) Ureteral anastomotic leak or obstruction
(e) Ureteral rupture (which may be due to rejection)

Late technical complications include lymphocele (which may cause ureteral obstruction) and renal artery stenosis (which may cause hypertension). The one complication worthy of discussion is acute oliguric renal failure. It often occurs after cadaveric transplantation and infrequently after living related donor transplantation. Oliguria in the immediate post-transplant period complicates detection of rejection since the hallmark of acute rejection is a decrease in urinary volume. Nevertheless, several tests, including ultrasound, renal scan, and fractional sodium excretion, allow distinction between acute tubular ne-

crosis and hyperacute or acute rejection, and thus appropriate management can be provided. Ultrasound is normal, renal blood flow generally well preserved, and fractional sodium excretion is high with acute tubular necrosis; the opposite is true in patients with renal transplant injection.

(2) **Drug-related complications.** Complications of prednisone, immunosuppressive agents, and antacids are as follows:

- **(a)** Steroid: infection, masking of infection, Cushing's syndrome, psychosis, peptic ulcer, pancreatitis, cataracts, osteonecrosis
- **(b)** Azathioprine: infection, bone marrow depression, liver damage, malignancy
- **(c)** Cyclophosphamide: infection, bone marrow depression, ovarian fibrosis, aspermia, hemorrhagic cystitis, pulmonary fibrosis, alopecia, malignancy
- **(d)** Cyclosporine: infection, renal and liver damage, lymphoma, tremor, hirsutism and gum hyperplasia
- **(e)** Antilymphocyte globulin: thrombocytopenia, anemia, disseminated intravascular coagulation, fever, arthritis, glomerulonephritis, anaphylaxis if given intravenously, pain if given intramuscularly, infection
- **(f)** Antacid: hypophosphatemia

Hypophosphatemia is a complication that may be due to decreased renal tubular reabsorption of phosphate, which in turn is due to secondary hyperparathyroidism failing to resolve in the early post-transplant period; it may also be drug-related, particularly secondary to antacids used to lessen the risk of peptic ulceration from prednisone.

(3) **Immunologic complications.** Four types of immunologic complications of renal transplantation are:

- **(a)** Rejection: hyperacute, acute, chronic
- **(b)** Infection: common or esoteric pathogens
- **(c)** Malignancy: reticulum cell sarcoma, lymphoma, cancer
- **(d)** Recurrent glomerulonephritis: 5 percent of allografts, 65 percent of isografts

Of these, transplant rejection deserves discussion since it may occur in any transplant other than between identical twins. Hyperacute rejection, which occurs within minutes to hours (occasionally days) following a transplant, is due to preformed circulating antibody and results in fulminant vascular disease of the renal graft. It may also cause microangiopathic hemolytic anemia, thrombocytopenia, hemorrhage, and even renal rupture. It is unresponsive to therapy, and nephrectomy should be performed without delay.

Acute (or classic) transplant rejection may begin as early as several days or as late as years following a transplant, but is most common within the first 2 months. Sometimes it appears to be triggered by intercurrent infection. Acute rejection may result in fever, tenderness over the graft, hypertension, decreased urinary volume, increased BUN and creatinine, an active urinary sediment, and a decrease in urinary sodium concentration. Fortunately, this form of rejection may respond to an increase in oral prednisone or an infusion of methylprednisolone for several days. Unless the patient is severely oliguric, azathioprine dosage is not decreased. If steroid therapy does not abrogate the rejection, antilymphocyte globulin, cyclosporine, heparin infusion, or lymphoplasmapheresis should be tried. If rejection fails to respond, nephrectomy may be necessary for fever, pain, or thrombocytopenia.

Chronic rejection does not begin for months to years following transplantation and occurs in either of two forms: a proliferative glomerulonephritis or an interstitial nephritis with fibrosis. Both forms are relentless, irreversible, and unresponsive to therapy, but nephrectomy is rarely necesary.

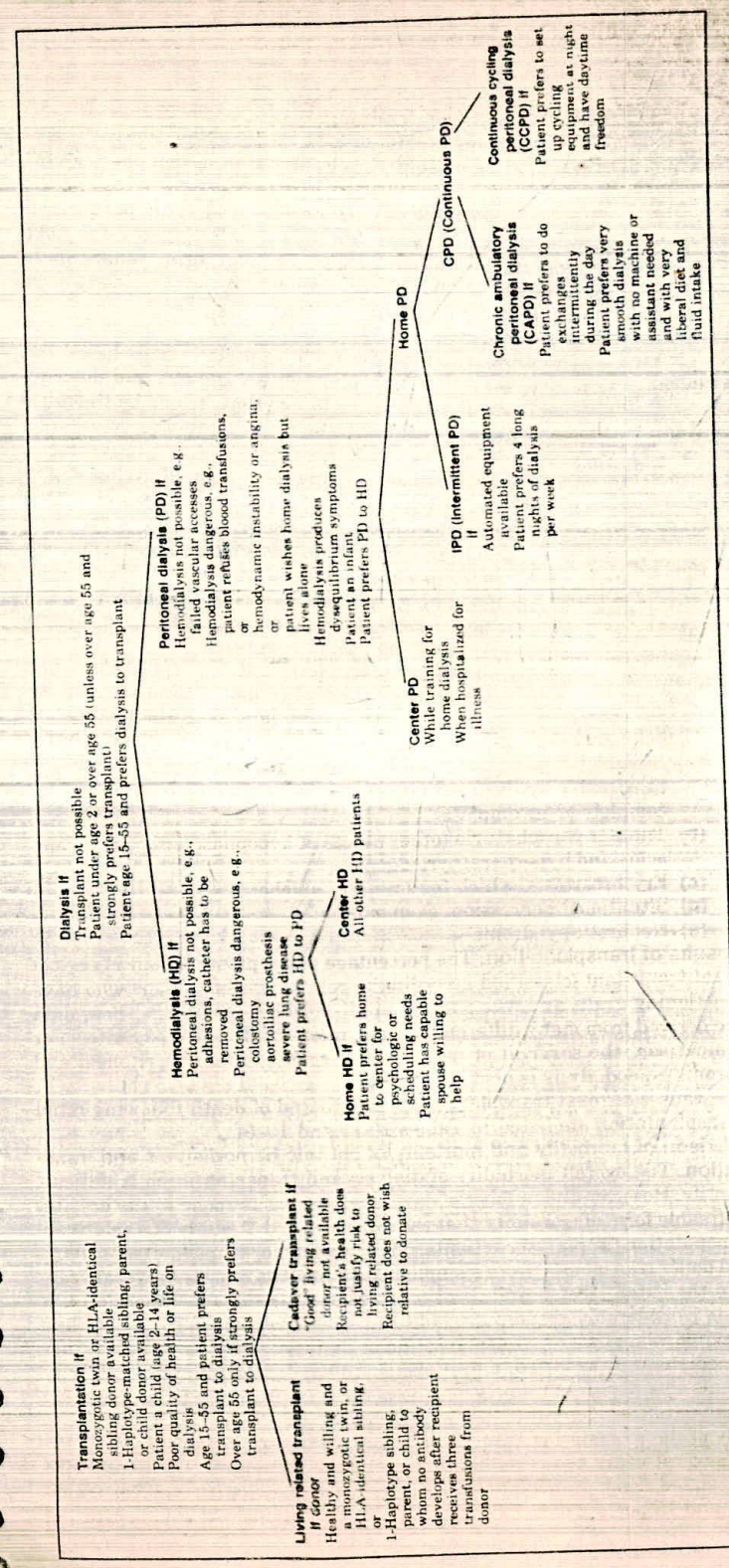

Fig. 10-1. Choice of therapy for end-stage renal disease.

Table 10-12. Results of Transplantation and Chronic Dialysis

Donor (if transplant)	Functioning Graft		Surviving Patient[a]	
	1 Year (%)	5 Years (%)	1 Year (%)	5 Years (%)
Identical twin	95	80	98	90
HLA-identical sibling	90	80	98	85
1-Haplotype-identical relative[b]	80	70	95	75
Continuous peritoneal dialysis	—	—	90[c]	[d]
Chronic hemodialysis	—	—	85	60
Cadaver[e]	60	40	85	60

[a]Survival of diabetics undergoing either hemodialysis or transplantation is 5 to 10 percent worse than the above data at 1 year (20% worse for CAPD) and 15 to 20 percent worse at 5 years
[b]Sibling, parent or child with donor-specific transfusions before transplant.
[c]But only 60 to 80 percent of patients who start are still undergoing CAPD at the end of 1 year.
[d]Data are not yet available.
[e]These results with azathioprine and prednisone appear to be substantially improved with cyclosporine and prednisone

(4) **Miscellaneous complications.** Additional complications include:
- (a) Renal tubular acidosis: early or late; with or without rejection; proximal, usually transient; distal, often persistent or recurrent; complete or incomplete
- (b) Tubular phosphaturia (other causes of hypophosphatemia are antacids and hyperparathyroidism)
- (c) Erythrocytosis, which may require phlebotomy
- (d) Situational depression, even suicide
- (e) Nephrotic syndrome

h. **Results of transplantation.** The percentage of recipients of four classes of renal transplant (classified according to relationship to donor) who have functioning grafts and who survive are listed in Table 10-12. These data are derived from many different sources, mostly in the United States. For comparison, the survival of patients undergoing chronic peritoneal and chronic hemodialysis is also listed.
The causes of renal transplant graft failure and of death following renal transplantation are listed in Tables 10-13 and 10-14.

6. **Comparison of morbidity and mortality of chronic hemodialysis and transplantation.** The overall morbidity of dialysis and transplantation is difficult to quantify. However, the number of days a patient has to spend in the hospital is a definable form of morbidity that can be quantified. A study of a relatively small population (92 dialysis patients, 64 cadaver donor transplants, 21 living related donor transplants) from a single institution was reported several years ago. To the extent that hospitalization correlates with overall morbidity, it suggests considerably greater morbidity from cadaver transplantation than from living related donor transplantation or dialysis; however, means rather than medians were reported, and it should be appreciated that the minority of patients who require extremely long hospitalization following transplantation skew the data considerably.
A study of the mortality of transplant and dialysis patients at a single institution several years ago revealed that at 1 year, 7 percent of patients with living related donor transplants, 11 percent of patients with cadaver transplants, and 15 percent of home dialysis patients had died. At this institution

Table 10-13. Causes of Renal Transplant Graft Failure

Cause	Percentage of Cases
Rejection	60
Death of patient	25
Technical	10
Acute tubular necrosis	4
Recurrent disease	1

Table 10-14. Causes of Death After Renal Transplantation

Cause	Percentage of Cases	
Sepsis	30	60
Rejection and sepsis	10	
Rejection	10	
Immunosuppression	10	
Technical	10	
Other	8	
Unrelated to transplant	5	
Cardiovascular	5	
Gastrointestinal hemorrhage	4	
Cerebrovascular	2	
Suicide	2	
Pulmonary embolus	1	
Neoplasm	1	
Hepatitis	1	
Pancreatitis	1	

the percentage of renal grafts functioning at 1 year was 72 percent for living related donor transplants and 64 percent for cadaver transplants.
A newer study of the mortality of transplant and dialysis patients at a single institution revealed significantly better survival in patients transplanted with a graft from a living related donor (98% at 1 year, 75% at 5 years) than in those transplanted with a cadaveric graft (85% at 1 year, 63% at 5 years) or in those undergoing chronic hemodialysis (90% at 1 year, 55% at 5 years). The differences in survival between cadaveric transplant and chronic hemodialysis were not significant, and it was concluded that a patient's decision between cadaveric transplantation and chronic hemodialysis should be based on pyschosocial rather than medical grounds. The paper noted that differences in survival of home hemodialysis versus center hemodialysis patients are not yet known.

7. **A proposed schema for choice of therapy for ESRD.** Figure 10-1 is the author's proposed schema for choice of therapy for ESRD. To recapitulate briefly, the physician should urge renal transplantation for children and particularly for patients with a healthy identical twin or HLA-identical sibling who is a willing donor. The physician should also offer transplantation to patients who have a 1-haplotype-matched relative willing to donate, or to informed patients who prefer it to dialysis. Conversely, the physician should recommend dialysis for patients incapable of successful transplantation and for elderly patients. The majority of these patients do not have contraindications to hemodialysis or to

peritoneal dialysis. After the patient is informed of the advantages and disadvantages of each, the choice between hemodialysis and peritoneal dialysis usually should be the patient's preference. Technologic developments in aseptic technique may so reduce the frequency of peritonitis that chronic peritoneal dialysis (CPD) may become the preferred mode of dialysis for all patients with ESRD who do not prefer transplantation.

Although progress in the simplification of dialysis and in transplantation immunology has been slower than desired, it should be appreciated that in less than 25 years, not one, not two, but three forms of therapy (transplantation, hemodialysis, and peritoneal dialysis) have become available for patients who previously would have died. Furthermore, these therapies are available throughout the world, and in this country are available to virtually all patients who can benefit from them. No longer does the physician select the proper patient for the treatment; rather, one selects the proper treatment for the patient.

Suggested Reading

Articles and Chapters for Extended Reading

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11

Approach to Drug Use in the Azotemic Patient

William M. Bennett

There are increasing numbers of patients with renal dysfunction who require therapy for intercurrent medical problems. Since most drugs or their metabolites undergo renal excretion, compromised renal function may allow accumulation of a drug to toxic levels unless proper dosage adjustments are made. Furthermore, the physiologic abnormalities of renal failure may alter the expected pharmacologic response of a drug, resulting in an untoward reaction. The goal of therapy in the patient with renal dysfunction is to tailor the dosage regimen to the individual patient's clinical situation to simulate normal therapeutic conditions.

I. Principles of prescribing to azotemic patients: stepwise approach

A. Assessment of renal function—step 1. The extent of accumulation of drugs given in the usual doses to patients with renal failure depends on the degree of renal dysfunction. For the proper adjustments to be made, the level of renal function must be known. Blood urea nitrogen (BUN) is an unsuitable parameter for this purpose, since it is influenced by extrarenal factors such as diet, steroid therapy, and gastrointestinal bleeding. Instead, measurement or approximation of glomerular filtration rate is necessary to prescribe optimally for patients with renal disease. The endogenous creatinine clearance is customarily used. Although measurement of creatinine clearance is widely available and convenient, the requirement of carefully timed urine collections limits its usefulness in acutely ill patients. Since creatinine excretion is proportional to lean body mass and inversely proportional to age, formulas and nomograms have been developed to estimate creatinine clearance from the serum creatinine without the need for urine collection. One convenient formula is:

$$\text{creatinine clearance} = \frac{(140 - \text{age})(\text{body weight in kg})}{72 \times \text{serum creatinine}}$$

(The calculated value should be multiplied by 0.85 for women).

If renal function is decreasing rapidly, the measured creatinine clearance or the estimated value will overestimate the actual value. Thus, in patients with acute renal failure dosage adjustments should be based on creatinine clearance of less than 10 ml per minute. Otherwise, serious overdosage may result. Conversely, if the patient has improving function, care should be taken to avoid underdosing, since serum creatinine may remain elevated for several days after urine output has increased. In this chapter a creatinine clearance of less than 10 ml per minute will be considered advanced or severe renal failure.

B. Determining the need for dosage adjustment—step 2. Drugs that have a normal renal route of elimination or that are transformed to active metabolites requiring intact renal function for excretion are the agents that generally require major dosage adjustments in renal insufficiency. Thus, some knowledge of a drug's pharmacology is essential to rational prescribing for these patients. This is especially true for drugs with a narrow toxic-therapeutic ratio, such as cardiac glycosides, antiarrhythmics, and aminoglycoside antibiotics. The situation is more complex when metabolites with pharmacologic activity are accumulated but the parent compound is normally metabolized by the liver. An example of this is normeperidine accumulation in patients with renal failure, which results in sei-

zures and coma despite normal hepatic biotransformation of the parent compound meperidine.

For measured or estimated creatinine clearances above 30 ml per minute it is seldom necessary to modify doses except for antibiotics and cardiovascular drugs. Common drugs with pharmacologically active or toxic metabolites are listed in Table 11-1. In situations in which the clinician is in doubt about the need for dosage modification it is safest to look up the usual pharmacologic handling of the compound or specific recommendations in a standard reference source.

C. **Choosing the loading doses of drugs—step 3.** When patients receive multiple drug doses at uniform close intervals, the average plasma concentration rises until a steady state concentration is reached. The time required to reach approximately 90 percent of this concentration is 3.3 times the half-life of drug elimination. Since the half-life may be markedly prolonged in renal failure, effective therapy may be greatly delayed if dosage is simply adjusted for a prolonged half-life. Therefore, a large initial dose, or loading dose, is usually required. This is of particular relevance in antibiotic, antiarrhythmic, and digitalis therapy, in which efficacy is needed quickly. In practice, the usual initial dose can be given. If there are adverse hemodynamic factors, such as extracellular fluid volume depletion or dehydration, it may be prudent to reduce the initial dose to 75 percent of that usually prescribed. This applies in particular to cardiac glycosides such as digoxin or ototoxic aminoglycoside antibiotics.

D. **Finding a maintenance dosage—step 4.** In practice, the desired dosage regimen can be reached either by lengthening the interval between doses to correspond to the delayed excretion of the particular drug in renal failure or by reducing the size of the individual dose prescribed at the same interval as usual. The interval extension method is particularly convenient for drugs with relatively long serum half-lives, whereas the dosage reduction method is preferred when a more constant serum level is desirable. The clinician usually uses a combination of these methods, based on guidelines published in the literature. Any fixed formula must be adapted to the individual situation since many complex variables may modify the recommendations.

E. **Use of the serum drug level to monitor therapy—step 5.** A standard drug dosage will lead to a variety of therapeutic effects in individual patients. To avoid serious over- or underdosage, serum drug concentrations can be used as therapeutic guides. Ranges of concentrations associated with safe, yet efficacious, therapy are being increasingly identified for most categories of drugs used to treat patients with renal failure. Therapeutic ranges of some common agents that can be used in clinical practice are shown in Table 11-2. Serum levels can be interpreted fully

Table 11-1. Common Drugs with Active or Toxic Metabolites Dependent on Renal Excretion

Parent Drug	Active Metabolite
Adriamycin	Adriamycinol
Allopurinol	Oxypurinol
Azathioprine	6-mercaptopurine
Cephalosporins	Desacetylcephalosporins
Chlordiazepoxide	Oxazepam
Clofibrate	Chlorophenoxyisobutyrate
Diazepam	Oxazepam
Meperidine	Normeperidine
Primidone	Phenobarbital
Procainamide	N-acetylprocainamide
Propranolol	4-hydroxypropranolol
Propoxyphene	Norpropoxyphene
Sulfonamides	Acetylsulfonamides

Table 11-2. Serum Drug Levels and Changes Produced by Decreased Protein Binding in Renal Failure

Drug	Therapeutic Serum Concentrations	Effect of Renal Disease on Protein Binding
Antibiotics		
Aminoglycosides		
Amikacin	15–30 μg/ml	No effect
Gentamicin	4–10 μg/ml	No effect
Netilmicin	4–10 μg/ml	No effect
Tobramycin	4–10 μg/ml	No effect
Cephalosporins	Serum levels not clinically useful	No effect
Penicillins		
Carbenicillin	100–300 mg/L	Some decreased binding in uremia
Penicillin G	1–25 mg/L	Some decreased binding in uremia
Ticarcillin	100–300 mg/L	Some decreased binding in uremia
Sulfonamides	Serum levels not clinically useful	Decreased binding in uremia
Cardiovascular Drugs		
Digoxin	0.8–2 ng/ml	No effect
Digitoxin	10–25 ng/ml	Decreased binding in uremia and with heparin therapy during dialysis
Disopyramide	2–7 mg/L	No effect
Furosemide	Serum levels not clinically useful	Decreased binding in uremia
Lidocaine	1.5–5 mg/L	No effect
Procainamide	4–8 mg/L	No effect
Propranolol	20–50 ng/ml	No effect
Quinidine	2–6 mg/L	No effect
Miscellaneous drugs		
Carbamazepine	2–6 mg/L	No effect
Ethosuximide	40–80 mg/L	No effect
Lithium	0.5–1.3 mEq/L	No effect
Nortriptyline	50–150 μg/L	No effect
Phenobarbital	15–30 mg/L	Decreased binding in uremia
Phenytoin	10–20 mg/L	Decreased binding in uremia; side effects can be seen at "therapeutic" levels
Primidone	6–12 mg/L	Decreased binding in uremia of major metabolite, phenobarbital
Salicylate	200–300 mg/L	Decreased binding in uremia
Theophylline	8–20 mg/L	Increased toxicity with low serum albumin

only if the elapsed time from the last dose and the elimination half-life in that particular patient are known. In practice, it is best to check a serum level 1 to 2 hours after an oral dose or 30 minutes to 1 hour after a parenteral dose to get a peak value. For drugs with long half-lives in renal failure, such as digoxin, the time of sampling is less critical, since in the steady state the serum levels vary relatively little between doses.

Many drugs, such as diphenylhydantoin, digitoxin, and quinidine, travel in the bloodstream bound extensively to serum proteins, predominantly albumin. Most techniques for measuring serum concentrations determine the total drug concentration. In clinical situations in which there is a low serum albumin, such as nephrotic syndrome, or in which drug affinity for plasma proteins is diminished by uremia, an adverse drug reaction may occur with serum levels within the accepted therapeutic range. This occurs because only the free drug in serum or plasma interacts with receptors at the sites of drug action to produce pharmacologic effects. Important changes in drug protein binding due to renal disease are also noted in Table 11-2. These should be kept in mind in interpreting serum levels in patients who experience symptoms and signs of drug toxicity at therapeutic levels. If decreased plasma protein binding occurs, it may not be possible to predict precisely the consequences on pharmacologic action. In uremia, the elimination half-life of phenytoin may actually be decreased, due to enhancement of conversion of free drug to the major metabolite 5-phenyl-5-parahydroxyphenylhydantoin. Although this metabolite depends on the kidney for elimination from the body, it is pharmacologically inactive. Thus, although protein binding must be considered in evaluating serum levels, it cannot be generalized that dosages of highly bound drugs necessarily should be reduced for patients with renal failure.

F. Drug interactions and interference with laboratory tests—step 6. In view of the multiple medications often prescribed for patients with renal disease, it is well to review any possible drug interactions before introducing the therapeutic regimen to the patient. This is best done by reference to a standard source, since the clinician will find it difficult to remember all of the potential interactions. This is particularly important when warfarin is ordered in patients with renal disease, since interaction with many compounds can displace warfarin from protein-binding sites. The drug interaction with warfarin combined with the platelet defect of uremia may cause severe bleeding. Other examples are the poor oral absorption of tetracycline antibiotics because of gastrointestinal binding by antacids prescribed for hyperphosphatemia, and interference with methotrexate excretion by concomitant penicillin treatment, which can potentiate bone marrow toxicity. Careful consideration of the pharmacologic properties of individual drugs and a mental check for possible interactions should prevent most problems.

With increasing use of automated laboratory tests in nephrology it has become evident that abnormal values that do not relate to any clinical disease in the patient may be obtained. These aberrant results may lead to unnecessary expense or even inappropriate treatment. The interference is most commonly due to a drug or metabolite altering the actual measurement. However, many drugs interfere with laboratory tests through their pharmacologic actions (Table 11-3). Examples of the latter include increases in serum creatinine produced by trimethoprim and cimetidine, which compete for transport sites of tubular secretion. The alert clinician should not rely on laboratory abnormalities alone without checking on possible drug interference.

G. Adjustments for hemodialysis or peritoneal dialysis—step 7. If the patient with renal failure is undergoing dialysis, the final step in formulating a therapeutic plan is to adjust for drug losses or physiologic changes induced by the procedure. Drugs that are effectively removed by clinical hemodialysis usually have molecular weights less than 500 daltons. The driving force in hemodialysis is the concentration gradient of unbound drug between plasma water and dialysate. As protein binding of the drug increases, dialysis clearance decreases. Semisynthetic penicillins that have greater than 90 percent protein binding are poorly removed by dialysis. Although propranolol has a molecular weight of only 260 daltons, it is not dialyzable because of a high degree of protein binding. In addition to protein binding and molecular size, removal of a drug during dialysis depends on the type of artificial kidney employed; most clinically used dialyzers have cuprophane or cellulose membranes, which have similar characteristics. In general, regularly scheduled drug doses should be given after dialysis to minimize removal. For drugs with considerable removal, it is best to replace a full maintenance dose following dialysis (Table 11-4). Since hemodynamic factors and various other patient variables make precise adjustments difficult in clinical situations, it is best to check serum levels before the next regularly scheduled dose. A serum level measured immediately postdialysis may not accurately reflect the total body burden since equilibration from intracellular pools may occur for several hours.

There has been a recent resurgence of interest in chronic peritoneal dialysis. Because of the relatively large surface area available for transfer, the peritoneal membrane is five to ten times more permeable to large-molecular-weight solutes

Table 11-3. Drug Interference With Laboratory Tests in Nephrology

Test	Drug	Effect
Serum creatinine	Ascorbic acid	Elevates total chromogen
	Para-aminohippurate	Elevates total chromogen
	Methyldopa/levodopa	Reducing agents interfere with autoanalyzer; increases when blood level > 2 mg/ml
	Trimethoprim	Raises serum level by competition for tubular secretion
	Acetylsalicylic acid	May raise serum level by secretory competition
	Cefoxitin	Increases serum level by interference with Jaffe reaction
	Cimetidine	Increases serum level by secretory competition
Serum urea nitrogen	Acetohexamide	Increases; mechanism unclear
Serum uric acid	Ascorbic acid	Increases in nonenzymatic methods
	Salicylates	Increases in nonenzymatic methods
	Aminophylline	Increases in nonenzymatic methods
	Methyldopa	Increases with phosphotungstate method
	Acetaminophen	Increases in nonenzymatic methods
	Levodopa	Interference in autoanalyzer
Change in urine color	Rifampin	Red-brown
	Sulfasalazine	Red-brown
	Phenothiazines	Red-brown
	Metronidazole	Darkens on standing
	Methyldopa	Darkens on standing
	Nitrofurantoin	Darkens on standing
	Amitriptyline	Blue-green
	Triamterene	Blue-green
Urinary protein determinations	Aminosalicylic acid	False-positive reaction
	Acetylsalicylic acid	False-positive reaction
	Cephalosporins	False-positive reaction
	Contrast media	False-positive reaction
	Penicillins	False-positive reaction
	Sulfonamides	False-positive reaction
	Acetazolamide	False-positive reaction
	Tolbutamide	False-positive reaction
	Tolmetin	Salicylic acid method only

Table 11-4. Common Drugs Requiring Supplemental Dosage After Conventional Hemodialysis

Antibiotics	
Aminoglycosides:	Amikacin, gentamicin, netilmicin, streptomycin, tobramycin
Cephalosporins:	Cephalothin, cefamandole, cephazolin, third-generation cephalosporins
Penicillins:	Amoxicillin, ampicillin, azlocillin, carbenicillin, mezlocillin, penicillin, piperacillin, ticarcillin
Antifungal drugs	5-flucytosine
Antituberculous drugs	Ethambutol, isoniazid, cycloserine
Miscellaneous antiinfective drugs	Acyclovir, chloramphenicol, metronidazole, sulfisoxazole, trimethoprim-sulfamethoxazole
Analgesics	Acetylsalicyclic acid, acetaminophen
Sedatives, hypnotics, and tranquilizers	Phenobarbital, lithium
Cardiovascular drugs	
Antiarrhythmics:	Disopyramide, procainamide, quinidine
Antihypertensives:	Atenolol, captopril, methyldopa, metoprolol, nadolol, sodium nitroprusside
Miscellaneous drugs	Azathioprine, cyclophosphamide, ethosuximide, 5-fluorouracil, gallamine, methotrexate, primidone, theophylline

than clinically used hemodialysis membranes. However, the relatively low blood flow to the peritoneum limits the removal of small-molecular-weight drugs. Recently, the use of continuous ambulatory peritoneal dialysis (CAPD) has gained widespread acceptance as a treatment for end-stage renal disease. Peritonitis is a major complication of this procedure. In general, there is excellent drug absorption following intraperitoneal administration. For the aminoglycosides, cephalosporins, and penicillins, the levels of drug achieved in peritoneal fluid following systemic administration are inconsistent. Table 11-5 lists drugs that require supplemental doses during peritoneal dialysis.

II. Use of specific common drugs in azotemic patients

A. Digitalis glycosides. In renal failure cardiac glycosides are usually given in reduced amounts at customary dosage intervals after adequate body stores are provided with the usual digitalizing dose. It is desirable for clinicians to become familiar with one or at most two digitalis preparations. Digitoxin half-life and serum levels are not altered by the presence of renal failure, which allows standard digitalizing and maintenance doses. However, the long half-life of 6 to 8.5 days makes it less desirable for unstable patients, especially those with cardiac arrhythmias. Heparin may cause some decrease in digitoxin-plasma protein binding; therefore patients undergoing hemodialysis necessitating heparin use may require a slightly lower digitoxin blood level to avoid toxicity. Digoxin appears to be the drug of choice for most patients. The half-life of digoxin is 1.6 days in patients with normal renal function and 4.4 days in anuric patients. After a digitalizing dose that is approximately 75% of normal, the daily maintenance dosage is equal to nonrenal losses (15% of body stores) plus urinary losses. Since urinary losses are inversely proportional to the creatinine clearance, patients with end-stage renal disease lose very little digoxin in the urine and may be adequately treated with 0.125 mg three to five times per week. Dialysis does not affect digoxin or digitoxin serum levels; however, shifts in potassium or hydrogen ion during dialysis may provoke cardiac arrhythmias. It is recommended that dialysate potassium be 3.0 mEq per liter in digitalized patients. Treatment regimens for use of digitalis glycosides in renal failure are shown in Table 11-6.

Table 11-5. Drugs Cleared by Peritoneal Dialysis that Require Supplementary Doses During Clinical Therapy

Antimicrobial agents	Antiarrhythmic agents
Amikacin	Procainamide*
Carbenicillin	Quinidine
Cephalothin	
Cephradine	Antihypertensive agents
Ethambutol	Methyldopa
Flucytosine	
Gentamicin	Neurologic agents
Isoniazid	Diphenylhydantoin
Streptomycin*	Gallamine
Sulfamethoxazole-trimethoprim*	Sedatives, hypnotics, tranquilizers
Sulfisoxazole	Lithium carbonate
Ticarcillin	Phenobarbital
Tobramycin	
Analgesics	Miscellaneous
Acetylsalicylic acid	Aminophylline*

*In vivo data are lacking, but indirect evidence strongly supports placing the drug in this category.
Source: Adapted from T. A. Golper, Drugs and peritoneal dialysis. *Dialysis and Transplantation.* 8:41, 1979.

B. Antiarrhythmic drugs

1. **Procainamide.** Procainamide is metabolized to a pharmacologically active metabolite *N*-acetylprocainamide, which has antiarrhythmic potency similar to the parent compound. The metabolite has a long life and is eliminated from the body almost entirely by renal excretion. Conventional plasma level determinations do not measure the metabolite. Doses of procainamide should be given every 8 to 12 hours in patients with end-stage renal disease. Procainamide and *N*-acetylprocainamide are readily removed by dialysis, and a full maintenance dose should be given following a dialysis treatment. Hypotension, arrhythmias, and conduction disturbances may occur as a consequence of overdosage.
2. **Lidocaine.** Lidocaine undergoes extensive hepatic metabolism similar to other antiarrhythmics. No increased central nervous system toxicity has been observed in patients with renal disease. The drug is not dialyzable, and it can be used in the usual way for azotemic patients.

Table 11-6. Cardiac Glycosides in Renal Failure

Drug	Digitalizing Dose	Maintenance Dose	Dialysis
Digitoxin	Customary	No change required	Keep dialysate K^+ at 3.0 mEq/L; monitor serum level if heparin is used
Digoxin	75–90% of usual	Creatinine clearance > 50 ml/min, 0.25–0.5 mg/day; 10–50 ml/min, 0.125–0.25 mg/day; < 10 ml/min, 0.0625–0.125 mg/day	Keep dialysate K^+ at 3.0 mEq/L; monitor serum level

ifications are needed only when creatinine clearance is less than 10 per minute. Cephalothin, cefazolin, and cephalexin follow similar pharmacokinetics. Cephalothin is given in the usual loading dose followed by maintenance doses every 8 to 12 hours for end-stage renal patients. For the orally active agents such as cephalexin, adequate blood levels are achieved by a 1-gm load, followed by 500 mg every 12 hours, in patients with creatinine clearances less than 10 ml per minute. Usual doses are necessary for urinary tract infections. Cephalosporins are removed from plasma by hemodialysis. A maintenance dose given after hemodialysis returns plasma concentrations to within the therapeutic range. The third-generation cephalosporins have characteristics similar to other drugs in the same class. An exception is cefoperazone, which undergoes nonrenal elimination and thus requires no dosage adjustment in renal disease.

4. **Miscellaneous antibiotic, antifungal, and antituberculous drugs**
   a. **Chloramphenicol.** No alteration in dose is necessary for chloramphenicol, even in patients with severe renal insufficiency. However, dose-related, reversible, hematopoietic depression is more common in patients with impaired renal function. This may be related to accumulation of toxic metabolites normally excreted by the kidneys.
   b. **Erythromycin and clindamycin.** Erythromycin and clindamycin, which are metabolized primarily by nonrenal mechanisms, are prescribed in usual therapeutic doses to patients with impaired renal function.
   c. **Lincomycin.** Lincomycin exhibits a prolonged half-life in renal insufficiency. The normal dose of lincomycin should be reduced by one-half in patients with advanced renal failure. Hemodialysis does not significantly alter the plasma concentrations of erythromycin, clindamycin, or lincomycin.
   d. **Nitrofurantoin.** Nitrofurantoin should be avoided in patients with renal insufficiency. It is ineffective therapy when the creatinine clearance decreases to less than 30 ml per minute. Moreover, toxic metabolites may cause peripheral neuropathy in patients with far advanced renal disease.
   e. **Sulfonamides.** Most sulfonamides are ineffective in patients with renal failure because their elimination and urine concentration is dependent largely on glomerular filtration. The sulfamethoxazole-trimethoprim combination has recently been shown to be efficacious in the therapy of *Pneumocystis carinii* infections in immunosuppressed patients. Dosage intervals should be extended to 24 hours when creatinine clearance is less than 10 ml per minute. Hemodialysis removes the drug from plasma; therefore, a maintenance dose should be given after dialysis.
   f. **Tetracyclines.** Tetracyclines have well-known antianabolic effects that may aggravate azotemia. They should be avoided if possible in patients with uremia. If a tetracycline is specifically indicated, doxycycline is the drug of choice. No alteration in the dosage schedule of this agent is required for patients with renal failure.
   g. **Vancomycin.** Vancomycin may cause damage to the eighth nerve if the serum levels are high (greater than 80 mg/ml). It is eliminated primarily by the kidneys, and dosage modification is needed in renal disease. The drug has a long half-life, and dosage intervals should be extended to 3 to 6 days in advanced renal failure. Since the drug is not removed by dialysis, vancomycin is a popular agent in the treatment of vascular access-related infections. Serum concentrations should be obtained to ensure optimal therapy.
   h. **Amphotericin.** Amphotericin B, a nephrotoxic agent, is widely used for treating systemic mycotic infections. Although decreases in renal function are commonly observed, serum drug concentrations do not rise. Dosage need not be altered except in severe renal failure. In such patients, the dose may be decreased by one-fourth. Amphotericin B is highly protein bound and is not removed by hemodialysis.
   i. **Flucytosinen Miconazole and Ketoconazole.** Flucytosine is excreted by the kidneys. Dosage intervals should be extended to 24 hours in patients with severe renal failure. Flucytosine is removed from plasma by hemodialysis. Single doses of 25 to 50 mg per kilogram body weight postdialysis produce nontoxic, therapeutic concentrations in patients undergoing hemodialysis every 48 to 72 hours. Frequent monitoring of serum concentrations is recommended. Miconazole and ketoconazole require no dosage adjustment in patients with renal failure.
   j. **Antituberculous drugs.** Isoniazid is eliminated from the body predominantly by hepatic acetylation to an inactive metabolite. In most patients no dosage alteration is required in renal insufficiency. However, in patients with reduced hepatic metabolism (slow acetylators), the dosage should be reduced by approximately one-third if the creatinine clearance is less than 10 ml per minute. Isoniazid is removed by hemodialysis. Serum concentrations may be followed as a guide to dosage. The dose of rifampin need not be altered in renal failure or adjusted for dialysis. Isolated case reports of nephrotoxicity have been reported in patients receiving rifampin. Renal function should be monitored in such patients. Ethambutol is excreted only through the kidneys. The dosage interval needs to be extended 24 to 48 hours for severe renal failure. Supplemental doses should be given after dialysis.

5. **Treatment of urinary tract infections in patients with renal disease.** In patients with renal dysfunction, effective treatment of urinary tract infection is difficult to achieve. Delivery of antibiotics in adequate concentration to sites of infection in the diseased urinary tract may not be possible.
   Drug therapy for urinary infection in patients with poor renal function needs to be selective to achieve effective antibiotic concentrations in the urine or renal parenchyma. Penicillins and cephalosporins, both of which undergo tubular secretion, seem to achieve adequate urinary levels despite severe reductions in creatinine clearance. Trimethoprim-sulfamethoxazole has also been reported to achieve clinical urinary sterilization in patients with severe reductions of renal function. It should be emphasized that the customary dosage adjustments for renal failure will prevent high blood concentrations of antibiotic but may reduce the concentrations achievable in the urine. Thus, ampicillin, cephalexin, and trimethoprim-sulfamethoxazole should be used in full dosage for urinary tract infections in patients with concomitant, severe renal disease. Aminoglycoside antibiotics do not penetrate well into diseased renal parenchyma or achieve reliable urinary tract levels in patients with severe renal failure (i.e., with creatinine clearances less than 10 ml/min). Thus, they should be reserved for patients with septicemia.
6. **Treatment of dialysis-access infections.** Of the infectious problems encountered in patients with chronic renal failure, infections of dialysis vascular access sites are most troublesome. External shunts have a much higher incidence of infection than internal arteriovenous fistulae. Although the predominant organism causing these infections is *Staphylococcus aureus*, there are increasing numbers of infections with gram-negative bacteria, especially *Pseudomonas aeruginosa*. In addition to definitive surgical management, antibiotics are often indicated. Penicillinase-resistant penicillins or vancomycin is preferred for staphylococcal infections, whereas an aminoglycoside is used for gram-negative involvement. Vancomycin, because of its long half-life and failure to be removed by dialysis, is particularly useful in a dose of 1 gm every 5 to 6 days administered after a dialysis.
7. **Treatment of peritonitis in patients undergoing peritoneal dialysis.** Chronic peritoneal dialysis is fast becoming a popular alternative for a growing number of patients with end-stage kidney disease. Peritonitis remains a major limiting complication. Once peritonitis is suspected on clinical grounds or after routine cultures, peritoneal fluid should be obtained for Gram stain, total and differential white blood count, and culture with antimicrobial sensitivity testing. Peritoneal dialysis should then be begun and antibiotics added on the basis of bacteriologic studies or Gram stain. Some typical regimens are outlined in Table 11-8. If the patient has systemic signs and symptoms it may be prudent to add appropriate parenteral antibiotics according to dosage guidelines described above.

3. **Quinidine.** Quinidine half-life is similar in uremic patients and normal persons. No dosage adjustment is required for renal failure, and the drug is not significantly dialyzed.
4. **Propranolol.** Propranolol has found widespread use not only as an antiarrhythmic agent but also as symptomatic treatment for angina pectoris and hypertension. The dosage need not be changed in patients with renal disease, because increased hepatic metabolism counterbalances reduced uptake of the drug by the liver. No significant amount of propranolol is removed by hemodialysis or peritoneal dialysis.
5. **Other drugs.** Disopyramide is excreted by the kidney and metabolized to a compound with antiarrhythmic activity. For this reason, the interval between doses should be extended to 12 to 24 hours in patients with end-stage renal failure. Calcium entry blocking drugs are metabolized by the liver and require no dosage adjustments for renal failure.

C. Antibiotic therapy

1. **Aminoglycoside antibiotics.** These widely used drugs (gentamicin, amikacin, kanamycin, tobramycin and netilmicin) have a narrow toxic-therapeutic ratio. In patients with renal disease, drug accumulation may lead to ototoxicity and additional renal damage. With very high blood levels, neuromuscular blockade may occur. This may be of importance to anesthesiologists, since aminoglycosides potentiate the neuromuscular blocking properties of the paralyzing drugs used in surgery. Loop diuretics such as furosemide and ethacrynic acid are known to enhance irreversible ototoxicity associated with aminoglycoside therapy of patients with renal disease. Serum levels are widely used to ensure antibacterial efficacy. It is not clear that maintaining serum levels in the therapeutic range prevents toxicity; however, a rising serum level drawn 1 hour following a dose (peak) or just before the next dose (trough) indicates renal dysfunction, since aminoglycosides depend primarily on glomerular filtration for excretion. Because aminoglycosides are removed by hemodialysis, supplements of 0.5 to 1.0 mg per kilogram after dialysis are necessary to maintain therapeutic effects. The addition of 5 mg of gentamicin or tobramycin to each liter of peritoneal dialysate maintains adequate serum concentrations during concomitant parenteral therapy. Suggested initial and maintenance regimens for aminoglycosides are given in Table 11-7.
2. **Penicillins.** The penicillins as a group are generally safe to administer to patients with renal failure since little clinical toxicity is noted despite drug accumulation. Isoxazoyl penicillins (cloxacillin, dicloxacillin, nafcillin) do not require dosage modification, nor are they significantly dialyzed. If penicillin G is prescribed for patients with creatinine clearance less than 10 ml per minute, half the usual loading dose should be given every 8 to 12 hours after the usual initial dose. Ampicillin and amoxicillin maintenance dosing intervals should be extended to 12 to 16 hours when treating extrarenal infections in patients with creatinine clearances less than 10 ml per minute. In the treatment of urinary tract infections, usual doses are required to achieve adequate antibiotic concentrations in the urine and renal interstitium. The doses of carbenicillin and ticarcillin should be reduced when creatinine clearance decreases to 25 to 30 ml per minute. In patients with end-stage renal disease the carbenicillin dose is 2 gm every 8 to 12 hours. Toxic effects of penicillins in renal failure include neurotoxicity at high serum levels, extracellular fluid volume expansion (carbenicillin contains 5 mEq sodium/gm), and hyperkalemia (1 million units of penicillin contain 1.7 mEq potassium). Hypokalemic metabolic alkalosis may also occur, since urinary excretion of large amounts of anion (carbenicillin or penicillin) enhances potassium and hydrogen ion excretion. The interval between doses of the new penicillins, azlocillin, mezlocillin, and piperacillin, should be extended to 8 hours in patients with end-stage renal disease to avoid drug accumulation.
3. **Cephalosporins.** Cephalothin and its related compounds are well-tolerated, effective antibiotics for patients with renal failure. Although they are primarily excreted by the kidneys, nephrotoxicity is rarely observed. Major dosage mod-

Table 11-7. Aminoglycoside Dosing Chart

1. Select loading dose in mg/kg (ideal weight) to provide peak serum levels in range listed below for desired aminoglycoside.

Aminoglycoside	Usual Loading Doses	Expected Peak Serum Levels
Netilmicin, Tobramycin, Gentamicin	1.5 to 2.0 mg/kg	4 to 10 /m
Amikacin, Kanamycin	5.0 to 7.5 mg/kg	15 to 30 g/m

2. Select maintenance dosage (as percentage of chosen loading dose) to continue peak serum levels indicated above according to desired dosing interval and the patient corrected creatinine clearance.

Percentage of Loading Dose Required For Dosage Interval Selected

Creatinine Clearance (ml/min)	Half-life (hr)[a]	8 Hr	12 Hr	24 Hr
90	3.1	84%	—	—
80	3.4	80	91%	
70	3.9	76	88	—
60	4.5	71	84	
50	5.3	65	79	
40	6.5	57	72	92%
30	8.4	48	63	3
25	9.9	43	57	81
20	11.9	37	50	65
17	13.6	33	46	0
15	15.1	31	42	67
12	17.9	27	37	51
10[b]	20.4	24	34	46
7	25.9	19	28	47
5	31.5	16	23	1
2	46.8	11	16	30
0	69.3	8	11	21

[a] Alternatively, one-half of the chosen loading dose may be given at an interval approximately equal to the estimated half-life.
[b] Dosing for patients with Ccr ≤ 10 ml/min should be assisted by measured serum levels
Source: Adapted from F. A. Sarubbi and J. H. Hull, Amikacin serum concentration Prediction of levels and dosage guidelines. *Ann. Intern. Med.* 89:612, 1978.

Table 11-8. Antibiotics Used to Treat Peritonitis During Dialysis

Generic Name	Intraperitoneal Dose (mg/L or μg/ml)	Safe Serum Level (μg/ml)	Serum Level Attained With Routine Parenteral Doses (μg/ml)	End-Stage Renal Disease, Half-life in Hours	Hours to Attain Therapeutic Serum Levels	Drug Stability in the Dialysate
Cephalothin	20–50	50–100	10–30	3–18	4–6	36 hr
Ampicillin	50	50	50–100	3–7	8–20	12 hr
Methicillin	100	100–200	16–72	4	1–6	8–24 hr
Penicillin G	1000–50,000 U/L (1 μg = 1.6 U)	80 U/ml	15 U/ml	6–20	6–12	Stable if acid pH
Carbenicillin	200	200	110–170	10–20	4–6	36 hr
Vancomycin[a]	15	15–25	23–40	240	8–12	36 hr
Tobramycin[a]	8	10–12	3–14	24–50	8–12 (probably)	Stable
Gentamicin[a]	8	10–12	5–7	24–48	8–12	36 hr[b]
Amphotericin B[c]	2–4		0.5–3.5	40		Stable
Clindamycin[d]	10	20–40	10	1.5–3.5		Stable

Chloramphenicol is the only parenteral preparation that does not become active intraperitoneally, and oral or parenteral administration does not lead to adequate intraperitoneal levels.
Tetracycline and erythromycin are not recommended.
[a]At least one parenteral loading does is recommended.
[b]Aminoglycoside half-life lessened by carbenicillin and possibly other penicillins. Follow serum levels.
[c]Low-dose parenteral therapy recommended also, 200–500 mg total; 5 mg IV day 1, 10 mg IV day 2, 15 mg IV day 3, 20 mg IV day 4, then 25 mg IV for 5–20 days.
[d]Requires metabolic conversion intraperitoneally before effective and, therefore, should be given parenterally as well.
Source: Adapted from T. A. Golper, Drugs and peritoneal dialysis. *Dialysis and Transplantation* 8:41, 1979.

D. Prescribing for pain, sedation, and sleep in the azotemic patient. Although narcotics are predominantly metabolized in the liver, biotransformed products may exhibit both pharmacologic activity and toxic manifestations when they accumulate in the presence of renal failure.

1. **Analgesics.** Normeperidine, a metabolite of meperidine, accumulates in patients with renal failure, producing seizures in some patients. Methadone undergoes hepatic metabolism to an inactive hepatic metabolite that is not known to cause adverse effects. Uremic patients are more sensitive to the respiratory depressant effects of morphine because of decreased plasma protein binding in uremic serum; thus, morphine should be administered with caution in uremic patients, particularly those with low serum albumin and/or concurrent liver disease. The propoxyphene metabolite, norpropoxyphene, accumulates with repetitive dosing in patients with advanced renal disease, but its pharmacologic activity is probably low. Codeine, pentazocine, and naloxone can be used without dose modification in patients with renal failure. None of the narcotics undergoes sufficient removal during dialysis to require dosage supplementation.
Salicylates should be used with caution in patients with renal failure because they enhance the platelet dysfunction and gastric irritant effects associated with the uremic state. Acetaminophen metabolites accumulate in patients with renal disease but have no pharmacologic activity or known toxic effects.
2. **Psychoactive drugs.** Emotional stress and depression are common in patients with renal failure. For mild-to-moderate symptoms, a benzodiazepine can be safely used. Diazepam or chlordiazepoxide are given in their usual dosage, with a careful watch for excessive sedation. Parenteral diazepam, which is poorly dialyzed, is particularly useful to treat symptoms of acute anxiety during the dialysis procedure itself. Flurazepam, for insomnia, can usually be given safely in usual doses to patients with renal failure. Clonazepam can be used in patients with renal failure to treat the troublesome problems of restless legs and hiccoughs. Barbiturates, particularly phenobarbital, which depends on renal excretion for elimination from the body, should be avoided.
There are no unique side effects of tricyclic antidepressants in the patient with renal failure. Orthostatic hypotension can be a problem when superimposed on dialysis-induced extracellular fluid volume depletion.
The pharmacologic therapy of major psychoses can be handled similarly to the therapy of nonuremic patients. Phenothiazine drugs are most useful, although the hypotensive potential and low seizure threshold of chlorpromazine, propensity of arrhythmias with thoridiazine, and extrapyramidal reactions caused by haloperidol need to be considered in selecting a drug for the individual patient.

E. Diuretics and antihypertensive drugs

1. **Diuretics.** Diuretics are generally less effective in the presence of renal insufficiency. Furosemide, bumetanide, and ethacrynic acid may produce a natriuresis in patients with glomerular filtration rates as low as 5 to 10 ml per minute; however, the large doses required may produce ototoxicity. Ethacrynic acid should be avoided in patients with severe renal disease since its ototoxic potential is greater than that of furosemide. Thiazide diuretics are generally ineffective in patients with glomerular filtration rates below 25 ml per minute. Metolazone may have some efficacy in far advanced renal failure; however, it is ineffective with glomerular filtration rates less than 10 ml per minute. Spironolactone, amiloride, and triamterene may cause fatal hyperkalemia in advanced renal failure and are contraindicated in such patients.
2. **Antihypertensive agents.** Antihypertensive drugs are generally administered to patients with renal failure based on the patient's blood pressure response, rather than on pharmacologic characteristics of individual drugs. For urgent lowering of blood pressure in patients with renal insufficiency, diazoxide is especially useful. Sodium nitroprusside administered by constant infusion can control almost any hypertensive emergency. The metabolism of nitroprusside to thiocyanate presents some risks to patients with renal failure. The symptoms

of thiocyanate toxicity, which include nausea, vomiting, myoclonic movements, and seizures, can be rapidly alleviated by dialysis. Because of the potential for accumulation of thiocyanate, nitroprusside infusions to patients with renal failure are best terminated within 48 hours. Although no dose adjustments for renal failure are required for clonidine, methyldopa, hydralazine, prazosin, guanethidine, or minoxidil, it may be wise to omit a dose just before dialysis in patients who are likely to have hypotension during the procedure.

F. Miscellaneous drugs often used in patients with renal failure

1. **Anticonvulsants.** Standard doses of phenytoin may be used in patients with all degrees of renal impairment. Although uremia decreases phenytoin binding to plasma proteins, accelerated metabolism by the liver keeps the amount of free drug at relatively therapeutic levels. Even so, either lower than therapeutic or toxic total phenytoin plasma levels may occur in patients with renal failure. Phenytoin is not removed significantly by hemodialysis, and supplemental doses postdialysis are not necessary. No good data are available on the dialyzability of other anticonvulsants.
   For the long-acting barbiturates, empiric decreases in drug dosage are needed, with close monitoring of plasma levels and observation for toxic effects. Phenobarbital is dialyzable. For treatment of status epilepticus, usual doses of parenteral diazepam may be administered.
2. **Immunosuppressive and antineoplastic agents.** The drugs most commonly used in therapy of immunologically mediated renal diseases and renal transplantation are azathioprine and cyclophosphamide. Considerable dosage reduction of cyclophosphamide is required in patients with renal failure since significant renal excretion of active alkylating metabolites occurs. In patients with renal insufficiency, empiric decreases in cyclophosphamide dosage are indicated in association with evidence of toxic effects (e.g., leukopenia). Some data suggest an increased pharmacologic effect when azathioprine is administered to patients with advanced renal failure, so careful monitoring is required when these drugs are used in patients with renal failure. Some cyclophosphamide and azathioprine may be lost during hemodialysis.
   The antineoplastic drugs actinomycin D, bleomycin, *cis*-platinum, 5-fluorouracil, melphalan, methotrexate, and streptozocin all undergo considerable renal elemination of either parent drug or active metabolites and therefore require empiric dosage decreases with evidence of toxic effects in patients with compromised renal function. Considerable dialyzability has been demonstrated for 5-fluorouracil and methotrexate, whereas bleomycin does not appear to be significantly dialyzable.
3. **Other drugs**
   a. **Clofibrate.** Clofibrate is used as a hypolipidemic agent in uremic patients. Because of the high degree of protein binding and considerable renal elimination of clofibrate, use of this drug may be associated with a high frequency of skeletal muscle damage when administered in standard doses to either nephrotic patients or patients with renal insufficiency. The drug probably can be used to lower serum triglycerides safely in patients undergoing maintenance hemodialysis if reduced doses are prescribed.
   b. **Anticholinergic agents.** The anticholinergic drugs are often used in treating gastrointestinal disorders. Little modification of dosage is needed in renal patients. Care must be taken with these agents to avoid urinary retention that may additionally compromise renal function.
   c. **Metoclopramide.** Metoclopramide, a dopamine antagonist, has proved very useful for management of nausea and vomiting associated with uremia or diabetic gastroparesis. The dose should be 50 percent of normal in patients with advanced renal failure.
   d. **Cimetidine.** Cimetidine, currently in widespread use for treatment and prophylaxis of peptic ulcer disease, undergoes considerable renal elimination. A dose of 300 mg every 12 hours should produce adequate inhibition of gastric acid output in anephric patients.

   e. **Bronchodilator drugs.** Bronchodilator drugs (theophylline, terbutaline, and ephedrine) can be safely administered to patients with renal failure. A slight decrease in dosage of terbutaline and ephedrine may be required. Because of some loss during dialysis, theophylline should be administered following the procedure.

III. Management of drug overdose: role of forced diuresis, dialysis, and hemoperfusion. Active measures to remove exogenous poison or drugs taken in overdoses are complex. Undoubtedly the major factor in patient survival is expert intensive supportive care. To be useful in treating poisoning, toxic drug effects should be related to the plasma concentration or the duration of the drug in the body. The amount of drug removed by diuresis, dialysis, or hemoperfusion should represent a considerable addition to the drug's or poison's usual elimination route. Peritoneal dialysis, because of relatively low clearance rates, has little role in acute overdoses. Resin and charcoal hemoperfusion are absorbent procedures in which blood passes directly over absorbent materials. Compounds poorly removed by conventional hemodialysis are often effectively eliminated. Exact indications are not yet established. Drugs that may be removed from the body effectively by forced diuresis, hemodialysis, and hemoperfusion are listed in Table 11-9.

Table 11-9. Drugs Removed by Forced Diuresis, Hemodialysis, and Hemoperfusion

Drug Removal	Drug	Comment
Forced diuresis: Intravenous fluid (plus osmotic agents such as mannitol, 25–50 gm, every 2–4 hr) to achieve urine flow of 3–6 ml/kg/hr	Bromide	Follow electrolytes; replace fluid losses with 0.45% NaCl to avoid hyperosmolarity
Alkaline diuresis. Sodium bicarbonate 1–2 mEq/kg IV	Isoniazid Phenobarbital Salicylates	Follow electrolytes closely, with early potassium supplementation
Acid diuresis. Add ascorbic acid, 500 mg to 2 gm IV or ammonium chloride, 75 mg/kg/day, in four divided IV doses	Amphetamines Phencyclidine Strychnine Quinine/quinidine	Contraindicated in liver and renal disease
Hemodialysis Immediate therapy indicated	Ethylene glycol, methanol if blood level >50 mg/dl	IV ethanol may be adjunctive therapy
Indicated for severe overdoses or if usual elimination routes unavailable (i.e., liver or kidney disease)	Ethyl alcohol if blood level > 90 mg/dl Salicylate blood level >100 mg/ml	Blood levels are only guides; clinical judgment must be exercised
Hemoperfusion: May be used in severe overdoses only	Long- and short-acting barbiturates Digoxin Ethchlorvynol Glutethimide Meprobamate Methaqualone	Most reports are anecdotal; procedure lowers blood platelets by 25–30%; contraindicated in patients at risk of bleeding

Suggested Reading

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12

The Patient With Kidney Disease and Hypertension in Pregnancy

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Gestation in women with preexisting renal disease, regardless of type or severity, alarms physicians. Their concern is frequently shared by consultant nephrologists, whose experience may be based on patients referred after complications have occurred. As a result, pregnancies are often interrupted and contraception advised. Such views, however, are unduly pessimistic. It is now apparent that in most instances gestations in women with renal disorders end successfully, especially when kidney function is well preserved and hypertension absent.

I. **The kidney and blood pressure in normal pregnancy.** The anatomy and function of the kidneys and lower urinary tract are altered in gestation. There are also physiologic alterations in volume homeostasis and blood pressure control, recognition of which is a prerequisite for the appropriate interpretation of data from pregnant patients with renal disease or hypertension (Table 12-1).

A. **Anatomic and functional changes in the urinary tract.** Kidney length increases approximately 1 cm during normal gestation. The major anatomic alterations of the urinary tract during pregnancy, however, are seen in the collecting system, where calyces, renal pelves, and ureters dilate, often giving the erroneous impression of obstructive uropathy. The dilatation is accompanied by hypertrophy of ureteral smooth muscle and hyperplasia of its connective tissue, but whether bladder reflux is more common in gravidas is unclear. The cause of the ureteral dilatation is disputed; some researchers favor hormonal mechanisms, whereas other researchers believe that it is obstructive in origin. It is clear that as pregnancy progresses, assumption of a supine or upright posture may cause ureteral obstruction when the enlarged uterus entraps the ureters at the pelvic brim (Fig 12-1). These morphologic changes have considerable clinical relevance. Stasis in the dilated urinary tract may contribute to the propensity of pregnant women with asymptomatic bacteriuria to develop frank pyelonephritis. The widened ureters contain substantial volumes of urine, which may lead to collection error in tests that require timed urine volumes. These errors may be avoided by the following simple protocol: gravidas to be tested receive a water load and remain in bed positioned in lateral recumbency for 1 hour before the start of the collection. This procedure minimizes inaccuracies by standardizing the procedure as well as by producing a modest water diuresis, so that residual urine is dilute and of recent origin.

Acceptable norms of kidney size should be increased by 1 cm if estimated during pregnancy or the immediate puerperium, and reductions of renal length noted several months postpartum need not be attributed to renal disease. Also, since dilatation of the ureters may persist until the twelfth postpartum week, elective radiologic examination of the urinary tract should be deferred, if possible, until after this time.

B. **Renal hemodynamics.** Values considered normal in nongravid women may reflect decreased renal function during pregnancy. For example, in gravid women concentrations of serum creatinine exceeding 0.8 mg per deciliter or of serum urea nitrogen greater than 13 mg per deciliter suggest the need for additional evaluation of renal function.

1. **Glomerular filtration rate (GFR) and renal plasma flow (RPF).** GFR and RPF increase to levels 30 to 50 percent above nongravid values. Increments that are already present during the days following conception become maximal by

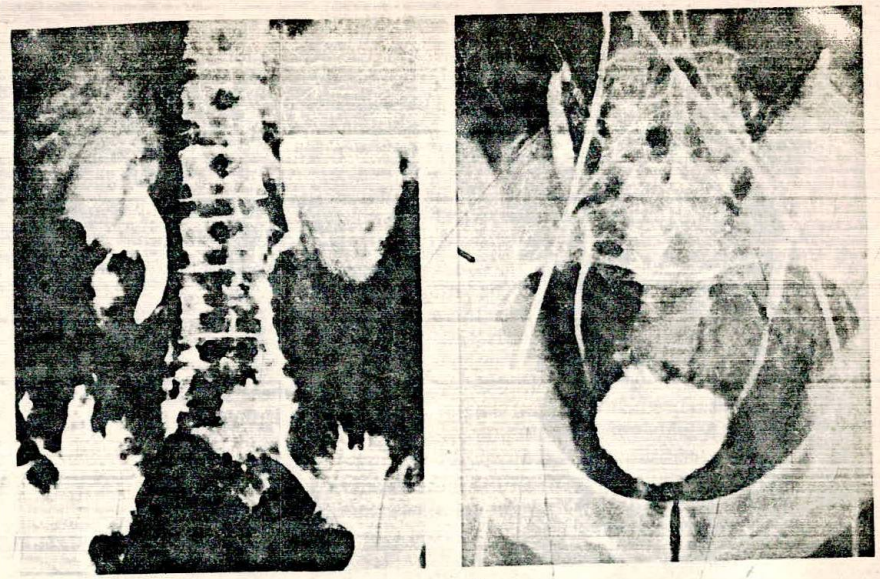
Table 12-1. Renal Changes in Normal Pregnancy

Alteration	Manifestation	Clinical Relevance
Increased renal size	Renal length approximately 1 cm greater on roentgenograms	Postpartum decreases in size should not be mistaken for parenchymal loss
Dilatation of pelvic calyces and ureters	Resembles hydronephrosis on intravenous pyelography (more marked on right)	Not to be mistaken for obstructive uropathy; elective pyelography should be deferred to the twelfth postpartum week; upper urinary tract infections are more virulent; retained urine leads to collection errors
Increased renal hemodynamics	Glomerular filtration rate and renal plasma flow increase 35–50%	Serum creatinine and urea N values decrease during normal gestation; so values > 0.8 mg% Cr and 13 mg % urea N are already suspect; albumin, amino acid, and glucose excretion all increase
Changes in acid-base metabolism	Renal bicarbonate threshold decreases	Serum bicarbonate is 4–5 mM/L lower in normal gestation
Renal water handling	Osmoregulation altered	Serum osmolality decreases 10 mOsm/L (serum sodium ↓ 5 mEq/L) during normal gestation

the end of the first trimester. According to some authors, these increments are sustained until term, whereas other investigators have observed a decline in creatinine clearance during the last four weeks of pregnancy.

The increase in GFR has important clinical implications. Since creatinine production is unchanged during pregnancy, increments in its clearance result in decreased serum levels. Using the Hare method, one group of investigators observed that true serum creatinine, which averaged 0.67 mg per deciliter in nongravid women, decreased to 0.46 mg per deciliter during gestation. In studies that also measured creatinine chromogen (resembling results reported in most clinical laboratories), values were 0.83 mg per deciliter in nonpregnant women and decreased to 0.74, 0.58, and 0.53 mg per deciliter in the first, second, and third trimesters, respectively.

2. **Blood urea nitrogen.** Similar changes occur in the mean value of blood urea, but some of these alterations may be due to enhanced protein synthesis in addition to increments in the clearance of this solute. In a serial study of 83 gravidas, blood urea nitrogen averaged 9.8, 9.2, and 9.2 mg per deciliter in each trimester and rose to 12.1 mg per deciliter 6 weeks postpartum.
3. **Other hemodynamic alterations.** Several other changes that occur in gestation may be due to altered hemodynamics. Excretion of glucose, most amino acids, and several water-soluble vitamins increases. Increments in urinary nutrient content, for instance, may be a factor in the enhanced susceptibility of gravidas to urinary tract infections. Urinary protein excretion also increases during gestation.



A B

Fig. 12-1. Intravenous pyelogram. **A.** Ureteral dilatation of pregnancy. The right ureter is sharply cut off at the pelvic brim where it crosses the iliac artery *(the iliac sign)*. **B.** Relationship between the ureters and iliac arteries can be demonstrated in postmortem studies. Note the iliac sign at the pelvic brim on the right. (From P. Dure-Smith, Pregnancy dilatation of the urinary tract. *Radiology* 96:545, 1970.)

C. **Acid-base regulation in pregnancy.** Renal regulation of acid-base is altered during gestation. The bicarbonate threshold decreases, and early morning urines are often more alkaline than those in the nongravid state. In addition, plasma bicarbonate concentrations decrease approximately 4 mM per liter, averaging 22 mM per liter. This change most likely represents a compensatory renal response to hypocapnia, because pregnant women hyperventilate and their PCO_2 averages only 30 torr. The mild alkalosis (arterial pH averages 7.44) found in pregnancy is in accord with this view. Since steady-state PCO_2 and HCO_3 levels are already diminished, pregnant women are in theory at a disadvantage when threatened by sudden metabolic acidosis (e.g., lactic acidosis in preeclampsia, diabetic ketoacidosis, or acute renal failure). However, they respond with appropriate increments in urinary titratable acid and ammonia after an acid load, and proton regeneration is already evident at blood pH levels higher than those in similarly tested nonpregnant women.

D. **Water excretion.** After conception there is a rapid decrease in plasma osmolality that levels off at 5 to 10 mOsm per kilogram below that of nongravid subjects. If this decrease occurred in a nonpregnant woman, she would cease secreting antidiuretic hormone and enter a state of water diuresis. However, gravidas maintain this new osmolality, diluting and concentrating their urine appropriately when subjected to water loading or dehydration. This suggests a "resetting" of the osmoreceptor system, and indeed recent data demonstrate that the osmotic thresholds for both thirst and vasopressin release are decreased in pregnant women.

There are also reports that women with diabetes insipidus who become pregnant require increments in their vasopressin injection (Pitressin) or dDAVP (1 desamino, 8 D-arginine vasopressin) dosage. Whether this relates to increased renal hemodynamics and/or prostaglandin production or to a placental enzyme that

destroys vasopressin (vasopressinase) remains to be elucidated. In addition two rare syndromes of transient diabetes insipidus in pregnancy have been described; one is responsive to exogenous vasopressin or dDAVP, and the other is due to in vivo destruction or renal resistance to vasopressin.

E. Volume regulation. Most healthy women gain approximately 12.5 kg during the first pregnancy, and 1 kg less during subsequent pregnancies. Generations of physicians have considered these averages as upper limits of permissible weight gains, forgetting that there is a plus and a minus to deviations about a mean. As a result, many gravidas were scolded for excessive weight gain, and their salt or calories, or both, were restricted. Most of the increment is fluid, total body water increasing 6 to 8 liters, 4 to 6 of which are extracellular. Plasma volume increases 50 percent during gestation, the largest rate of increment occurring during midpregnancy, whereas increments in the interstitial space are greatest in the third trimester. There is also a gradual cumulative retention of approximately 900 mEq of sodium in pregnancy that is distributed between the product of conception and the maternal extracellular space. These alterations in maternal intravascular and interstitial compartments produce a physiologic hypervolemia, yet the gravida's volume receptors sense these changes as normal, and when salt restriction or diuretic therapy limits this physiologic expansion, maternal responses resemble those in salt-depleted nonpregnant women. This is one compelling reason that a policy common less than a decade ago, whereby gravidas were sodium restricted and often given diuretics, is now condemned. Pregnant women are now advised to salt their food to taste, and some researchers believe that a liberal sodium intake is beneficial during gestation.

The influence of humoral changes during normal pregnancy on renal sodium handling and volume regulation is incompletely understood. The increment in GFR means that up to 10,000 additional mEq of sodium must be reabsorbed by the renal tubules each day, a quantity considerably greater than the expected salt-retaining potency of several mineralocorticoids (aldosterone, desoxycorticosterone, estrogen), the blood levels of which increase in pregnancy.

F. Blood pressure regulation. Mean blood pressure starts to decrease early in gestation, diastolic levels in midpregnancy averaging 10 mm Hg less than measurements postpartum. In later pregnancy blood pressure increases, gradually approaching prepregnancy values near term. Since cardiac output rises quickly in the first trimester and remains relatively constant thereafter, the decrease in pressure is due to a marked decrement in peripheral vascular resistance. The slow rise toward nonpregnant levels following a midtrimester nadir is interesting, since it demonstrates that increasing vasoconstrictor tone is a feature of late gestation in normal women as well as in those in whom preeclampsia is developing. The cause of the initial decrease in peripheral resistance during pregnancy is obscure. Levels of estrogen and progesterone that may relax smooth muscle are elevated, and increments in vasodilating prostaglandins (of either the E or the I series) may also occur during gestation. On the other hand, concentrations of renin, its activity, and its substrate, as well as angiotensin levels, increase substantially, but gravidas are extremely resistant to the pressor effects of angiotensin II. Catecholamine levels appear to be unaltered in gestation.

Lack of awareness of the fluctuation in blood pressure during normal gestation may lead to diagnostic errors. For example, certain women with mild essential hypertension who in the first trimester experience the normal decrease in blood pressure display near normal levels early in pregnancy. They are then erroneously labeled preeclamptic in the last trimester, when frankly elevated pressures occur. Such errors can be avoided if diastolic levels of 75 mm Hg in the second and 85 mm Hg in the third trimester are considered as upper limits of normal.

II. Clinical evaluation of renal function in pregnancy

A. Examination of the urine. The association of proteinuria with eclampsia was first noted in the 1840s, and the science of prenatal care advanced dramatically when physicians began to examine systematically the urine of gravidas, primarily for albuminuria. In certain instances, latent renal disease is first uncovered by the detection of excessive protein excretion or microscopic hematuria during a routine prenatal evaluation.

Healthy nonpregnant women excrete considerably less than 100 mg of protein in the urine daily, but due to the relative imprecision and variability of testing methods used in hospital laboratories, proteinuria is not considered abnormal until it exceeds 150 mg per day. During pregnancy protein excretion increases, and excretion up to 300 mg per day (some authors accept 0.5 gm/day) may still be normal. On occasion, a healthy gravida can excrete more than that amount. The problem is compounded by the fact that about 5 percent of healthy adolescents and young adults have postural proteinuria, which may become apparent only during pregnancy. In addition, postural proteinuria may increase near term, when gravidas tend to assume a more lordotic posture, which augments excretion. Another cause of increased proteinuria in pregnancy may be compression of the renal veins by the enlarged uterus, especially when gravidas lie supine. Thus, when the gravida is tested for postural proteinuria (see Chap. 8, sec. **I.D**, under Proteinuria), she should be positioned in lateral recumbency.

There have been few attempts to quantitate urine sediments in pregnancy. The excretion of red blood cells may increase during normal gestation. Whether increased leukocyturia also occurs during pregnancy is not clear. Since microscopic examination of the urine sediment is an important and noninvasive technique, it is unfortunate that so little has been done to standardize this test for pregnant women.

B. Renal function tests. The clearance of endogenous creatinine, the most satisfactory approximation of GFR in nongravid subjects, is equally useful for assessing renal function in gravidas. Gravidas as well as nonpregnant women show little variation (approximately 10 percent per day) in urinary creatinine excretion and, presumably, in creatinine production, which in a given woman is similar both during and after gestation. The lower limit of normal creatinine clearance during gestation should be 30 percent greater than that of nongravid women, which in most hospitals averages 110 to 115 ml/min/1.73 sq m.

Acid excretion and urinary concentration and dilution are similar in gravid and nonpregnant women. Thus, tests such as ammonium loading (rarely indicated in gestation) give values similar to those in nongravid women. When examining urinary diluting ability, the clinician should be aware that supine posture can interfere with this test. Therefore, studies to detect minimal urinary osmolal concentrations should be performed with the patient lying on her side. However, although lateral recumbency is the required position for prenatal measurement of most renal function parameters, this posture interferes with tests of concentration. For example, a urine osmolality that was 800 mOsm per kilogram after overnight dehydration may decrease to 400 mOsm per kilogram within an hour when a lateral recumbent position is assumed. Such changes may be explained by fluid mobilization from the extremities during bed rest, resulting in either volume-induced inhibition of vasopressin secretion or a mild osmotic diuresis. Such observations demonstrate the importance of upright posture, such as quiet sitting, when maximum urinary concentration is measured in pregnancy.

C. Role of renal biopsy in pregnancy. Percutaneous renal biopsies were introduced in the 1950s, and subsequent investigations correlating light, electron, and immunofluorescent microscopy with alterations in renal function have revolutionized our understanding of the pathology and natural history of kidney disease in nonpregnant populations. Few such studies have been reported on renal disease in pregnancy, mainly because clinical circumstances rarely justify the slight risks of biopsy during gestation and the procedure is usually deferred to the postpartum period. Another reason may have been a report of excessive bleeding and other complications in gravid women that led some physicians to consider pregnancy a relative contraindication to renal biopsy. These views, however, were based on the earlier practice of performing prepartum and intrapartum (i.e., during cesarean section) biopsies in women who were hypertensive, and at a time that predated current understanding of the coagulation abnormalities occasionally seen in

preeclampsia. It is now evident that if the biopsy is performed in the immediate puerperium in a woman with well-controlled blood pressure and normal coagulation indices, morbidity is similar to that in nongravid patients.

There are relatively few indications for antepartum renal biopsy, one being nephrotic syndrome of unknown cause first diagnosed in midpregnancy or early in the third trimester. Diagnosis of preeclampsia may influence decisions concerning termination of pregnancy, whereas demonstration of other pathology by biopsy helps in the determination of appropriate therapy. Renal biopsies should not be performed after gestational week 32 since at this stage the fetus will probably be delivered in any case, and the decision usually has to be made quickly and independent of biopsy results.

D. Clinical application. Some of the normal morphologic and physiologic adjustments that affect the kidney during pregnancy and the application of such information to detecting disease are illustrated in the following case report.

Example: A 25-year-old multipara with known hypertension was hospitalized at 31 weeks of gestation with a blood pressure of 200/140 mm Hg. Treatment included a single 20-mg dose of hydralazine, 2 mg trichlormethiazide daily for 3 days, bed rest in the position of lateral recumbency, and restriction of dietary sodium. After 2 weeks, weight decreased 4.6 kg and diastolic blood pressure now averaged 90 to 100 mm Hg. Unfortunately, urine volumes declined, and the creatinine clearance decreased from 106 ml per minute on the sixth to 82 ml per minute on the sixteenth hospital day (Table 12-2). Simultaneously, blood urea nitrogen increased from 8 to 25 mg per deciliter. Interruption of gestation was considered, since deteriorating renal function was regarded as a sign of superimposed and progressing preeclampsia. However, a diagnosis of salt depletion was also entertained. A trial period in which sodium intake was increased to 206 mEq per day followed. After sodium intake was liberalized, weight increased 1.5 kg, but diastolic blood pressures remained between 90 and 100 mm Hg and the creatinine clearance increased to 118 ml per minute. Serum creatinine and urea nitrogen decreased to 0.9 and 16 mg/100 ml, respectively. The gestation was allowed to continue until labor ensued spontaneously.*

This report demonstrates the advantage of estimating GFR from serum creatinine rather than plasma urea levels. Alterations in serum creatinine mirrored changes in its clearance, whereas this relation was less clear in the case of urea nitrogen. The GFR was low for pregnancy, illustrated by the serum creatinine values of 0.9 to 1.3 mg per deciliter, which are acceptable in nonpregnant women but abnormal during gestation. On the other hand, there was a normal plasma urea nitrogen on admission, perhaps reflecting poor nutrition. It is also interesting how easily this patient became dehydrated (a fact not appreciated by many who manage pregnant women). With dehydration and oliguria the concentration of urea increased threefold while the serum creatinine clearance decreased only 23 percent. However, when GFR increased to values greater than those measured on admission, urea nitrogen was still 16 mg per deciliter, probably reflecting a good hospital diet.

III. Renal disease in pregnancy

A. Asymptomatic bacteriuria. Urinary tract infection is the most common renal problem occurring in pregnancy. The urine of gravidas supports bacterial growth better than that of nonpregnant women, due to its increased nutrient content. This, as well as ureteral dilatation, stasis, and occasional obstruction, would be expected to increase the susceptibility of pregnant women to urinary tract infection. Surprisingly, this is not the case, and, with the exception of certain high-risk groups (diabetics and gravidas with sickle cell trait), prevalence of asymptomatic bacteriuria during gestation varies between 4 and 7 percent, a value similar to that of sexually active nonpregnant women. The natural history of asymptomatic urinary tract infections is, however, quite different in pregnancy.

* Adapted from J. Palomaki and M. D. Lindheimer, Sodium depletion simulating deterioration in a toxemic pregnancy. *N. Engl. J. Med.* 282:88, 1970.

Table 12-2. Renal Function During Hospitalization

Function	Day 6	Day 16	Day 26
Creatinine clearance (ml/min)	106.0	82.0	118.0
Serum creatinine (mg/dl)	1.1	1.3	0.9
Serum urea nitrogen (mg/dl)	8.0	25.0	16.0
Maximal urine flow (ml/min)		2.3	8.7

Although in the nonpregnant state the situation is quite benign, progression to overt cystitis or pyelonephritis occurs in up to 40 percent of affected gravidas (Table 12-3). Therefore, it is important to screen all pregnant women for the presence of asymptomatic bacteriuria and to treat those with positive urine cultures.

1. **Method of urine collection.** Pregnant women contaminate midstream urine specimens more frequently than do nonpregnant persons. The incidence can be reduced by the use of multiple vulval washings combined with carefully supervised collection procedures. There are some women in whom suprapubic aspiration is required to differentiate contamination from true infection. There is no contraindication to this procedure in pregnancy.

   If the urine is sterile at the beginning of pregnancy, it usually remains so until term. Still, a small number (1 to 2 percent) of gravidas whose original urine cultures are negative subsequently have bacteriuria. Abnormal urinalysis and the presence of dysuria do not differentiate between contamination and true infection. For example, dysuria occurs in 30 percent of gravidas whose urines are sterile, and the urine may be infected and still contain fewer than two leukocytes per high power field.
2. **Method of treatment.** There is some controversy about the optimum treatment of asymptomatic bacteriuria in gestation. Some authors, believing that gravidas have a high relapse rate, recommend prolonged antibiotic treatment. However, approximately 50 percent of patients have bladder involvement only, and most infections appear to respond to a simple 8- to 12-day course of therapy. Thus, we recommend a 2-week course, preferring the initial use of short-acting sulfa drugs or a nitrofurantoin derivative and reserving the more potent agents (ampicillin, cephalosporins, or carbenicillin) for treatment failures and for symptomatic infection. Of course, the choice of antibiotic agent in both situations should always be based on the sensitivity of the isolated organism.
3. **Importance of postpartum evaluation.** Asymptomatic urinary tract infection has been linked to premature labor, hypertension, and anemia during gestation, but these assertions have not been proved. On the other hand, there is an increased incidence of occult urinary tract pathology in these gravidas. Therefore, women with bacteriuria during pregnancy may benefit from evaluation of their urinary tract postpartum by excretory urography.

Table 12-3. Relation Between Asymptomatic Bacteriuria and Antenatal Symptomatic Urinary Tract Infection

Patient Status	Number Followed	Number Symptomatic	Percentage
Untreated bacteriuric	1609	464	28.8
Treated bacteriuric	421	15	3.6
Nonbacteriuric	13,742	246	1.8

Source: M. D. Lindheimer and A. I. Katz, *Renal Function and Disease in Pregnancy*. New York: Lea & Febiger, 1977.

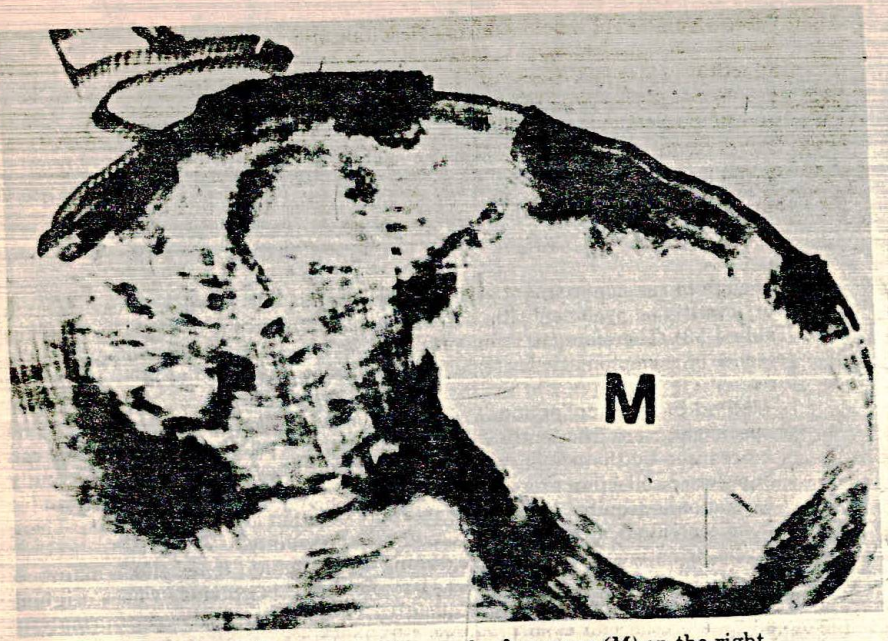


Fig. 12-2. Transverse sonogram. The large echo-free mass *(M)* on the right corresponded to an enlarged, fluid containing mass, which was first discovered and subsequently became infected during pregnancy. The uterus is on the left, the placenta *(P)* is posterior. (From M. D. Lindheimer, A. I. Katz, *Kidney Function and Disease in Pregnancy*. New York: Lea & Febiger, 1977. Courtesy of J. D. Bowie, M.D.)

B. **Symptomatic bacteriuria.** The clinical approach to symptomatic urinary tract infection during gestation differs from that for asymptomatic bacteriuria.
   1. **Acute pyelonephritis.** Pyelonephritis, which occurs in 1 to 2 percent of all pregnancies, was a cause of maternal death in the preantibiotic era, and 3 percent of patients in a recently reported series developed septic shock. Acute pyelonephritis has been implicated in intrauterine growth retardation, prematurity, congenital anomalies, and fetal death. Thus, treatment of symptomatic infection should be aggressive and performed in a hospital setting. Most patients with pyelonephritis respond quickly (temperatures return to normal within 48 to 72 hours), but, in contrast to gravidas with asymptomatic bacteriuria, they are very likely to relapse or become reinfected. Therefore, after initial therapy (often with parenteral ampicillin) such women should receive appropriate antibiotics for 3 to 4 weeks, after which their urine should be screened frequently during the remainder of their pregnancies. Some authors also recommend continuous antibiotic prophylaxis to term in such patients.
   2. **Perirenal and renal abscess.** Perirenal abscess and renal abscess formation or carbuncle, although infrequent complications of gestation, should be considered in the differential diagnosis of postpartum fever (Fig. 12-2). The incidence of positive urine cultures may reach 17 to 20 percent during the first days after delivery and decrease to 4 percent after the third postpartum day. This apparent spontaneous resolution probably reflects the inability to prevent urine contamination rather than a true high incidence of infection. Thus, when pyrexia is evaluated during the first 72 hours of the puerperium, suprapubic aspiration of urine is preferable to midstream specimens.
   3. **Antibiotic use in pregnancy.** Tetracyclines should not be used in pregnancy. Sulfonamides are inadvisable near term as they may precipitate kernicterus in the newborn. Ampicillin, the cephalosporins, and carbenicillin are the agents most commonly used in the treatment of symptomatic infections during pregnancy. The combination of trimethoprim and sulfamethoxazole is gaining in popularity, but we await more careful scrutiny of its effect on the fetus. Naturally, the drugs chosen should preferably be those that have stood the test of time for safety in pregnant women.

C. **Acute renal failure**
   1. **Incidence.** Two decades ago the incidence of acute renal failure in pregnancy was estimated at between 1 in 2000 and 1 in 5000 gestations and represented a considerable proportion of cases reported in large series. More recently the number of patients with acute renal failure from obstetric causes has declined markedly and the incidence is now estimated to be less than 1 in 10,000 pregnancies. This trend, attributed to liberalization of abortion laws and improvement of prenatal care, has not been shared by the poorer and less industrialized nations, in which such patients comprise up to 25 percent of referrals to dialysis centers and in which renal failure in pregnancy continues to be an important cause of maternal and fetal mortality.
      The frequency distribution of acute renal failure during gestation is bimodal, with one peak early in pregnancy (12–18 weeks) comprising most of the cases associated with septic abortion, and a second peak between gestational week 35 and the puerperium, primarily due to preeclampsia and bleeding complications, especially placental abruption.
   2. **Causes.** Most gravidas with acute renal failure have acute tubular necrosis. Rarely, glomerular disease or obstructive nephropathy is also seen. In contradistinction to the etiologic breakdown in nonpregnant populations, there is a greater incidence of acute cortical necrosis during pregnancy. The latter entity is most likely to occur late in gestation, as it is frequently associated with abruptio placentae. Although the necrosis may involve the whole renal cortex and cause irreversible anuria, the "patchy" variety occurs more often in pregnancy. This patchy necrosis has a distinctive course, with an initial episode of severe oliguria followed by a variable return of function, characterized by a stable period of moderate renal insufficiency. However, after several years (and for obscure reasons) renal function again declines, often leading to terminal kidney failure.
      There are two rare forms of acute renal failure specific to pregnancy. One is associated with acute fatty liver of pregnancy and is characterized by jaundice and severe hepatic dysfunction in late gestation or the immediate puerperium. Renal failure in this condition may be due to hemodynamic factors (analogous to the hepatorenal syndrome), and some cases have been associated with intravascular coagulation and hepatic fibrin deposition. The mortality rate is high and is due primarily to liver failure, but a substantial number of these patients recover following rapid termination of the pregnancy.
      The second disease, known by a variety of names, is best labeled *idiopathic postpartum renal failure*. Such patients have uncomplicated pregnancies and deliveries, but present 3 to 6 weeks in the puerperium with uremia, severe hypertension, and often, evidence of microangiopathic hemolytic anemia. The cause of the condition is unknown, although viral agents, ergot compounds, oral contraceptives, and retained placental fragments have all been suggested. Most of the affected women succumb, or if they survive do so with severely reduced renal function, but recoveries have been recorded. Since there are claims that the disease has been contained and/or reversed with anticoagulant therapy, this therapeutic approach combined with dilatation and curettage of the uterus may be tried. Poststreptococcal glomerulonephritis secondary to endometritis may cause acute renal failure postpartum and there is also an increased incidence of thrombotic thrombocytopenic purpura postpartum.
   3. **Management.** The management of acute renal failure occurring in gestation or immediately postpartum is similar to that in nongravid subjects (see Chap. 9), but several points peculiar to pregnancy deserve emphasis. Since uterine

hemorrhage near term may be concealed and blood loss underestimated, any overt blood loss should be replaced early. Gravidas should be slightly overtransfused to forestall the development of acute tubular or cortical necrosis. Both peritoneal dialysis and hemodialysis have been successfully used in patients with obstetric acute renal failure. Neither pelvic peritonitis nor the enlarged uterus is a contraindication to the former method. However, when circumstances dictate the use of peritoneal dialysis rather than hemodialysis, the catheter should be inserted high in the abdomen, preferably under direct vision. Finally, since urea, creatinine, and other metabolites that accumulate in uremia traverse the placenta, dialysis should be undertaken early, with the aim of maintaining the blood urea nitrogen at approximately 30 mg per deciliter. The advantages of early dialysis in nongravid patients are even more important in pregnancy, making arguments for prophylactic dialysis quite compelling.

D. Pregnancy in women with preexisting renal disease. The current approach to pregnancy in women with chronic renal disease is primarily based on retrospective studies, and more definitive views must await prospective data from large series in which clinical, pathologic, and functional observations are correlated. Nevertheless, several generalizations can be made and guidelines presented regarding gestation in women with chronic kidney dysfunction (Table 12-4).

1. Prognosis

a. Degree of renal impairment. The ability to sustain a viable pregnancy decreases as renal function declines, and when serum creatinine and urea nitrogen exceed 3 and 30 mg per deciliter, respectively, before conception, normal gestation is rare. Contraception or early termination of pregnancy is generally recommended in women whose serum creatinine exceeds 2 mg per deciliter, but it should be noted that women with moderately severe disease manifesting azotemia greater than that described above have borne viable infants. There are even rare instances in which women undergoing maintenance hemodialysis have conceived and the gestation has ended successfully.

b. Level of blood pressure. The blood pressure level at time of gestation is an important prognostic index. In the absence of hypertension, the natural history of most established renal parenchymal diseases is unaffected by gestation (although preeclampsia may occur more readily). In contrast, when renal disease and hypertension coexist the gestation is more likely to be complicated, either by severe increments in blood pressure or by additional reductions in renal function. Such women should be counseled to avoid conception and if they do become pregnant to terminate the pregnancy. If they wish to continue the pregnancy and to take the risks explained to them, these gravidas must be seen weekly and should understand that their gestation must be terminated if renal function deteriorates or if their blood pressure becomes difficult to control.

c. Proteinuria. Urinary protein excretion, which increases in normal pregnancy, may increase markedly in pregnant women with underlying parenchymal renal disease. In one large series one-third of the patients developed nephrotic-range proteinuria during gestation. In most instances, however, these increments do not reflect worsening of the underlying kidney disease.

d. Renal hemodynamics. Gravidas with kidney disorders who have only minimal renal dysfunction usually experience increments in GFR during gestation, even though levels do not reach those seen in normal pregnant women. Thus a decrement in serum creatinine level early in pregnancy is a good prognostic sign. If serum creatinine levels before conception exceed 1.4 mg%, decrements during gestation are less common and the prognosis of such pregnancies is more guarded.

2. Glomerulonephritis. Absence of gravidas in large epidemiologic surveys of poststreptococcal glomerulonephritis is remarkable and has led to speculations that pregnancy protects women from this disease. However, this form of immune complex nephritis does occur rarely in gestation, in which it may mimic preeclampsia. Its prognosis is favorable, since in those instances in which the occurrence of acute poststreptococcal glomerulonephritis during gestation was properly documented, renal function recovered rapidly and the pregnancy usually had a successful outcome.

The prognosis of chronic glomerulonephritis during pregnancy is difficult to evaluate because most reported cases are poorly documented, especially the prepregnancy level of renal function and blood pressure. Still it appears that if proteinuria or abnormal urinary sediment is the sole manifestation of the disease, pregnancy will proceed normally. Gravidas with membranoproliferative glomerulonephritis, especially those with dense intramembranous deposits demonstrated ultrastructurally and women with IgA nephropathy, may be especially prone to hypertensive complications. Although C_3 nephritic factor may pass from mother to fetus, the neonate appears unaffected and maternal complement levels may actually rise in gestation.

Hereditary nephritis is an uncommon disorder that may first be manifested during pregnancy, when women with this disease develop frank nephrotic syndrome. A variety of hereditary nephritis accompanied by platelet abnormalities has been described. Pregnancy in these women has been successful

Table 12-4. Summary of Pregnancy in Women with Preexisting Renal Disease*

Disease	Comments
Chronic glomerulonephritis, noninfectious tubulointerstitial disease (e.g., polycystic kidneys)	Usually no adverse effect in the absence of hypertension; urinary tract infections may occur more frequently
Lupus nephropathy	Controversial; prognosis favorable if disease in remission at conception; monitor complement levels during gestation and increase treatment when values decrease; steroid dosage should be increased in the puerperium
Diabetic nephropathy	Probably no adverse effect on the renal lesion, although frequency of leg edema, preeclampsia, and perhaps urinary tract infection is higher
Nephrotic syndrome	Tolerated well; infants may have low birth weight. Diuretics should not be used
Chronic infectious pyelonephritis	Bacteriuria during pregnancy leads to more frequent exacerbation
Urolithiasis	Infection may be more frequent; otherwise, ureteral dilatation and stasis do not seem to affect the natural history
Status postnephrectomy; solitary and pelvic kidneys	Pregnancy usually well tolerated; dystocia has been attributed to pelvic kidneys
Transplanted kidneys	Most pregnancies succeed, but hypertensive and infectious problems are more frequent than in normal gravidas; immunosuppressive therapy may cause fetal adrenal failure and congenital anomalies

*Generalizations are for women with only mild renal dysfunction (serum creatinine level < 1.5 mg/dl). The natural course of renal disease in women with greater functional impairment remains to be determined.

from a renal standpoint, but their gestations have been complicated by bleeding problems.

3. **Collagen vascular diseases**
   a. **Lupus nephritis.** Pregnancy has variable effects on lupus nephropathy, with either transient improvement, no change in the natural history of the disease, or a tendency toward relapse. It appears that the longer the disease has been in remission before conception, the greater the likelihood of a symptom-free gestation. The serum complement should be closely monitored throughout pregnancy, and treatment begun or increased when values decrease.
   Some believe that patients with lupus nephropathy are more prone to relapse in the puerperium. Since these exacerbations can be quite severe (in the past a significant number of maternal deaths were recorded during this period), one should be alert to this possibility and initiate steroids or increase the steroid dosage in the immediate puerperium.
   b. **Periarteritis nodosa and scleroderma.** Pregnancy in patients with periarteritis nodosa and scleroderma with renal involvement appears to be disastrous, possibly due to the associated hypertension, which frequently becomes malignant in nature. Not only is fetal prognosis dismal, but most reported cases end in maternal death. Although such a poor prognosis reflects the selectivity of a handful of case reports, prudence dictates that the pregnancies of gravidas with these diseases be terminated at an early stage until more is known about their natural history during pregnancy.
4. **Diabetes mellitus.** Diabetes is among the more common medical disorders encountered in the prenatal clinic. Many of the patients are juvenile diabetics, who probably harbor early microscopic changes in their kidneys. Nevertheless, most gestations in diabetic patients with normal renal function succeed, especially if blood glucose levels are maintained close to the normal range during the prenatal period. These diabetic women have an increased prevalence of bacteriuria and an increased susceptibility to symptomatic infection during pregnancy. With these exceptions, such women rarely have renal complications, although they seem to have a higher incidence of preeclampsia.
   The effects of gestation in diabetics with overt nephropathy are similar to those in women with other forms of renal parenchymal disease. Those with the mildest functional impairment have little trouble (although on occasion proteinuria may be massive), whereas the presence of hypertension imparts a poorer prognosis. Older reports of frequent deterioration reflect experience from centers in which the gravidas were managed with stringent salt restriction as well as prophylactic diuretics. Without such restrictions, women with biopsy-proven diabetic nephropathy actually display increases in GFR during gestation.
5. **Nephrotic syndrome.** The most common cause of nephrotic-range proteinuria (greater than 3.5 gm per day) in late pregnancy is preeclampsia, a diagnosis that may not be considered when diastolic pressures are between 85 and 95 mm Hg. The fetal prognosis in preeclampsia with heavy proteinuria is poorer than it is in other preeclamptic states, but maternal prognosis is similar. Most of the usual causes of nephrotic syndrome, including membranous nephropathy, proliferative or membranoproliferative glomerulonephritis, lipoid nephrosis, diabetic nephropathy, amyloidosis, and secondary syphilis, have been described in gravidas. Many of these conditions do not respond to corticosteroids, and some may be aggravated by them, underscoring the importance of establishing a tissue diagnosis before starting therapy. If renal function is adequate and hypertension absent, several of the physiologic alterations of normal pregnancy may simulate aggravation of the nephrotic syndrome (Table 12-5). Increments in renal hemodynamics or renal vein pressure may enhance protein excretion. Levels of serum albumin normally decrease during gestation, and this may increase the tendency toward fluid retention. Despite edema, diuretics are to be avoided because these women have decreased intravascular volumes, and

Table 12-5. Manifestations and Management of Nephrotic Syndrome in Pregnancy

Manifestation	Effect of Pregnancy	Management
Proteinuria	Increments in renal hemodynamics as well as increases in renal vein pressure may enhance protein excretion and simulate aggravation of disease. Protein loss may also lead to intrauterine fetal growth retardation	Prescribe high protein diet (3 gm/kg body weight). The infusion of salt-poor albumin is recommended for patients with decreasing renal function secondary to marked oligemia and for those with postural hypotension
Hypoalbuminemia	Levels of serum albumin usually decrease 0.5–1 gm/100 ml in normal pregnancy. The additional decrease in nephrotic patients may enhance the tendency toward fluid retention	
Edema	Usually increases during pregnancy	Avoid diuretics, which may increase the intravascular oligemia and compromise uteroplacental perfusion.
Infectious complications	There may be a high incidence of infectious complications in nephrotic gravidas	Screen frequently for asymptomatic bacteruria
Thrombotic episodes	Pregnancy is a hypercoagulable state and some have claimed that there are more frequent episodes of thrombotic episodes in pregnant patients with nephrotic syndrome	We do not anticoagulate these patients prophylactically, but if anticoagulation is required, heparin, which does not cross the placenta, is the preferred mode of therapy
Hyperlipidemia	Cholesterol and free fatty acids normally increase during gestation	Treatment is rarely required in pregnancy and most lipid-lowering agents have not been tested in gravidas

Source: M. D. Lindheimer and A. I. Katz, *Renal Function and Disease in Pregnancy*. New York: Lea & Febiger, 1977.

saliuretic therapy could conceivably compromise uteroplacental perfusion or aggravate the increased tendency to thrombotic episodes.

6. **Tubolo-interstitial disease**
   a. **Chronic pyelonephritis.** Dilatation and stasis in the urinary tract make chronic pyelonephritis in gravidas more prone to exacerbation. These women should have a high fluid intake prescribed and should be told to rest frequently on their sides. Prognosis of pregnant women with noninfectious interstitial nephritis seems similar to that of pregnant women with glomerular disease. Renal functional deterioration may occur rapidly in this group of patients when they are inadvertently salt restricted during gestation.
   b. **Polycystic disease.** Polycystic kidney disease may remain undetected in gestation. Careful questioning of gravidas for a family history of renal problems and judicious use of ultrasonography may lead to its earlier detection. Patients with minimal functional impairment have few complications, but a greater propensity toward preeclampsia exists. Hypertension usually accompanies the onset of increased functional deterioration, and pregnancy in such gravidas is more hazardous. Of interest is a report of pregnancy in a woman with the infantile variety of polycystic disease who, although hypertensive before conception, had a successful gestation.
   c. **Renal tuberculosis and solitary and pelvic kidneys.** Renal tuberculosis does not seem affected by pregnancy. Women with solitary kidneys appear to tolerate gestation well. However, if the nephrectomy was performed for nephrolithiasis or chronic pyelonephritis, the remaining kidney is often infected. Patients with these conditions must be carefully scrutinized by frequent examination and culture of the urine throughout pregnancy and in the puerperium.
   Pelvic kidneys are apparently associated with decreased fetal survival, often due to the presence of other malformations of the urogenital tract of the mother. In addition, dystocia may occur when the kidney is in the true pelvis.
7. **Urolithiasis.** Prevalence of stone disease in gestation varies between 0.03 percent and 0.35 percent in the Western hemisphere. The older literature stressed the dramatic complications that occur in pregnancy when calculi cause obstructive uropathy and infection supervenes. However, a recent survey of nonselected stone formers indicates that the course of the disease is unaffected by pregnancy, although urinary tract infections may be more common. Still, renal calculi are the most common cause of nonuterine-related abdominal pain severe enough to require hospitalization during pregnancy. Clinicians should not be deterred from pyelographic x-ray examinations because the patient is pregnant when complications suggest the need for surgical intervention.

E. **Renal transplantation**
1. **Fetal and maternal complications.** Pregnancy in women who have received renal allografts is becoming more common. As expected, prognosis is better when the transplanted kidney comes from a living donor. Most gestations succeed, but both maternal and fetal complications, due in part to the immunosuppressive therapy, can be anticipated; these include steroid-induced hyperglycemia, severe hypertension, septicemia, ectopic pregnancy, and uterine rupture. Fetal problems such as intrauterine growth retardation, congenital anomalies, prematurity, hypoadrenalism, hepatic insufficiency, thrombocytopenia, and serious infection in the neonate have been reported.
2. **Suggested criteria for pregnancy.** The following criteria for transplant recipients wishing conception are suggested.
   a. Good health and stable renal function for 2 years after transplantation
   b. Stature compatible with good obstetric outcome
   c. Absent or, at most, minimal proteinuria
   d. No hypertension
   e. No evidence of pelvicalyceal distention on an excretory urogram performed before attempting pregnancy

   f. Serum creatinine of 2 mg per deciliter or less and preferably < 1.5 mg/dl
   g. Drug therapy: prednisone 15 mg per day or less; azathioprine 2 mg/kg/day or less

   Although stringent, these criteria constitute appropriate prudence until more information on pregnancy in transplant recipients becomes available.

F. **Case history.** The following example of two successful gestations in a woman with diffuse lupus glomerulonephritis demonstrates certain principles in the management of gravidas with chronic renal disease.

Example: A 24-year-old white gravida 3 para 1 abortus 1 was electively admitted for induction of labor. Five years previously, she developed fever, arthritis, pleuritic chest pains, and a malar skin rash 2 weeks after a miscarriage. Systemic lupus erythematosus was diagnosed, based on a positive LE test and presence in her serum of antinuclear and DNA antibodies. Her blood pressure was 115/75 mm Hg. Laboratory examination revealed anemia and leukopenia. Serum creatinine and urea nitrogen were 1.0 and 15 mg per deciliter, respectively. Protein excretion (qualitative) was negative, and the creatinine clearance was 110 ml per minute. A renal biopsy demonstrated diffuse glomerulonephritis. She was treated initially with prednisone 100 mg per day, which was slowly tapered to 30 mg per day. Therapy was complicated by development of a gastric ulcer.

The patient became pregnant one year later while in remission and after her predinsone dosage had been additionally tapered to 15 mg per day. Her prenatal course was uneventful. During gestation her serum creatinine and urea nitrogen decreased to 0.8 and 11 mg/100 ml, respectively. Her diastolic blood pressures ranged between 70 and 80 mm Hg. Prednisone was discontinued during her fifth gestational month, at a time when all clinical and serologic parameters were normal.

Labor was induced at 40 weeks gestation, resulting in the delivery of a healthy 3420-gm baby. The patient received hydrocortisone 100 mg during labor and 50 to 75 mg every 6 to 8 hours for the next 2 days. During the third postpartum day she developed transient hypotension, which apparently responded to hydration and 150 mg of additional hydrocortisone. Oral prednisone was then restarted and maintained at 20 mg per day.

One year after delivery she was operated on for acute appendicitis. Serum creatinine was 0.9 mg per deciliter and the blood pressure 136/70 mm Hg. The patient's third pregnancy occurred in 1977, 4 years after the initial diagnosis of systemic lupus erythematosus. At that time she was in clinical remission and her prednisone dosage was increased to 15 mg daily. During gestation the blood pressure was in the 125/80 mm Hg range, and serum creatinine, urea nitrogen, and uric acid were 0.8, 7, and 4.6 mg per deciliter, respectively. Urine protein excretion (qualitative) ranged between negative and trace. Inulin and p-aminohippurate clearances during her seventh gestational month were 157 ml per minute and 678 ml per minute.

The prenatal course continued uneventfully until gestational week 37, when decrements in her hemolytic complement and a rise in her antinuclear factor titer led the patient's physicians to increase the prednisone dosage to 30 mg per day. The complement activity then increased to low normal values.

Delivery was induced at 39 weeks, resulting in a 3675-gm healthy baby. Again, she received intravenous hydrocortisone during labor and in the immediate puerperium, after which oral prednisone was restarted.

Three months postpartum, the patient's blood pressure was 100/65 mm Hg. Serum creatinine and urea nitrogen were 0.9 and 17 mg per deciliter, respectively, and urinary protein excretion was 350 mg in a 24-hour collection. Repeat inulin and p-aminohippurate clearances were 93.5 ml per minute and 405 ml per minute. Her steroid therapy had been tapered to 5 mg per day.

The following points are illustrated in this case. The patient's initial manifestations of lupus erythematosus appeared to be related to gestation, and her renal biopsy contained a lesion that has a guarded prognosis. Nevertheless, because functional parameters and blood pressure were normal, she was allowed to conceive again twice, and both gestations succeeded. During the first pregnancy steroid therapy

was tapered but was wisely restarted in the puerperium. During the second gestation, scrutiny of her serologic factors suggested the possibility of exacerbation near term. Again, steroid therapy was judiciously increased. Finally, it is noteworthy that despite biopsy evidence of a diffuse glomerular lesion, the patient experienced the physiologic increments in renal hemodynamics during gestation.

IV. Hypertensive disorders of pregnancy. Hypertension during gestation remains a major cause of morbidity and death in both mother and child.

A. Classification. Of the many classifications proposed for hypertension complicating pregnancy, that of the Committee on Terminology of the American College of Obstetricians and Gynecologists is the most simple and useful. They classify the hypertensive disorders of pregnancy into four categories:

Preeclampsia-eclampsia (hypertension peculiar to pregnancy)
Chronic hypertension (of whatever cause)
Chronic hypertension with superimposed preeclampsia
Late or transient hypertension

A fifth grouping, unclassified hypertensive disorder, has also been suggested, but we do not use or recommend it.

1. **Preeclampsia.** Preeclampsia, characterized by hypertension, proteinuria, edema, and, at times, coagulation abnormalities, occurs in late pregnancy, primarily in nulliparas. Third-trimester hypertension is defined as a blood pressure of 140/85 mm Hg or greater sustained for 4 to 6 hours. Also, increments over earlier systolic and diastolic pressures exceeding 30 and 15 mm Hg, respectively, are considered abnormal.
   Attempts have been made to categorize this disease as severe (e.g., diastolic and systolic pressures of 110 and 160 mm Hg or greater, heavy proteinuria, oliguria, and neurologic symptoms) and mild. Since a seemingly mild preeclamptic patient (e.g., a teenage gravida with a systolic blood pressure of 140/85 mm Hg and trace proteinuria) may suddenly convulse, terms such as *mild* and *severe* may be misleading. Hypertension during late pregnancy in a nulipara, whether or not other signs are present, is sufficient reason to proceed with hospitalization and treatment as if the patient were a potential preeclamptic.
2. **Chronic hypertension.** Most women in this second category have essential hypertension, but in some the elevated blood pressure is secondary to such conditions as renal artery stenosis, coarctation of the aorta, renal disease, primary aldosteronism, or pheochromocytoma. Evidence of arteriolar disease, as well as knowledge that hypertension was present before conception or early in gestation, is helpful in establishing a diagnosis. Hypertensive patients are more prone than normal gravidas to develop superimposed preeclampsia, but, with the exception of patients with pheochromocytoma (in whom maternal mortality is high), their course and prognosis resemble that of nongravid hypertensive women. Since pheochromocytoma has such a catastrophic outcome during pregnancy, measurement of urinary catecholamines or vanillylmandelic acid excretion is recommended in all hypertensive gravidas.
3. **Chronic hypertension with superimposed preeclampsia.** A group of women with chronic hypertension develop an accelerated phase of their disease in late pregnancy. This exacerbation may be accompanied by oliguria or evidence of disseminated intravascular coagulation. It represents a rapidly developing medical emergency. Should the patient conceive again, there is a strong probability that this life-threatening syndrome will recur.
4. **Late or transient hypertension.** The last category includes a number of patients otherwise difficult to classify. Some women develop hypertension only in the last trimester or the immediate puerperium, but blood pressure normalizes by the tenth postpartum day. Among nulliparas some patients may be preeclamptics who have not manifested other signs of the disease. (It is prudent to manage all such primigravidas as if they were preeclamptics.) Another group of gravidas develop hypertension in two or more pregnancies and become normotensive following delivery. Patients with transient hypertension probably represent women destined to have essential hypertension develop later in life.

B. Pathophysiology and pathology of preeclampsia. The increment in blood pressure in preeclampsia is characterized by its lability, especially when compared to other hypertensive disorders. This probably reflects the intense sensitivity of these women's vasculature to changing concentrations of their own endogenous pressor peptides and catecholamines. Whereas normal pregnant women are extremely resistant to the pressor effects of infused angiotensin, those destined to develop preeclampsia manifest increased pressor responsiveness to the infused peptide weeks before the appearance of abnormal blood pressure, weight gain, or signs of coagulopathy.

In the past much attention was given to edema occurring in preeclampsia. However, preeclampsia can occur in the absence of fluid retention. Even when interstitial edema is present, plasma volume is decreased and hemoconcentration is present.

The incidence of coagulation abnormalities in preeclampsia is debated; in our experience disordered coagulation occurs in only a minority of patients and usually in those with the most severe disease.

C. Kidney function and morphology in preeclampsia

1. **GFR and RPF.** Both GFR and RPF decrease in preeclampsia. The decrements approximate 25 percent in most instances, so the GFR of preeclamptic women often remains above pregravid values. However, in rare instances large decreases in function may occur and, on occasion, lead to acute tubular or cortical necrosis.
2. **Uric acid.** There are changes in the renal handling of urate in preeclampsia. A decrease in the clearance of uric acid, accompanied by increments in blood levels of this solute, may occur weeks before any clinical signs of the disease appear. In pregnancy, serum urate levels above 4.5 mg/100 ml are suspect. The level of hyperuricemia also correlates with the severity of the preeclamptic renal lesion, as well as with fetal outcome.
3. **Proteinuria.** Increased proteinuria, which may be moderate or heavy, is a feature of preeclampsia, and the diagnosis is suspect in its absence. The magnitude of proteinuria does not appear to affect maternal prognosis, but protein excretion in the nephrotic range is associated with greater fetal loss.
4. **Glomerular capillary endotheliosis.** Preeclampsia is accompanied by a characteristic lesion, glomerular capillary endotheliosis (Fig. 12-3). In women diagnosed clinically as preeclamptic, this lesion is present in only about 75 percent of biopsies obtained from primiparas and in considerably fewer biopsies from multiparas; the remainder of patients have evidence of nephrosclerosis or another parenchymal disease. The usefulness of postpartum renal biopsy in preeclamptic patients is underscored by observations that renal vascular abnormalities may have prognostic implications for future pregnancies. Women with glomerular endotheliosis alone tend to have uneventful subsequent gestations, but when alterations in the renal vessels are present, hypertension is more likely to recur in later pregnancies.

D. Management of preeclampsia

1. **Hospitalization.** Ambulatory treatment has no place in the management of preeclampsia. All suspected preeclamptic patients should be hospitalized. This approach diminishes the frequency of convulsions and other consequences of diagnostic error. In general, fetal maturity is evaluated; if the gestation is near term, induction is the therapy of choice, whereas attempts to temporize are made if the pregnancy is at an earlier stage. Rest is an extremely important part of the therapeutic regimen, which must be prescribed rather than suggested. Termination of pregnancy should be considered when hyperreflexia develops or persists; blood pressure cannot be controlled; serum creatinine, urea nitrogen, or uric acid rise; laboratory evidence suggests disseminated intravascular coagulation or abnormal liver function (increased transaminases); or specific obstetric tests suggest fetal jeopardy. When signs of impending convulsions (eclampsia) are present, parenteral magnesium sulfate is the drug of choice in most obstetric centers.
2. **Treatment of hypertension.** The approach to treatment of high blood pressure in gravidas is disputed. Results of morphologic examination of placentae dem-

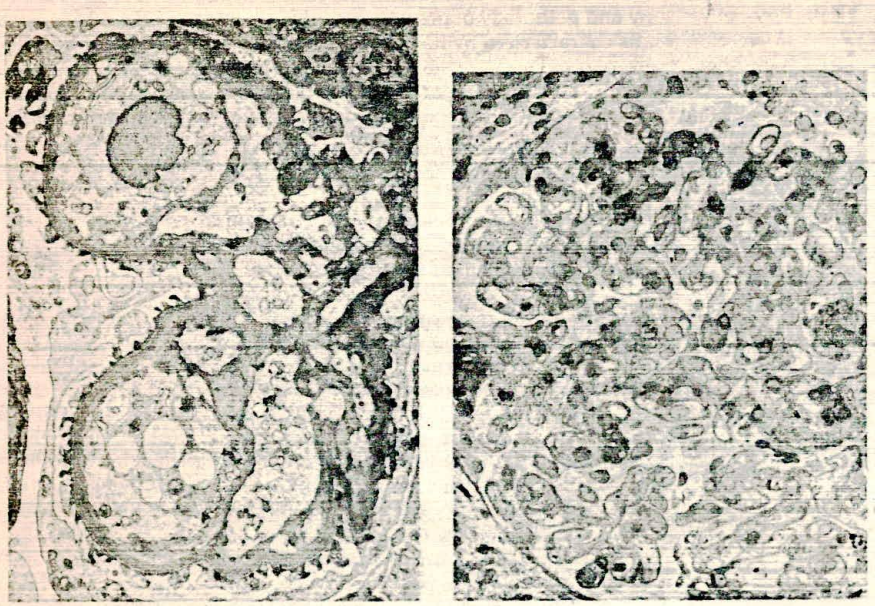


Fig. 12-3. (Left) Electron micrograph demonstrating complete capillary obliteration by a swollen endothelial cell. Note, however, that the basement is normal and the foot processes are intact. **(Right)** Micrograph showing glomerulus from a preeclamptic's kidney. Swollen endothelial and mesangial cells that display prominent vacuolization encroach upon the capillary lumina. (Courtesy of B. H. Spargo, M.D.)

onstrating trophoblastic invasion of the uterine spiral arteries, as well as observations by investigators who use unanesthetized sheep or primate models, suggest that uterine arteries behave like rigid conduits or are normally maximally dilated. These authors believe that reduction in maternal blood pressure decreases uteroplacental perfusion (i.e., poor autoregulation of uterine blood flow) and caution against large decrements in the mother's mean pressure, especially in acute emergencies. They are especially cautious in preeclampsia, since placental flow is already compromised. In contrast, investigators working with anesthetized rabbits note that autoregulation of uterine flow is rapid and complete, and they suggest an aggressive approach to human hypertension. Data in human pregnancy are limited, but they suggest that drops in maternal pressure may reduce placental perfusion. Assuming that autoregulation of uterine blood flow exists, a critical but unanswered question is how quickly it takes place, since fetuses may be damaged by short periods of ischemia. There are documented instances in which precipitous decreases of pressure in response to diazoxide (even to diastolic levels above 85 mm Hg) were followed by immediate monitor signs of fetal distress. Thus, we prescribe the careful use of parenteral hydralazine when acute hypertension exceeds diastolic levels of 105 mm Hg, along with close maternal scrutiny and fetal monitoring. This approach is successful in most gravidas, and diazoxide is restricted to the occasional case resistant to this therapy. Diazoxide should be administered in small doses (30 mg at a time), because hypertensive gravidas are usually controlled with a total dosage one-third that required in nongravid women. Diazoxide causes uterine atony, which is easily reversed with the judicious use of oxytocin.

There is debate as to whether or not women with mild essential hypertension should be treated during gestation since fetal outcome in this group seems no

different than in normotensive gravidas. Current practice is to withhold therapy until diastolic levels reach 95 mm Hg in the second trimester and 100 mm Hg in the third trimester. Some authorities suggest even slightly higher values. Methyldopa, which can be combined with hydralazine, is the agent most frequently used in gravidas with chronic hypertension. Data from trials testing a variety of beta-blocking drugs appear promising, and such agents can also be used when those listed above are not sufficient. Finally, since diuretic therapy limits the physiologic increment in plasma volume, these agents are not usually prescribed to hypertensive gravidas. However, there are some instances in which vasodilating agents alone fail and, faced with the choice of terminating a gestation, diuretics may be prescribed as a last alternative.

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14 Use of Radiologic Techniques in the Patient With Renal Problems

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Diagnostic imaging of the urinary tract is undergoing rapid expansion. This provides a wider choice of examinations for any individual problem, but it also necessitates an understanding of each study and a knowledge of its indications. In the first part of this chapter we discuss each of the imaging studies currently available and their general indications. The second part of the chapter is problem oriented; here we present a rational approach to using the various imaging techniques when faced with a particular diagnostic problem.

I. **Urographic procedures providing information about the urinary tract**

A. **Abdominal film.** The routine abdominal film provides considerable information about disease processes involving the urinary tract. These can be considered in four main categories.

1. **Bone.** Changes of renal osteodystrophy and either lytic or blastic metastatic lesions can be demonstrated.
2. **Soft tissue changes.** Obliteration of the psoas outline, the renal outline, or both of these gives a clue to the presence of pathologic processes such as inflammation, hemorrhage, tumor, or urinoma.
3. **Abnormalities of "air."** Dilated small or large bowel will be evident in cases of ileus or obstruction. Areas in which there is decreased abdominal air may indicate displacement by a mass.
   Air outside of the normal intestinal tract indicates considerable pathology. Intraperitoneal air is best visualized just under the diaphragm on an upright chest film. Intraperitoneal free air is usually related to bowel perforation, trauma, recent abdominal surgery, or a severe infectious process such as abscess. Retroperitoneal air outside of the intestinal tract also occurs; this can be visualized in several areas, including in and around the kidneys, in and around the bladder, and along the lateral abdominal walls. Air within the kidneys or bladder may be due to severe infections, particularly in diabetic patients. Trauma to the retroperitoneal portions of the intestines can also produce free retroperitoneal air, as can the postoperative setting.
4. **Calcifications**
   a. **Renal.** Collecting structures—nephrolithiasis
      (1) **Medulla.** Nephrocalcinosis (hypercalcemic states, medullary sponge kidney, papillary necrosis)
      (2) **Cortex.** Chronic glomerulonephritis, acute cortical necrosis
   b. **Ureter.** Calcified stones
   c. **Bladder.** Tuberculosis, schistosomiasis, bladder stones

B. **Renal tomograms without contrast media.** Renal tomography provides an estimation of renal size and may also reveal renal calcification not observed on the plain abdominal film.

C. **Excretory urography.** Excretory urography is the primary study for evaluation of the urinary tract. The diagnostic information obtained is directly related to the quality of study performed.

1. **Factors determining quality of excretory urography.** Factors that influence the quality and, therefore, the diagnostic capabilities of the excretory urogram are:
   a. **Bowel preparation**
   b. **Fluid restriction**

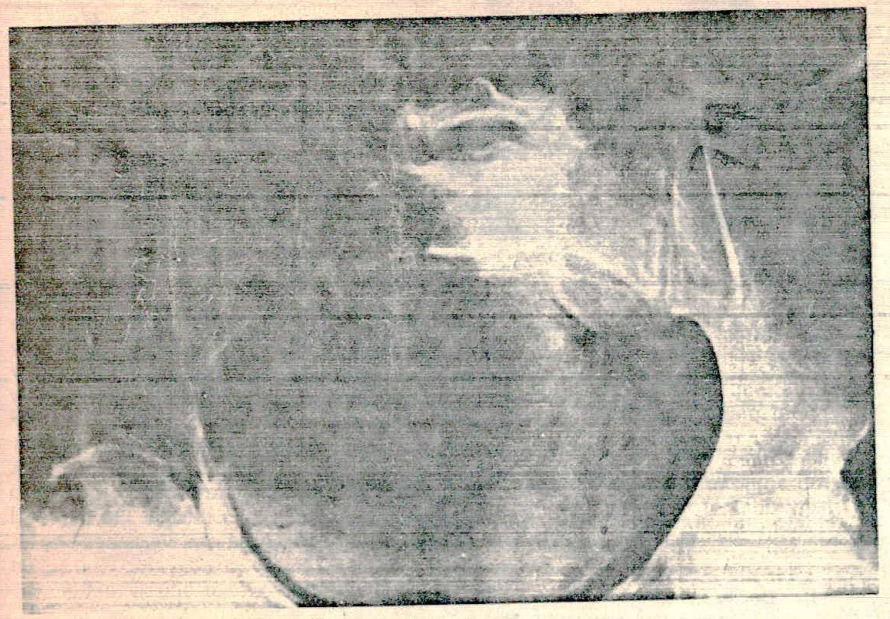

Fig. 14-1. Abnormal air outlines the bladder in a diabetic patient with emphysematous cystitis.

Fig. 14-2. Medullary calcification typical of renal tubular acidosis or hyperparathyroidism.

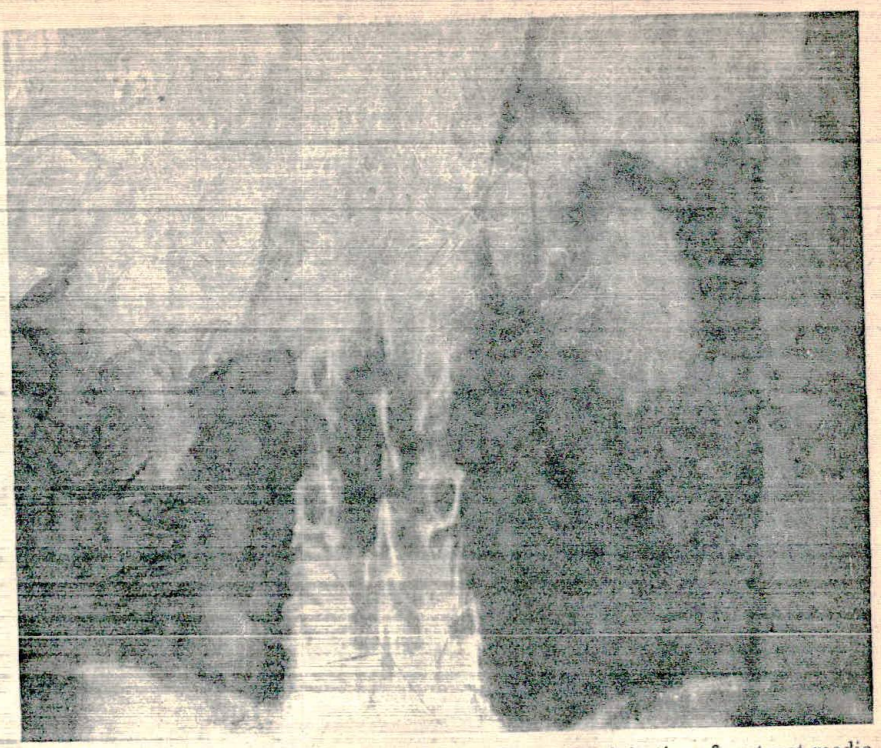

Fig. 14-3. Tomogram obtained immediately after the bolus injection of contrast media. The entire renal parenchyma and outlines are well visualized. The intensity of the nephrogram allows detection of a small hypovascular mass *(arrows)*.

c. **Amount of contrast used**—50 to 100 ml of 50 to 60% contrast media for an average adult
d. **Technical factors such as proper coning and the use of low kV technique**
e. **Tomography**
f. **Abdominal compression**
g. **Radiographs "tailored" for each patient**

Excretory urography is an accurate diagnostic procedure when properly performed and individualized for each patient. The use of tomography immediately after the injection of a bolus of contrast produces maximal visualization of the renal parenchyma, both normal and abnormal (Fig. 14-3). Films obtained at 5 and 10 minutes following the injection of contrast are used for evaluation of the collecting structures, ureters, and bladder. Abdominal compression is used to produce greater distention of the calyceal system and to allow better visualization of the entire ureter after the compression is released (Fig. 14-4).

Excretory urography performed without the use of tomography is a limited examination, highly dependent on the patient's bowel preparation. Lesions of all types, including considerable numbers of mass lesions, will not be detected. The referring physician must be aware of these limitations. Urography without tomography is best used on patients with a low suspicion of pathology.

Excretory urography provides the most information relative to the anatomy (both normal and abnormal) of the urinary tract as well as a very gross eval-

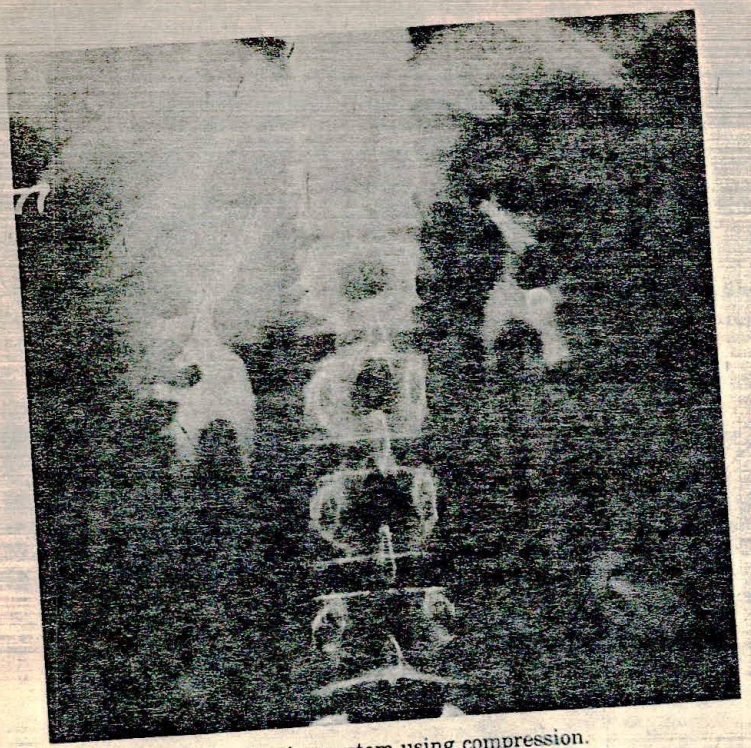

Fig. 14-4. Normal collecting system using compression.

uation of function. It serves as the primary screening modality for most forms of renal pathology. Certain relative contraindications should be mentioned.

2. **Relative contraindications for excretory urography**
   a. **Previous allergic reaction to contrast media.** Although this is only a relative contraindication, the need for urography should be carefully considered. Patients with a history of a previous severe reaction can benefit from premedication with steroids and antihistamines.
   b. **Contrast toxicity.** Several groups of patients are at higher risk to develop renal toxicity from contrast media. These include patients with (a) preexisting renal insufficiency, even mild (see Chap. 9), (b) diabetic nephropathy, (c) multiple myeloma, and (d) volume depletion. These patients should be studied in a well-hydrated state, but even this may not prevent renal damage from contrast media.
   c. **Cardiac disease.** Patients with known arrhythmias and cardiac irritability are at higher risk to develop such arrhythmias during urography. The relatively large osmotic load can also be a problem for patients in borderline congestive heart failure.
   d. **Pregnancy.** Because of the radiation hazards, urography should not be performed during pregnancy unless absolutely necessary. When it is necessary, high-speed rare earth screens can be used to reduce the radiation dose.

D. **Retrograde pyelography.** Retrograde pyelography is performed under cystoscopic control with the placement of an acorn bulb catheter in the ureteral orifice or through passage of a catheter up the ureter. Contrast media injected through the catheter demonstrates the ureter, renal pelvis, and calyces but not the parenchyma. Since the advent of high-dose excretory urography, the use of retrograde studies has markedly declined. Although many institutions have almost completely eliminated the use of the retrograde pyelogram, it does have a place in urologic diagnosis.

Uses of retrograde pyelography are:

1. **Additional evaluation of possible filling defects** not definite on excretory urography
2. **Selective cytologic studies and cultures**
3. **Additional delineation of an obstructing lesion,** especially the length of the obstruction and ureter distal to the obstruction
4. **To rule out obstruction** if all noninvasive studies are inconclusive
5. **Cases of ureteral trauma** (Fig. 14-5)

E. **Retrograde cystography and voiding cystourethrography**
   1. **Indications for retrograde cystography**
      a. **Vesicoureteral reflux.** Retrograde cystography, performed after filling the bladder with iodinated contrast media through a catheter, is used primarily for the evaluation of vesicoureteral reflux in children with recurrent urinary tract infections. The yield of demonstrating reflux in the adult with urinary tract infection is low, especially if there are no abnormalities of the kidneys demonstrated with excretory urography.
      b. **Anatomic delineation of bladder in patient with reduced renal function.** The retrograde cystogram provides somewhat better anatomic delineation of the bladder in instances in which there is reduced or even absent renal function and the bladder cannot be demonstrated with excretory urography. An example of this is the evaluation of the bladder of a potential transplant recipient before surgery.

      Other indications for retrograde cystography include:

      (1) **Pelvic trauma**
      (2) **Possible vesicovaginal or vesicoenteric fistulae**
      (3) **Postoperative evaluation**

Fig. 14-5. Right retrograde pyelogram demonstrates extravasation of contrast *(arrows)* from a partially transected right ureter. Both the exact point of injury and the degree of extravasation are apparent.

2. **Indications for voiding cystourethrography.** Voiding cystourethrography can be performed as part of retrograde cystography or as part of excretory urography (Fig. 14-6). Indications for this procedure are:
   a. **Posterior urethral valves in male children**
   b. **Strictures of either the posterior or anterior urethra in both children and adults**

F. **Retrograde urethrogram.** Retrograde urethrography is a limited, but useful, examination. Indications are:
1. **Evaluation of strictures of the anterior urethra**
2. **Pelvic trauma.** This is an important study in patients with severe pelvic trauma and should be performed before attempted catheterization of the bladder.

G. **Nuclear cystography.** This technique provides an alternative method for evaluation of vesicoureteral reflux in infants and children. ^{99m} Technetium pertechnetate is instilled directly into the bladder via catheterization. Continuous imaging allows detection of reflux. A major advantage of this technique is a considerable reduction in radiation dose to the child, a factor that is of particular concern when multiple follow-up studies are necessary. It does not, however, provide clear anatomic evaluation of the bladder or urethra. Routine cystography with iodinated contrast media is usually performed as the initial study, with isotope examinations used for follow-up.

II. **Ultrasound in evaluation of renal disease.** Because of its simplicity, noninvasiveness, low risk, and relatively low cost, ultrasound has found considerable use in the urinary tract. Results, however, are dependent on operator expertise and experience. The following are clinical circumstances in which ultrasound may be of value.

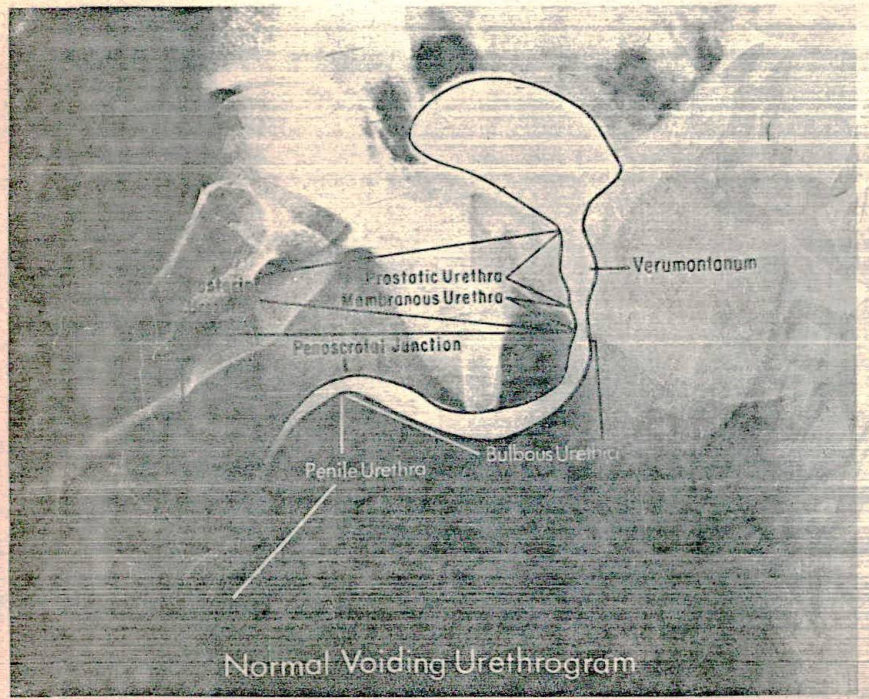

Fig. 14-6. Normal voiding cystourethrogram.

A. **Renal mass lesions.** Ultrasound is not a screening method, but once the mass has been identified it is the simplest modality for establishing whether the mass is cystic or solid (Fig. 14-7).

B. **Patients for whom an IVP is appropriate**
1. **Renal failure.** When an elevated serum creatinine is indicative of renal failure, intravenous contrast for an intravenous pyelogram (IVP) may be hazardous. Ultrasound can distinguish between obstruction and parenchymal disease as a cause of the failure. An absent or atrophic kidney can also be discovered.
2. **Allergic patients.** Patients who have a serious allergic history to iodinated contrast media can be studied with ultrasound, from which important information regarding renal size and contour, parenchyma, and collecting system may be obtained.

C. **Peripheral space.** The perirenal and pararenal spaces can be well evaluated with ultrasound, specifically for the presence of abnormal fluid, as in urinoma, he-

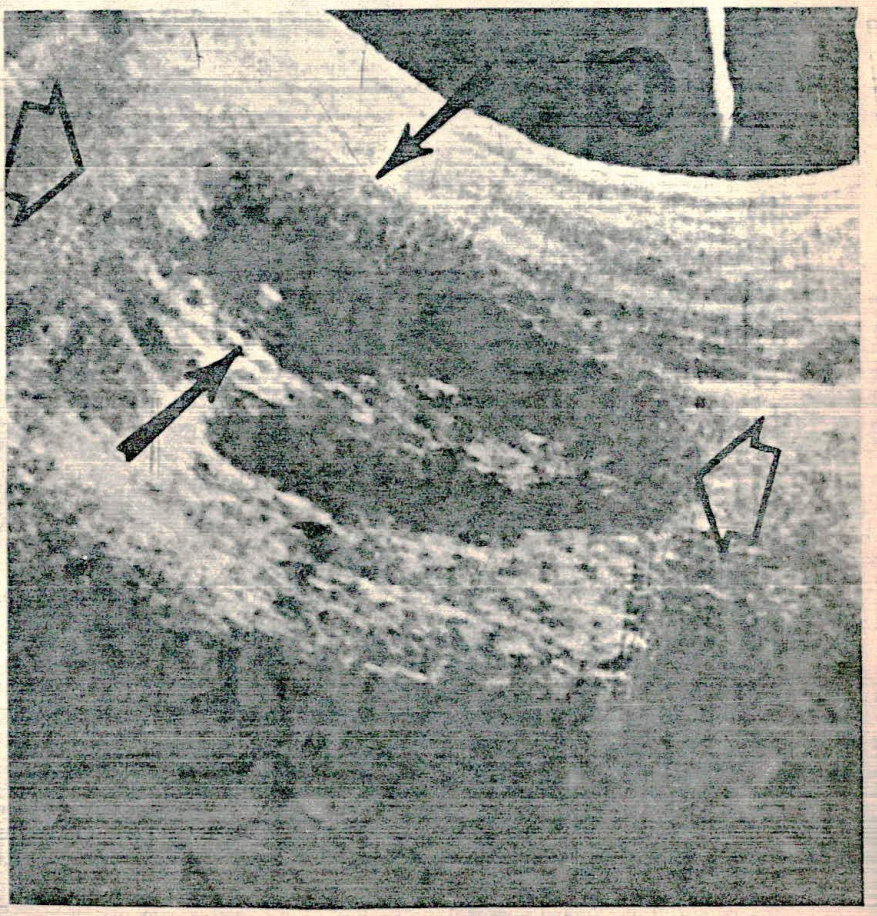

Fig. 14-7. Renal ultrasound demonstrates a solid lesion *(black arrows)*. Internal echoes are present and the overall echogenicity is similar to the normal kidney. *Open arrows = upper and lower poles of the kidney; P = posterior.)*

matoma, or abscess. Ultrasound also can be used to guide aspiration of these perinephric processes for both diagnosis and therapy.

D. **Transplant evaluation.** The acute enlargement associated with rejection can be detected, as can the presence of hydronephrosis if the transplanted kidney is obstructed. Perirenal collections about the transplanted kidney, such as lymphoceles, urinomas, and possibly, hematomas, can be detected and followed with ultrasound.

E. **Parenchymal disease.** Cortical thickness can be monitored in patients with chronic parenchymal disease or chronic obstruction. Both the localized abscess and more general changes of inflammatory swelling also can be detected by ultrasound.

III. **Computerized tomography for evaluation of renal disease.** Computerized tomography (CT) of the body is in its early stages and is undergoing continual changes in the technology, quality, and indications. It is a system in which multiple radiographic images are reconstructed with the use of a computer to produce a cross-sectional image. Currently used scanners produce a high quality image, especially if the image can be obtained in 5 seconds or less (Fig. 14-8). CT is both competitive with and complementary to diagnostic ultrasound. Because it is less operator-dependent, it can produce diagnostic images more consistently. However, it does involve patient radiation, is more expensive, and may require intravenous contrast. It also may not be as generally available as ultrasound. The following are clinical circumstances in which CT may be helpful.

A. **Renal mass.** The major renal use of CT is in the evaluation of renal masses that are not definitely diagnosed after excretory urography and ultrasound. CT is generally accurate in separating cysts from tumors, and in some instances obviates the need for more invasive procedures such as cyst puncture or arteriography (Fig. 14-9). It is particularly helpful in small lesions observed by excretory urography that are difficult to evaluate with ultrasound. In many instances CT has replaced angiography in the diagnosis of renal tumors and determination of their extent.

B. **Obstruction with renal failure.** CT scanning is also helpful in the obstructed patient, especially when there is reduced or absent renal function on the involved side. The principal use of CT in obstructed patients is to evaluate for a possible obstructive mass. In some instances CT-guided biopsies can be performed. Information regarding size, shape, and the presence or absence of obstruction can be obtained even without use of contrast media. The ability to obtain information without the use of contrast makes CT scanning an alternative method in a patient with known severe allergy to contrast media or one considered at high risk for contrast toxicity.

C. **Perirenal space.** Evaluation of the perirenal space, pararenal space, and Gerota's fascia can be performed easily with CT because of the cross-sectional images obtained. This can be of help in inflammatory processes, extension of tumors, and evaluation of trauma such as subcapsular hematoma.

D. **Evaluation of retroperitoneum-adrenal area.** Computerized tomography has established itself as the most efficacious imaging modality in the retroperitoneum, including the adrenal gland (Fig. 14-10). The retroperitoneum has been very difficult to study with conventional radiography, and, before the advent of computerized tomography, evaluation of the adrenal gland often required expensive and invasive arteriographic and venographic studies. The normal adrenal gland can now be imaged routinely, and even very small lesions such as aldosteronomas can be visualized. Retroperitoneal processes such as adenopathy, tumor, hematoma, and urinoma that have in the past been difficult to evaluate are now being routinely studied with good results.

Probably one of the most important uses of computerized tomography relative to the retroperitoneum is to establish that no disease process is present. Computerized tomography has been particularly helpful in excluding the presence of disease when somewhat unusual positions of the kidney or changes in the renal axis have suggested retroperitoneal masses.

E. **Uses within the pelvis.** Uses for computerized tomography within the pelvis include:

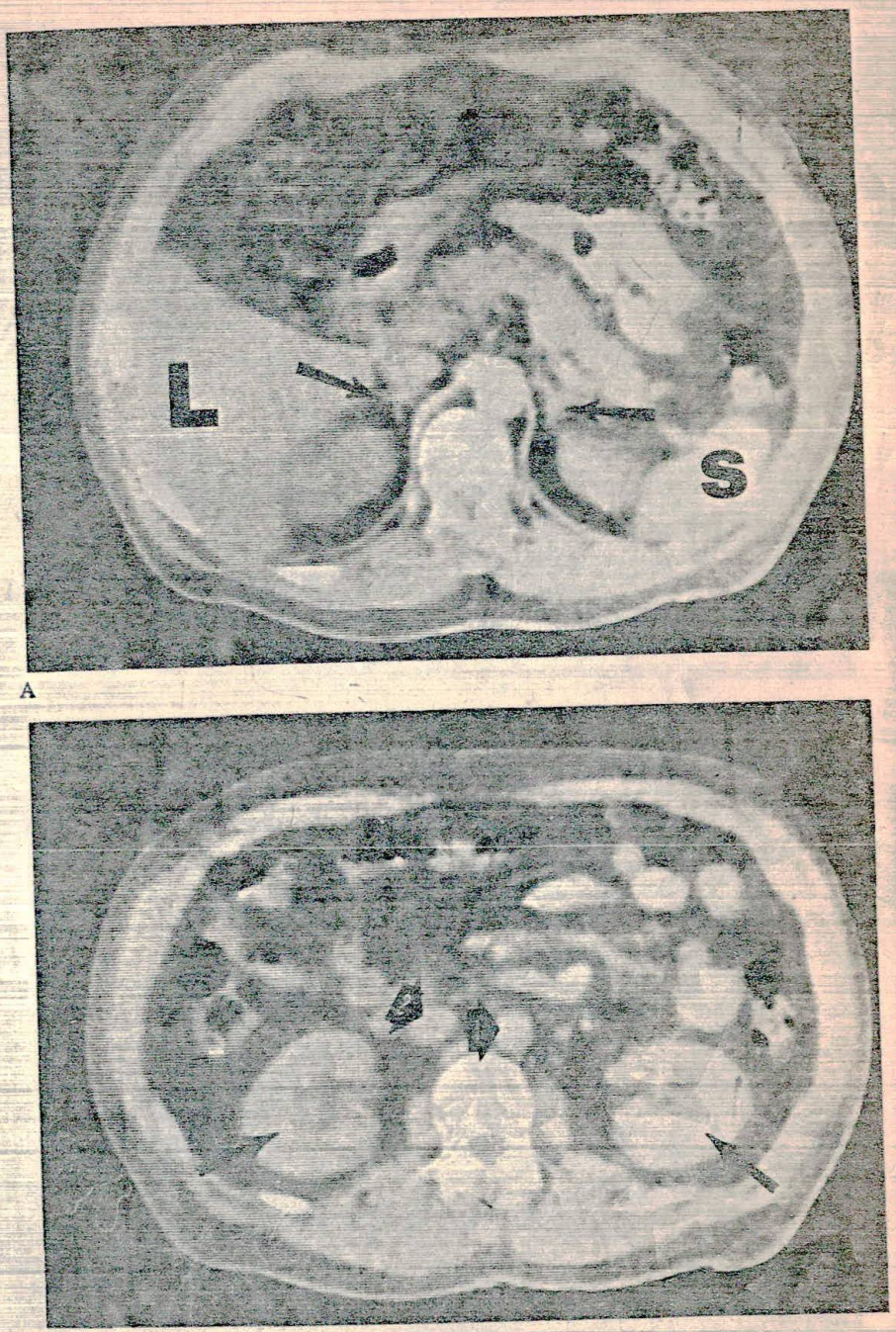

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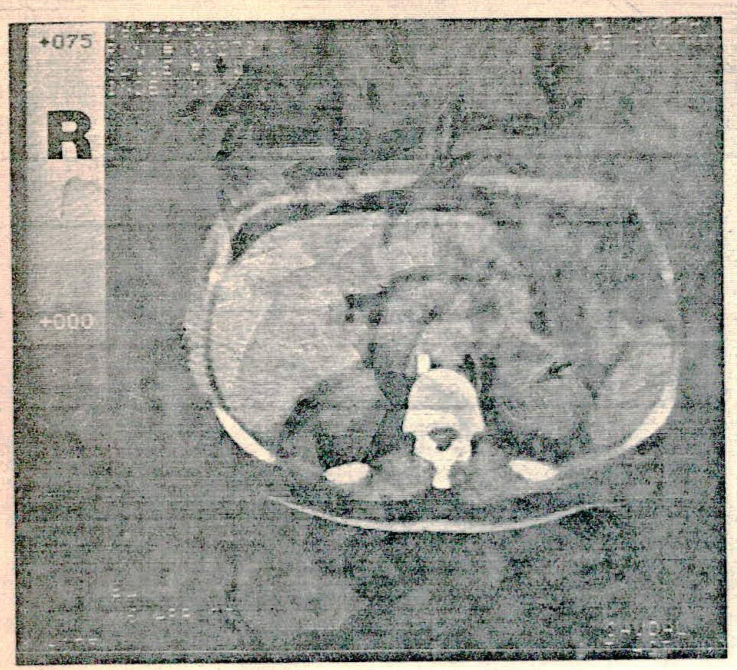
Fig. 14-8. A. Normal computerized tomographic scan through the level of the adrenals and upper kidney. Even without the use of contrast media the adrenals are well visualized *(arrows). (L = liver; S = spleen).* **B.** Computerized tomographic scan through the level of the midkidneys *(black arrows). (Arrow 1 = the aorta; arrow 2 = the inferior vena cava.)*



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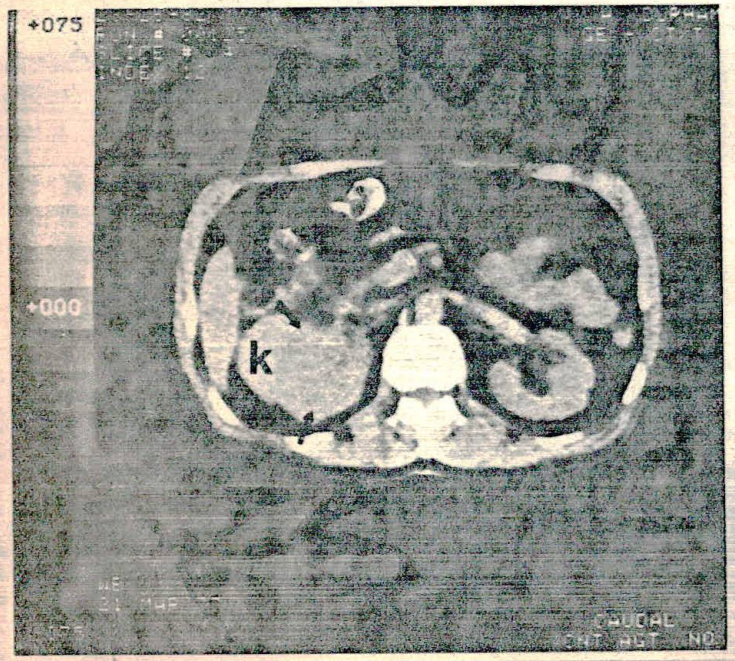

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Fig. 14-9. A. Well-marginated, low-density cyst of the left kidney *(black arrow)*. B. Large solid tumor with density similar to the kidney *(black arrows)*. Kidney *(k)* is displaced laterally.

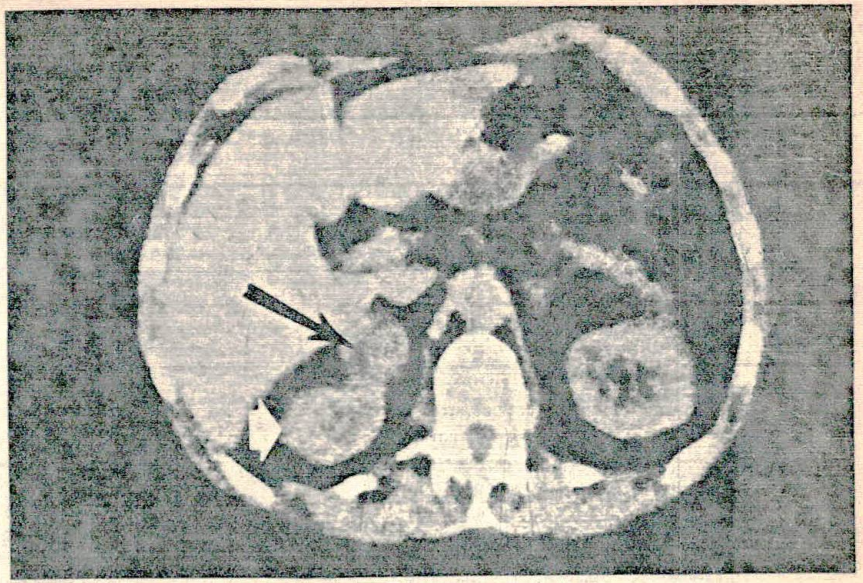


Fig. 14-10. Computerized tomographic scan of the abdomen shows an obvious mass *(arrow)* in the region of the right adrenal gland. This lesion measures 3.5 cm in diameter. The normal kidney *(white arrow)* is seen posterior to the lesion.

1. **Staging of the bladder carcinoma**
2. **Evaluation of pelvic masses** (tumor, abscess, hematoma)
3. **Post-transplant evaluation**
4. **Confirmation of pelvic lipomatosis**

IV. **Radionuclide evaluation of renal disease.** Radionuclide imaging of the kidneys for both morphology and function is somewhat controversial. Its use varies considerably, depending on the institution and the experience and interest of the persons responsible for the studies. There are three basic areas in which isotope studies of the kidney can be helpful. These are (a) renal function studies, (b) renal morphology, and (c) localization of inflammatory processes.

A. **Evaluation of renal function.** Renal function has traditionally been evaluated using the Hippuran renogram, and curves characteristic for obstructive versus parenchymal disease have been described. Unfortunately, in clinical practice these entities often overlap, and the renogram curves have only limited usefulness in making these differentiations. At some institutions the Hippuran renogram study has been extended to include serial measurements of blood and urine activity. With these data more quantitative information, such as effective renal blood flow, can be evaluated. Relative function of each kidney as well as function of parts of the kidney can also be evaluated. This information can be helpful in determining therapy in a number of disease states, such as congenital anomalies, vesicoureteral reflux, stone disease, and neurogenic bladder. The use of this more extensive study, however, is limited. In a number of institutions ^{99m}technetium DTPA has replaced ^{131}I Hippuran for assessing function. Although it does not provide as much functional information, the technetium study has the advantages of producing images of the kidney and of being somewhat easier to perform. It provides functional information similar to that obtained with excretory urography and is of particular use in patients in whom iodinated contrast is contraindicated.

B. **Evaluation of renal morphology.** Normal and abnormal renal anatomy can be evaluated with radionuclides. There are currently a number of excellent imaging

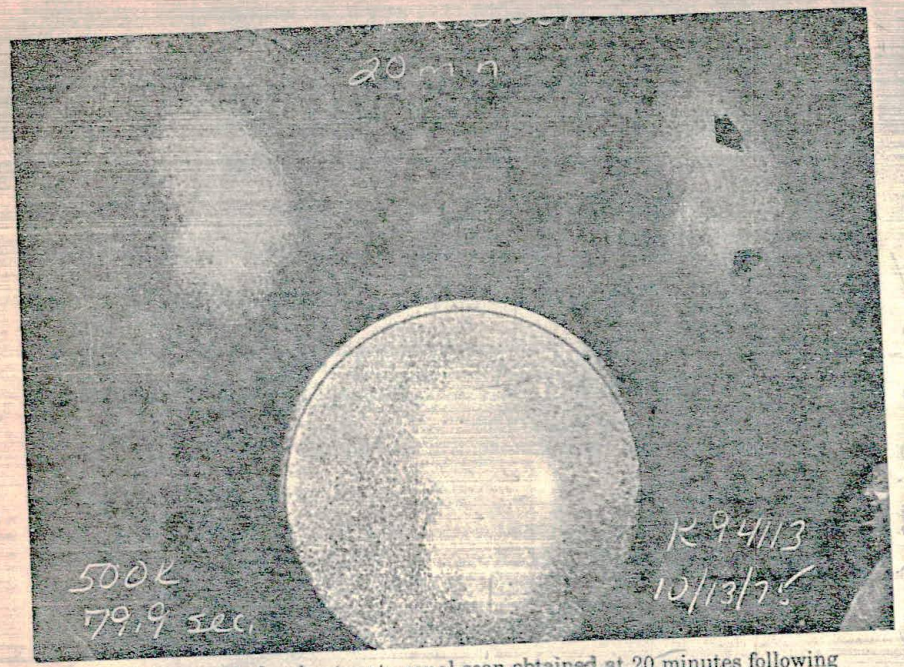


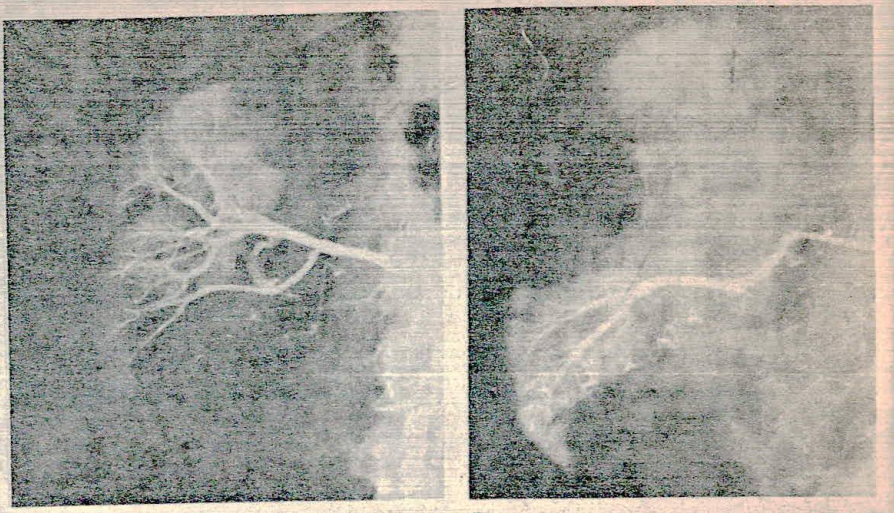
Fig. 14-11. A normal glucoheptonate renal scan obtained at 20 minutes following injection shows the calyceal structures *(arrow)* and the renal parenchyma. The three images vary only in photographic density.

isotopes, including ^{99m}technetium dimercaptosuccinate (DMSA) and ^{99m}technetium glucoheptonate (GHA). Images of somewhat lesser quality can be obtained with ^{99m}technetium DTPA. With DTPA and glucoheptonate both the parenchyma and collecting structures can be evaluated (Fig. 14-11). DMSA is used primarily for visualizing renal parenchyma. The radionuclide renal scan is of particular value in distinguishing between true tumors and pseudotumors of the kidney when the excretory urogram is equivocal. In addition, these studies can produce satisfactory images of the kidney in patients in whom iodinated contrast material is contraindicated.

C. **Localization of inflammatory processes.** ^{67}Gallium citrate is used in the detection of inflammatory processes, including renal and perinephric disease, pyelonephritis, and subphrenic abscess. The usefulness of gallium relates to its accumulation in areas of inflammation, in which it produces an area of increased radioactivity. Although there has been considerable success in the localization of both renal and perirenal abscesses using this technique, it must be noted that localization by gallium is not totally specific for inflammatory lesions. In fact, gallium was originally used for localization of abdominal neoplasms. However, in a patient with a suspected inflammatory process that has not been localized the use of gallium may indicate the pathologic area.

V. **Renal angiography for evaluation of renal vascular and parenchymal disease.** The use of diagnostic renal angiography has diminished in the past few years with the greater use of ultrasound and computerized tomography. There are, however, several areas in which angiography plays a major role.

A. **Evaluation of renal masses.** Most renal masses no longer require arteriography, especially if they can be documented to be a cyst with either ultrasound, cyst puncture, or computerized tomography. If these studies are not definitive, renal arteriography is used for diagnosis. Arteriography is also used if the less invasive studies indicate a renal tumor. Here arteriography is used to confirm the nature of the mass, to determine extension into the vascular structures, and to provide a vascular road map for the surgeons.



A B

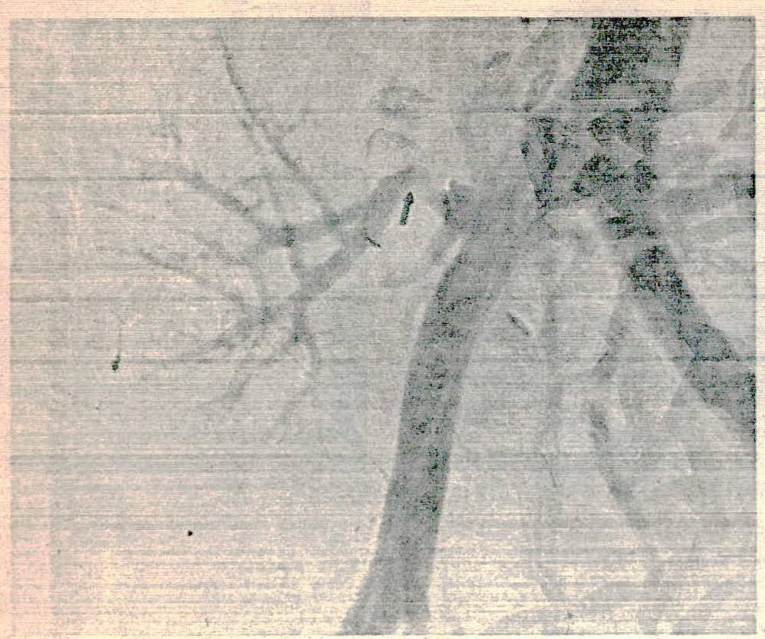
Fig. 14-12. A. Selected right renal ateriography demonstrates post-traumatic extravasation of contrast in a branch of the renal artery *(arrows.)* **B.** Following injection of clotting material to embolize the renal artery, the bleeding has stopped.

B. **Evaluation of renal vascular hypertension.** When available the procedure of choice in screening for renovascular hypertension is now digital subtraction angiography. Computer-enhanced imaging allows visualization of arterial anatomy following intravenous administration of contrast. Thus, the study can be performed on an outpatient basis with less risk and discomfort for the patient. Renal arteriography and renal vein catheterization for renin samples, however, continue to be the definitive tests for evaluation of renal vascular hypertension (see Chap. 13, V.B. 1.b.).

C. **Renal transplantation evaluation.** Renal arteriography is used for preoperative evaluation of the donor kidney. It is also used in the evaluation of the recipient kidney if the clinical course suggests arterial occlusion. Digital subtraction angiography is a less invasive alternative to arterial injection in evaluating the renal vasculature in the transplant patient.

D. **Traumatized kidney without function.** Changes in therapeutic approach to a more conservative method of handling blunt renal trauma have reduced the need for renal arteriography. It is, however, indicated in the traumatized kidney that shows no function with urography. Arteriography will outline the specific renal lesions more clearly and may be of particular help if the less invasive studies, such as urography, are indefinite or if the patient's clinical course is unstable.

E. **Interventional angiography.** Interventional uses of angiography are increasing. This includes the use of special catheters and embolization techniques to control hemorrhage (Fig. 14-12) or to occlude entities such as arteriovenous fistulae, which can be either congenital or traumatic. Embolization techniques are also used to infarct renal cell carcinomas before surgery and occasionally as the only therapy. Interventional angiographic techniques are now used in the management of renovascular hypertension. Hypertension in transplant recipients caused by excess renin production from the patient's native kidneys can be treated by renal ablation with intraarterial absolute ethanol. Intraluminal renal angioplasty has rapidly



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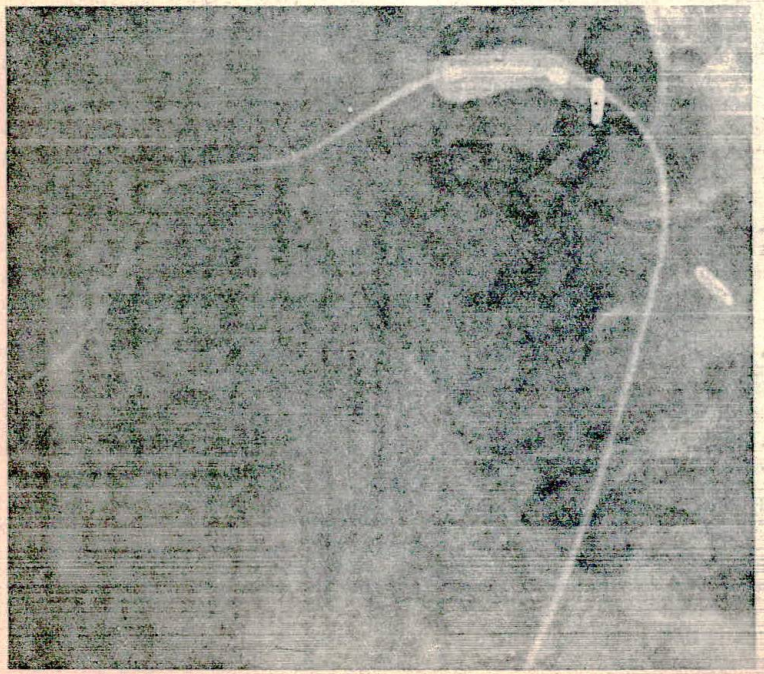

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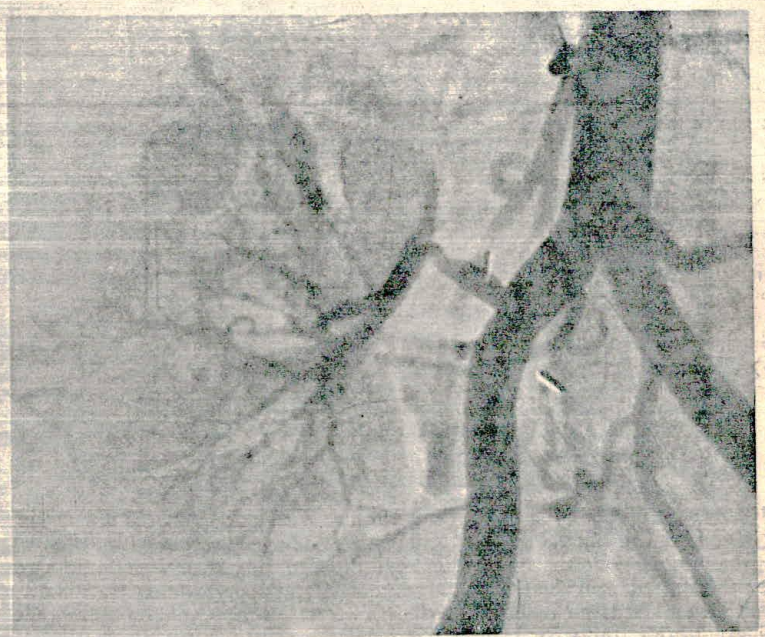
gained acceptance as an alternative to surgery in the management of renovascular hypertension (Fig. 14-13A, B, and C). Success in treatment of renovascular hypertension due to fibromuscular dysplasia exceeds 90 percent, and angioplasty is now considered the treatment of choice in the management of this condition. Angioplasty is also effective in most instances of renal artery stenosis due to atherosclerosis. Clinical improvement in the severity of the patient's hypertension is seen in about 70 percent of cases; in unsuccessful cases surgical correction can then be undertaken.

F. **Renal vein thrombosis.** Both renal arteriography and renal venography can establish the diagnosis of renal vein thrombosis.

VI. **Renal puncture techniques: cyst puncture, antegrade pyelography, and percutaneous nephrostomy**

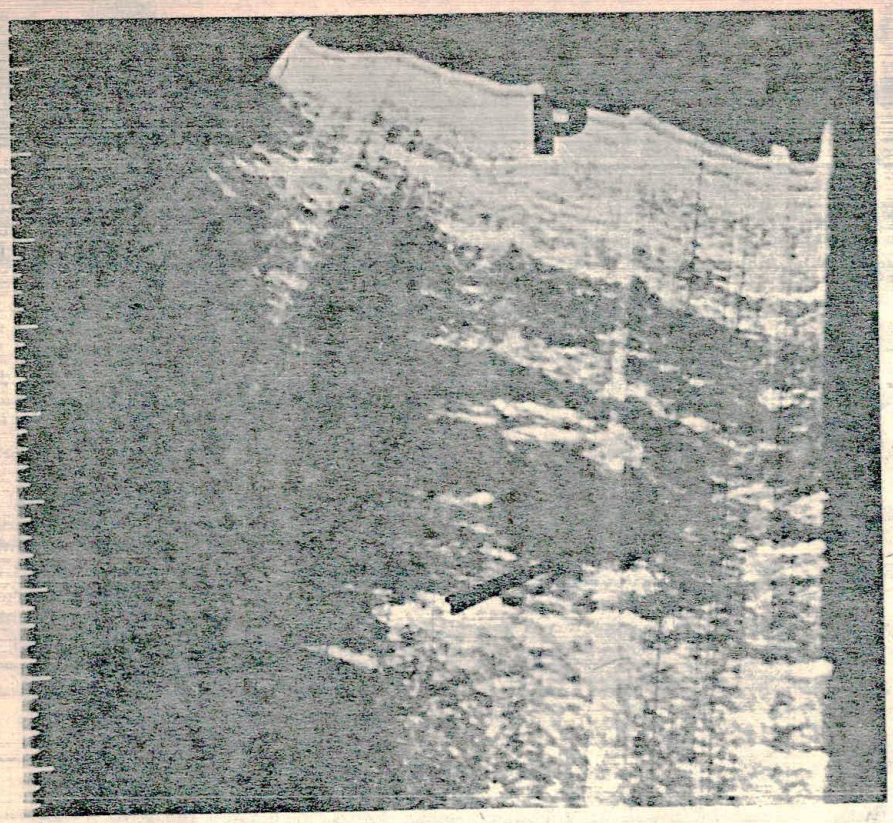
A. **Cyst puncture.** Cyst puncture is used for the definitive diagnosis of a simple cyst. The combination of the radiographic images and the fluid samples is highly reliable. Although it is used routinely in some institutions, in others it is used only in specific instances. The indications include:

1. **Probable but not definite cyst** after ultrasound and computerized tomography
2. **Patients under 50 years of age**
3. **Patients whose clinical presentation suggests neoplasm**



C

Fig. 14-13. Renal artery angioplasty in a renal transplant patient. The patient was a 15-year-old male with progressive hypertension 6 months following renal allograft transplant. **A.** Aortogram reveals 80 percent stenosis of transplant renal artery *(arrow)*. Pressure gradient was 30 mm Hg. **B.** Angioplasty balloon inflated in region of stenosis. **C.** Postdilation arteriogram with improved blood flow to kidney. Pressure gradient across stenosis is decreased to zero.



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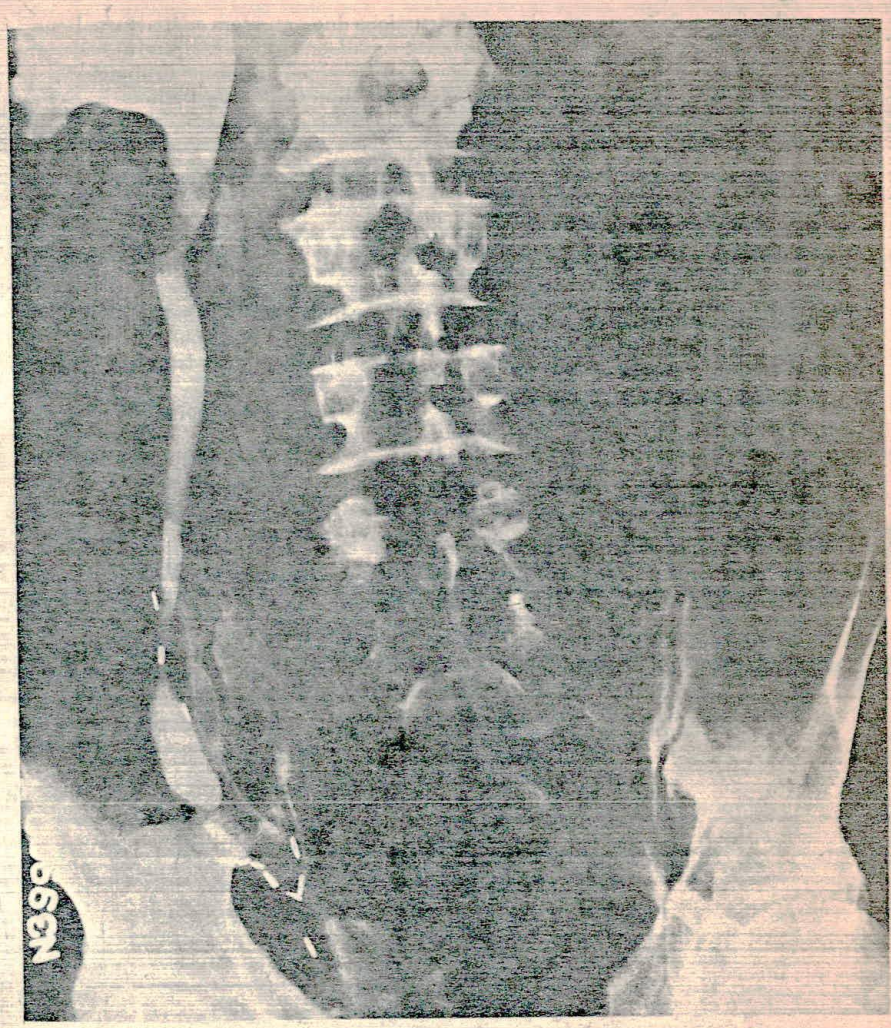

B

Fig. 14-14. Ultrasound examination of a nonvisualized kidney at excretory urography shows marked dilatation of the collecting structures and renal pelvis *(arrow)* indicating significant hydronephrosis. *(P = posterior; C = cephalad.)* **B.** Antegrade pyelography performed with a direct puncture to the calyceal structures was used to demonstrate the kidney, ureter, and the exact point of obstruction *(arrow)*. Retrograde pyelography was not technically possible in this patient.

B. Antegrade pyelography. This study is performed with placement of a thin needle into the renal collecting structures and subsequent opacification with iodinated contrast media. It can be performed under ultrasonic guidance or with fluoroscopy. It is indicated when evaluation of the anatomy of the upper urinary tract is necessary and when this cannot be done with excretory urography or retrograde pyelography (Fig. 14-14). In addition to diagnosing a site of obstruction, antegrade pyelography may be used in conjunction with pressure measurements to help differentiate between true obstruction and persistent hydronephrosis without obstruction.

C. Percutaneous nephrostomy. This procedure, which consists of nonoperative placement of a catheter into the renal pelvis under imaging control, is gaining greater acceptance by both radiologists and urologists. It provides an alternative method to surgical nephrostomy for drainage of an obstructed kidney. It can be used for both short- and long-term drainage, and either small or large catheters can be used, depending on the consistency of the material to be drained. Material for diagnostic culture can be obtained and antibiotics can be directly instilled into the infected kidney. Although ultrasound may be useful in the initial antegrade pyelogram to outline the calyceal system, especially if there is no urographic visualization, we prefer to place the nephrostomy tube under fluoroscopic visualization.

D. Endo-urology. With percutaneous access to the kidney the interventional radiologist now can provide a useful array of therapeutic procedures. A percutaneous nephrostomy tract can be enlarged to accept a 26 French sheath. This sheath allows percutaneous access to the collecting system by the urologist. Using this technique, small stones can be removed directly and larger ones fragmented by an ultrasonic lithotriptor and removed in pieces. Stents can be placed by the

radiologist to bypass and palliate obstructions due to tumors or stricture. Benign strictures can be dilated effectively with a balloon catheter. Ureteral leaks and fistulae can be treated with stent placement and percutaneous drainage.

VII. Problem-oriented approach to radiologic evaluation of urinary tract

A. Factors determining choice of procedure. The use of diagnostic imaging studies in any given situation depends to a large extent on the following four factors:

1. **Need for information to determine patient management**
2. **Accuracy and reliability of a given study**
3. **Invasiveness of the study (i.e., risks)**
4. **Cost of the study**

In general, this means the simple noninvasive studies are performed first, but if the diagnostic yield from these simpler studies is sufficiently low, then more expensive and invasive procedures may be warranted. In the schemes that follow we have tried to balance these four factors. Although a number of studies may be listed for a given problem this does not necessarily imply that any imaging studies are required. This must be a clinical decision.

B. Evaluation of the renal mass. Evaluation of renal masses involves more than a scheme of imaging modalities, such as that given in Fig. 14-15. In each case the overall clinical condition of the patient must be considered. The outline below acts only as a guide to the use of imaging modalities. These studies fall essentially into two groups: screening procedures (excretory urography, radionuclide renal scanning) and diagnostic procedures (ultrasound, computerized tomography, cyst puncture, angiography).

C. Evaluation of the patient with renal failure. In patients with renal failure, imaging techniques are used primarily to define the size and shape of the kidney and to exclude obstruction as the cause of renal failure. Defining the renal size will in most cases allow differentiation of the acute processes, which may be associated with normal or large kidneys, from the chronic states, which produce bilaterally small kidneys. This differentiation and the exclusion of obstruction can provide the basic information necessary to determine additional management. The outline below presents an imaging approach to certain categories of renal failure, with the studies listed roughly in order of preference.

1. **Chronic renal failure without acute exacerbations.** Obstruction is not a strong clinical consideration.
   a. **Nephrotomography without contrast media.** This procedure provides information regarding kidney size and shape, and calcification.

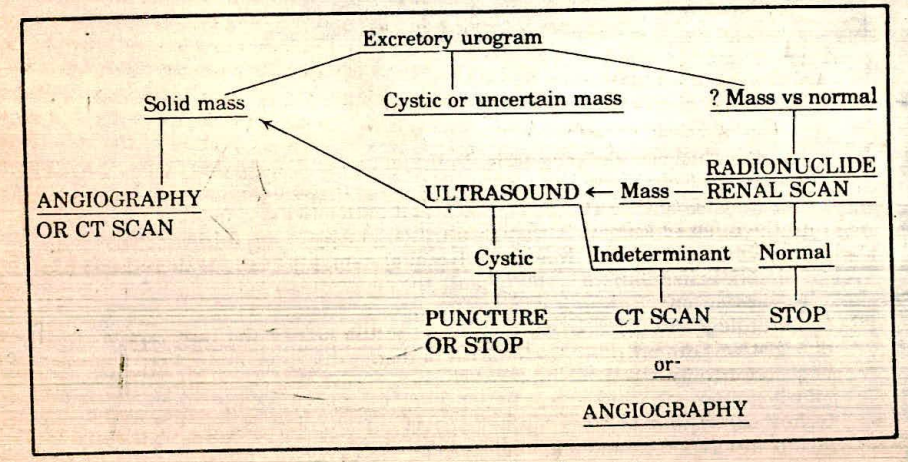

Fig. 14-15. A suggested approach to the evaluation of a renal mass.

   b. **Ultrasound.** This procedure allows evaluation of kidney size and shape as well as providing evidence of hydronephrosis.
   c. **Computerized tomography.** Size, shape, and evidence regarding obstruction can be obtained. This procedure is reserved for cases in which this information cannot be obtained with the simpler and less expensive studies.
2. **Acute renal failure, chronic renal failure with acute exacerbation, or unknown duration of renal failure**
   a. **Serum creatinine 4 mg/100 ml or below**
      (1) **Ultrasound.** If urography is considered high risk or felt to provide inadequate visualization of the calyceal structures, ultrasound can be used to exclude the presence of obstruction. Accuracy will depend on the expertise of the operator.
      (2) **Computerized tomography.** Computerized tomography may exclude obstruction without use of contrast, but accuracy in this situation is not established.
      (3) **Excretory urography.** Excretory urography with a high dose of radiocontrast media (100 ml of 50 to 60% solution) and tomography will generally provide information regarding size, shape, and status of the collecting structures, ureters, and bladder. Patients must be well hydrated before urography and the information to be gained must be balanced against the increased risk of renal toxicity from iodinated contrast. Urography will, however, provide the most information and should be used if this information is necessary for patient management.
      (4) **Retrograde pyelography.** Retrograde pyelography provides definitive evaluation of the collecting systems and ureters, but generally is not necessary unless the above procedures are equivocal or unavailable, or if confidence levels in these studies are not optimal due to lack of operator experience.
      (5) **Radionuclide studies.** Radionuclide studies are not as specific but can be useful, especially in patients in whom excretory urography presents a high risk.
   b. **Serum creatinine greater than 4 ml/100 ml**
      (1) **Ultrasound.** Ultrasonography allows the exclusion of obstruction and determines kidney size and shape. Fine detail of the calyceal structures and parenchyma is not provided but generally is not necessary in this situation.
      (2) **Computerized tomography.** Computerized tomography provides the same information as ultrasound without the use of contrast. It should be used if the more simple ultrasound examination is not definitive.
      (3) **Retrograde pyelography.** The use of retrograde pyelography will depend on the confidence level of ultrasound in excluding obstruction. It also may demonstrate the presence of papillary necrosis and calyceal abnormalities not evident on ultrasound or computerized tomography. Both retrograde pyelography and computerized tomography may demonstrate retroperitoneal fibrosis as the cause of renal failure.
      (4) **Excretory urography.** The information from excretory urography is variable, depending on degree of visualization; the test is probably not worth performing if other imaging modalities are available.

This outline, as with all outlines, cannot include all possible exceptions. All of the studies vary in their quality from one institution to another, and the reliability and expertise with which any given study is performed in an institution must be strongly considered when making the choice of imaging modalities in renal failure as well as in all other forms of renal disease. As a general statement, the problem usually faced with acute renal failure is to exclude obstruction, and the least invasive study that will accurately and reliably do this should be used.

D. Evaluation of urinary tract obstruction in the absence of renal failure. The following sequence is suggested (Fig. 14-16):

1. **Abdominal film.** Possible stones or soft tissue masses causing obstruction with marked hydronephrosis can be demonstrated on the preliminary abdominal film.

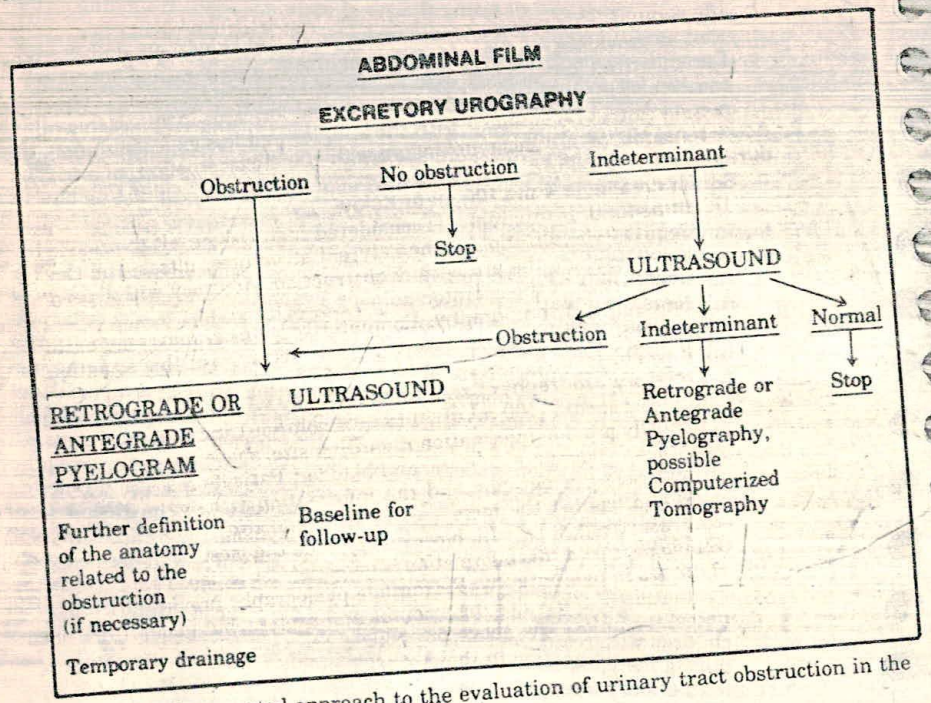

Fig. 14-16. A suggested approach to the evaluation of urinary tract obstruction in the absence of renal failure.

2. **Excretory urography.** Excretory urography is the primary study in most cases and will document presence and site of obstruction. Direct signs include the abrupt termination of contrast-filled pelvis or ureter. Indirect signs include "rim" signs, which represent visualization of remaining parenchyma as dense structures contrasted against the lucency of the dilated calyces in which the iodinated contrast is not visualized.
3. **Ultrasound.** Ultrasonography allows documentation of hydronephrosis in a kidney not visualized with excretory urography. It may also be used to follow documented hydronephrosis. Large renal calculi may also be visualized.
4. **Retrograde pyelography.** Retrograde pyelography may allow better delineation of the exact point of obstruction, cause of obstruction, and ureter distal to the point of obstruction.
5. **Computerized tomography.** Computerized tomography is of most benefit in obstruction related to retroperitoneal tumor mass such as adenopathy. The calyceal structures, ureters, and mass causing obstruction can be delineated and the exact point of obstruction shown. It is useful in evaluating hydronephrosis of any cause if simpler methods of evaluation are unsuccessful (Fig. 14-17).
6. **Antegrade studies.** Percutaneous antegrade pyelography may be used to delineate accurately the point of obstruction and also to provide drainage from above. This approach is particularly helpful when retrograde examination cannot be performed for technical reasons and function is sufficiently reduced so that excretory urography does not accurately delineate the anatomy. Pressure measurements (Whitaker test) may be helpful in separating nonobstructive hydronephrosis from obstruction.

E. Evaluation of hematuria

1. **Excretory urography.** Excretory urography is the primary study for hematuria. An excretory urogram with tomography and compressions may demonstrate:
   a. **Parenchymal lesions,** such as tumor, arteriovenous malformation, or swelling of the kidneys

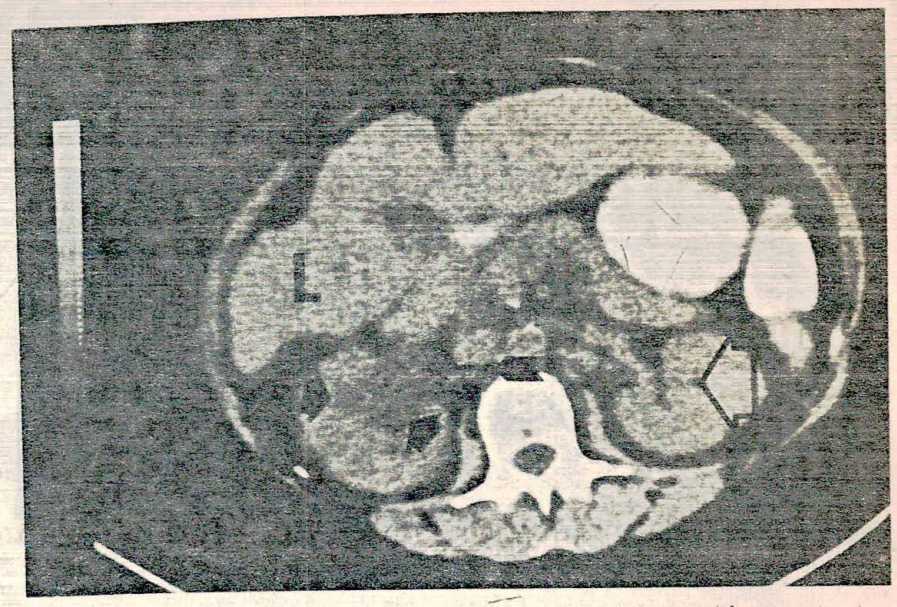

Fig. 14-17. Computerized tomographic examination of the kidneys without contrast media shows dilatation of the right renal pelvis *(long black arrow)* and the calyceal system *(short black arrows)* in a patient whose kidney was only poorly visualized with excretory urography. The open arrow indicates the normal appearance of the left collecting system. *(L = liver.)*

   b. **Collecting systems** with tumor, stones, leukoplakia, submucosal hemorrhage, or papillary necrosis
2. **Cystoscopy or renal biopsy.** Cystoscopy allows evaluation of bladder lesions; however, if clinical evidence suggests acute glomerular inflammatory lesions, such as those with associated proteinuria, renal biopsy may be of most value after excretory urography.
3. **Computerized tomography.** With persistent hematuria and the above studies negative, it is reasonable to perform computerized tomography specifically for relatively hypovascular and small tumors. Computerized tomography is also used to evaluate solid masses and their extent before surgery (Fig. 14-18).
4. **Bilateral retrograde studies with cytologic study.** This procedure provides information regarding small lesions with abnormal cytologic results that may not yet be visible and can also provide another evaluation of the collecting structures in case any small lesions were not seen at urography. If the above studies fail to delineate the cause of hematuria, the yield with additional studies will be very low.
5. **Selective renal angiography.** Vascular lesions such as arteriovenous malformations and small renal cell carcinomas can produce hematuria and not be visible on any of the above studies. In these cases the lesions may be observed by renal angiography.

F. Evaluation of the renal transplant. Evaluation of the renal transplant is best performed by comparison with baseline examination obtained in the immediate postoperative period.

1. **Baseline studies after renal transplantation**
   a. **Radionuclide studies.** ^{99m}Technetium DTPA provides estimation of both vascularity and function of the transplanted kidney. ^{131}I Hippuran renograms add additional functional information.

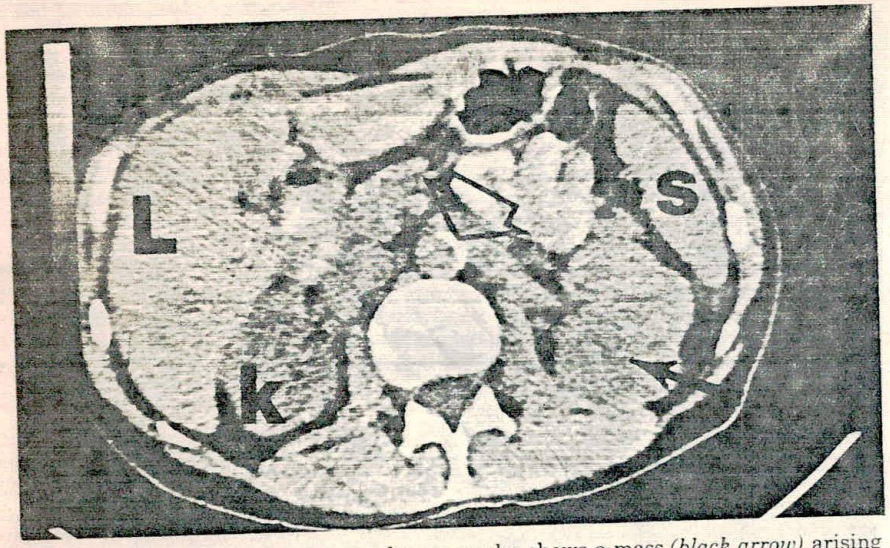

Fig. 14-18. Noncontrast computerized tomography shows a mass *(black arrow)* arising from the posterior aspect of the left kidney. This was an avascular mass not detected with arteriography. The presence of hematuria leads to further evaluation with computerized tomography. *(L = liver; S = spleen; K = normal right kidney; open arrow = calcified aorta.)*

b. **Ultrasound.** Ultrasonography has been used more in recent years and is excellent for evaluation of abnormal fluid collections around the kidney as well as of renal size. Collecting system obstruction can also be visualized.

c. **Excretory urography.** Excretory urography allows evaluation of anatomy, position, and size of the kidney, exclusion of obstruction and extravasation, and evaluation of the bladder position. Because of potential toxicity of contrast media, urography should not be used routinely. When urography is performed it should be delayed 5 to 7 days post-transplantation.

2. **Evaluation of complication after renal transplantation.** Although any one study may be best for a specific transplant complication, it is often clinically necessary to use a combination of studies to separate the multiple variables.

a. **Radionuclide studies.** Changes in renal function such as those related to rejection or acute tubular necrosis are best evaluated with renal radionuclide studies. Although not specific, these isotope studies may provide information that can help to differentiate between rejection and acute renal failure (i.e., renal perfusion is better preserved in the latter condition). A rough assessment of vascularity to the kidney, as well as a gross evaluation of anatomy, is also obtained.

b. **Ultrasound.** Ultrasonography is used to assess additionally any suspected masses in the pelvis, such as lymphocele, hematoma, or urinoma. Obstruction can also be detected with ultrasound and differentiated from rejection and acute tubular necrosis.

c. **Excretory urography.** Excretory urography provides only gross evaluation of renal function, but the presence of a functioning kidney excludes major arterial lesions. Urography is primarily used to exclude the development of an obstructive process or the presence of extravasation. Masses such as hematomas or lymphoceles may be detected but only if they are of sufficient size.

d. **Renal angiography.** If any of the above studies or strong clinical suspicions suggest the presence of a major arterial lesion, digital venous subtraction angiography or renal arteriography may be necessary.

e. **Computerized tomography.** Computerized tomography can provide excellent information regarding the renal anatomy and surrounding structures. Additional data are needed to determine whether it will replace any of the other modalities or add new information.

f. **Scheme for evaluation of oliguria and anuria in the transplant patient (Fig. 14-19)**

G. **Evaluation of renal and perirenal infection.** In many instances it is impossible clinically to separate the various forms of renal infection. Without renal imaging it may only be possible to suspect that an inflammatory process is occurring. The separation into specific entities, therefore, is somewhat artificial, yet helpful in understanding the usefulness of the various imaging techniques.

1. **Acute pyelonephritis.** Imaging studies are not always indicated.

a. **Abdominal film.** The abdominal film will exclude radiopaque urinary tract calculi as the underlying cause and allow evaluation of the retroperitoneal soft tissues for evidence of inflammatory change, such as loss of renal outlines and/or psoas margins.

b. **Excretory urography.** Excretory urography is the primary imaging modality even though radiographic changes may be minimal or nonexistent in the majority of patients with acute pyelonephritis. Findings may include increased renal size due to swelling, decreased concentration of contrast, asymmetry of function, spidery calyces, mucosal striations, and an irregular nephrogram. The procedure is not generally indicated acutely unless a complicating factor, such as urinary tract obstruction, is suspected.

c. **Ultrasound.** Ultrasonography can detect focal and generalized areas of swelling, but it is of more use in the evaluation of a well-defined renal abscess or perinephric inflammation.

d. **Retrograde cystogram.** The retrograde cystogram is primarily used in children with recurrent bouts of pyelonephritis. It is not usually performed during the episode of acute pyelonephritis.

2. **Chronic urinary tract infection**

a. **Abdominal film.** The abdominal film will reveal the 90 percent of nephrolithiases that are radiopaque. Uric acid stones are radiolucent.

b. **Excretory urography.** The ability of this study to demonstrate both parenchymal scars and calyceal blunting makes it the most useful study diagnostically.

c. **Retrograde cystogram.** This procedure will exclude vesicorenal reflux and underlying causes of chronic urinary tract infection in children and is especially important if upper tract changes are demonstrated.

3. **Renal abscess**

a. **Abdominal film.** The plain abdominal film may reveal loss of soft tissue outlines, thus suggesting inflammation.

b. **Excretory urography.** Excretory urography may demonstrate a mass lesion, possibly associated with loss of renal outline if there has been extension of the inflammation.

c. **Computerized tomography.** This study can define a mass as solid but cannot always separate an inflammatory from a neoplastic lesion. CT is excellent for guiding percutaneous aspiration to make this distinction.

d. **Ultrasound.** Ultrasonography allows additional assessment of the renal mass detected with urography. The clinical characteristics of the mass as well as perirenal extension can be evaluated. Diagnostic puncture and drainage can be performed with ultrasonography.

e. **^{67}Gallium scanning.** This procedure may be helpful in localization of renal and perirenal inflammatory lesions when these are not defined with other studies.

f. **Arteriography.** Renal arteriographic patterns suggesting an inflammatory lesion as opposed to a neoplastic lesion have been described, but the specificity and accuracy of this differentiation is very variable.

4. **Perinephric abscess**

a. **Abdominal film.** The abdominal film will demonstrate loss of renal and/or psoas margins.

Fig. 14-19. Evaluation of oliguria and anuria following renal transplantation. (From M. Parker. Radiology of Renal Failure. In M. Resnick and R. Older (Eds.), *Diagnosis of Genitourinary Diseases*. New York: Thieme-Stratton, 1982.)

b. Excretory urography. Excretory urography is less specific for processes occurring primarily in the perirenal space. It is performed primarily to exclude intrarenal disease. Loss of renal outline, displacement of kidney, and decreased mobility of the kidney suggest a perinephric process.

c. Computerized tomography. Computerized tomography is excellent for evaluation of the perirenal spaces and can be used for guidance of diagnostic aspiration. It is, however, more expensive than ultrasonography. The radiation exposure is also a consideration.

d. Ultrasound. This study provides better evaluation of the perirenal spaces for determination of abnormal fluid collections and the characteristics of these collections (Fig. 14-20).

e. ^{67}Gallium scanning. This study is used primarily for generalized localization of an inflammatory process. It can be of particular help when other studies fail to localize a suspected source of inflammation. It does however take considerable time and, with the availability of computerized tomography, is rarely used.

H. Evaluation of renal hypertension

1. Criteria for patient selection. Renal hypertension is defined as an anatomic renal abnormality that causes hypertension. The abnormality may be renal artery stenosis, renal parenchymal disease, renal masses, renin-secreting tumors, or other vascular abnormalities. The most important of these are lesions of the main renal artery (renovascular hypertension). Development of effective antihypertensive medication has made mass screening of all hypertensive patients for renovascular lesions no longer necessary. Patient selection for evaluation is made using the following criteria:

a. Acceptable surgical risk

b. Age less than 55 years

Fig. 14-20. Transverse ultrasound examination performed in the prone position shows a large fluid collection *(arrow 1)* with internal echoes adjacent to the left kidney *(arrow 2)*. This represented a left perinephric abscess confirmed surgically. The right kidney *(arrow 3)* was normal.

c. **Sudden onset or acute exacerbation of hypertension**
d. **Abdominal or flank bruit** on examination.

2. **Screening procedures**
   a. **Saralasin screening test.** Saralasin (1-sar-8-ala angiotensin II), an angiotensin-blocking agent, has been used as a screening test for renovascular hypertension. An infusion or bolus injection of saralasin followed by a blood pressure decrease of greater than 10/8 mm Hg has been used for selection of patients for urography and arteriography. The results, however, have been variable, and the test has not become widely used.
   b. **Excretory urography.** The excretory urogram demonstrates anatomic diseases of the renal parenchyma or collecting system and may detect adrenal masses. Hypertensive patients are studied with the rapid-sequence excretory urogram with films at 1, 2, 3, and 5 minutes after injection of contrast media. Ischemia secondary to renal artery stenosis is suggested by the following findings:
      (1) **Disparity in renal length** (>2 cm difference)
      (2) **Difference in time of opacification of the collecting structures**
      (3) **Delayed hyperconcentration of contrast media in the collecting system of the affected kidney**
      (4) **Ureteral notching due to collateral arterial supply**
   c. **Digital subtraction angiography.** Digital subtraction angiography, using an intravenous contrast bolus for imaging of arterial structures, is considered by many to be the procedure of choice in screening for renovascular hypertension. The procedure can be performed on an outpatient basis and is usually followed with a conventional excretory urogram to evaluate for structural abnormalities and tumors.
   d. **Radionuclide studies.** Renograms and scintiphotos obtained with either orthoiodohippurate (^{131}I Hippuran) or ^{99m}Tc-DTPA are also used as preliminary studies to evaluate renal blood flow. These are currently used infrequently at our institution.
   e. **Renal angiography.** Selective renal arteriography provides the definitive diagnosis of renal arterial lesions. Atherosclerosis that involves the main renal artery at or near its origin is most common in the older population. Fibromuscular hypertrophy is the most common cause of renovascular hypertension in patients under 40 years of age and occurs more peripherally. Arteriography can also additionally define renal parenchymal disease, renal masses, renin-secreting tumors, and other forms of vascular disease.
   f. **Renal vein renin assay.** Renal vein renin assay provides a measurement of the causal relation of renovascular lesions and hypertension. Both renal veins and the inferior vena cava below the renal veins are sampled. Segmental renal vein sampling is indicated if localized arterial or parenchymal abnormalities are present. Renal vein renin ratios of 1.5 : 1.0 are the upper limits of normal; a ratio of 2 : 1 is diagnostic of severe renovascular pathology. Suppression of renal vein renin in the contralateral kidney (i.e., a value comparable to the vena cava renin) is predictive of a good surgical outcome, as is an elevated peripheral plasma renin activity.

Suggested Reading

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Index