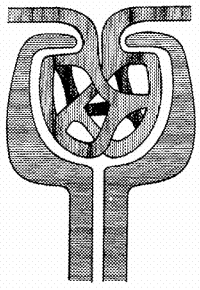
MANUAL OF CLINICAL NEPHROLOGY



ROGOSIN KIDNEY CENTER

DEVELOPMENTS IN NEPHROLOGY

VOLUME 1

MANUAL OF CLINICAL NEPHROLOGY

of the Rogosin Kidney Center

edited by

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PREFACE

Over the past two decades remarkable progress has been made in the understanding and treatment of kidney disease. The solid foundations of renal physiology have been added to by further understanding of the pathophysiology brought about by renal biopsy and improved pathologic techniques. At the same time, recent advances in the treatment of renal disease with dialysis and renal transplantation have led to further immunologic and biochemical approaches to our understanding of the disease process. Clearly the understanding, treatment, and investigation of renal disease involves many disciplines. To this end, the Rogosin Kidney Center was organized as a categorical disease center devoted to the care of patients with kidney disease. The core of the Kidney Center is the Nephrology Division of the Department of Medicine. There are also major and vital inputs from Departments of Surgery, Pediatrics, Psychiatry, Radiology, and Obstetrics and Gynecology; and the Basic Science Departments of Biochemistry, Immunology, Pharmacology, Pathology, and Physiology are actively involved in basic research. The Kidney Center has its own nursing staff, social workers, dieticians, and technical staff. It serves as the hub of a major network with over 40 hospitals referring patients for consultation, dialysis, and transplantation.

The major purpose of this book is to establish an approach to kidney disease from a major center that has interdisciplinary teams working closely together. The information contained herein is a result of over 20 years' experience with contributions from many who have participated in the activities of the Kidney Center. This experience provides the basis for the judgements and principles that we use to treat patients with renal disease. As more and more tertiary care centers develop, it becomes increasingly important for those participating in these activities to clearly define the principles they follow in diagnosis and treatment. We trust that these principles will be useful to the student and house-officer as well as to the practicing physicians and other individuals engaged in the care of patients with renal disease.

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1. EVALUATION OF PATIENTS WITH RENAL DISEASE

KENYON B. FIELD

1. INTRODUCTION

The physician should maintain two important perspectives when confronted with a patient with renal disease. One is the physician's perspective of disease. He should understand the limitations of the diagnostic process and be alert to discover new information that will provide further insights into the pathogenesis of renal disease. Second, he should be able to understand the patient's perspective of his disease. This perspective is critical if the physician is to be sensitive to the fears and insecurities that the disease process elicits in a particular individual. It is also important to understand when active intervention in the disease process improves a patient's condition and when such intervention results in iatrogenic disease.

Table 1 is a list of currently recognized syndromes of renal disease. Two features of this list deserve comment. First, although the list is short, the list of etiologies for each of these syndromes is lengthy. Thus, the kidney has a limited number of ways of expressing disease due to a wide variety of insults. Second, these syndromes are not distinct categories, but blend into each other. The syndromes used to describe renal events are in some instances different ways of describing the same disease. Thus, a patient with an acute nephritic syndrome might also

Table 1. Syndromes of renal disease

Acute renal failure
Chronic renal failure
Acute nephritic syndrome
Nephrotic syndrome
Urinary tract infection and pyelonephritis
Obstructive nephropathy
Nephrolithiasis
Accelerated hypertension

Table 2. Levels of description in renal disease.

1. Etiology (infectious, toxic, metabolic, others)
2. Pathogenesis (immune, non-immune, others)
3. Histopathologic description (glomerular, interstitial, vascular)
4. Biologic and biochemical features (creatinine, BUN, electrolytes, others)
5. Clinical syndromes
6. Stage of evolution
7. Behavior in time (acute or chronic)
8. Therapeutic phase (no treatment, symptomatic treatment, steroids, dialysis, transplantation, others)

have acute renal failure. Renal disease may be studied and described from many different yet equally valid viewpoints, as shown in Table 2.

2. IDENTIFYING RENAL DISEASE

2.1. History

The most important part of the data base is the medical history. It is here that the physician sets the pattern of his continuing relationship with the patient. In this present age of concern over costs and complications of procedures, a carefully conducted history can be of great value. Many times, expensive and invasive procedures can be avoided by simply asking the right questions.

2.1.1. Urinary symptoms

Patients should be questioned about the volume (increased or decreased), pattern, color and odor of the urine and the presence of pain on urination. Many renal diseases are silent and do not result in gross changes in the urine or in urination. Thus, questions about urine are often unrevealing even in the presence of severe renal disease. In addition, the changes in urine volume or pattern of urination occur so gradually that they often go unnoticed by the patient. Careful questioning, however, may often reveal the change.

2.1.1.1. Change in volume. Urine volumes normally are between 1500-2000 ml/day depending on fluid intake. If there is any doubt about urine output, it should be measured over a 24-hour period. Many renal diseases are identified by the way in which they alter urine volume.

Urine output less than 400-500 ml/24 h is termed oliguria; urine output less than 50 ml/24 h, or no output at all, is called anuria. The differential diagnosis of decreased urine output includes prerenal, renal and postrenal causes, and these are discussed in the chapter on acute renal failure (Chapter 10).

An increase in urine excretion above what would be expected in a normal individual is termed polyuria. Generally, this means a urine output greater than 2000 ml/24 h. Polyuria may be secondary to a number of factors including excessive fluid intake, osmotic diuresis or defective renal concentrating ability. These are discussed in the chapter on disorders of water and electrolyte balance (Chapter 2).

2.1.1.2. Pattern. Pattern of urination means the frequency, time and characteristics of urination. Patients do not usually mention changes in their urinary pattern and must be asked specifically about them. Increased urgency or frequency may suggest inflammation of the urinary tract, usually indicating lower urinary tract infection. Increased frequency of urination is also seen in stone disease due to irritation of the mucosa of the lower urinary tract.

Normally, urinary output during the day exceeds the night output. This diurnal variation in urine output is such that individuals with normal renal function should not have to void during the night. Nightly urination on nocturia, usually indicates inflammatory disease of the lower urinary tract or signs of chronic renal failure.

Another variation in urinary pattern, alternating periods of polyuria with low or normal output, is seen in obstructive disorders. Elderly males with urethral narrowing from prostate disease may notice hesitancy or urination, as well as decreased size and force of the urinary stream. Nocturia and polyuria may also result from obstructive nephropathy such as prostatic hypertrophy.

2.1.1.3. Color and appearance. Normally, urine is clear and the color varies from pale yellow to amber, depending on its degree of concentration. Quantitative or qualitative changes in chemical substances and cellular elements in urine may produce changes in the urine's color and appearance. The clinical significance of these changes are described in the section on urinalysis and in Table 4.

2.1.1.4. Pain. Pain associated with the kidneys or urinary tract is usually described as burning or an irritating sensation on voiding or as abdominal or back pain. Urinary tract infections frequently are present

with burning on voiding and back pain. Not all patients describe burning and some notice only frequency or urgency. Back pain is a frequent accompaniment of renal disease and occurs in pyelonephritis, urinary tract infection, acute and chronic renal failure, renal tumors, and nephrolithiasis. It is particularly important to realize that many such patients often consult an orthopedist or neurosurgeon before coming to the attention of an internist or nephrologist. This pain is often described as a dull constant ache or a "tired sensation" in the back and may be difficult to differentiate from low back pain of musculoskeletal origin on history alone.

2.1.1.5. Odor. Malodorous urine is seen with urinary tract infection due to E. Coli or similar enterococcal species and is also seen when a specimen has been standing too long and is unsuitable for examination. Characteristic urine odors may be noted after eating asparagus, in maple syrup urine disease, and phenoylketonuria (mousy odor). A sweet fruity odor is often noted in patients in diabetic ketoacidosis.

2.1.2. Systemic symptoms

Renal disease often leads to symptoms referable to other organ systems or to nonspecific symptoms such as fever, generalized weakness, muscle cramps, back pain, headache or rash. The list of such symptoms is vast and the only way to discover subtle manifestations of renal disease by history is to be aware that renal disease usually presents extrarenally.

2.1.3. Water balance

Water balance is usually disturbed in patients with renal disease. Large changes in water balance that result in dehydration or anasarca are readily identified. Smaller changes, resulting in water deficits or excesses of 5-10% of body weight, are not as easily discovered. Historical information can be helpful in assessing water balance, particularly if no accurate serial weights are available. Patients should be questioned about weight gain or loss, frequency and volume of urination, diarrhea or vomiting, excessive sweating or fluid intake.

2.2. Family history

Inquiry into the family history is particularly important in evaluating renal disease. Many renal diseases are recognized as being clearly familial while in others the pathogenesis is less well understood. The list of currently recognized heritable disorders of the kidney is long and com-

Table 3. Renal disease caused by single mutant genes.

	Transmission Pattern
Diffuse Nephropathy	
Hereditary nephritis including Alport's syndrome	Dominant
Hereditary nephritis in Allstrom's syndrome	Recessive
Renal dysplasia with retinal aplasia	Recessive
Fabry's disease	X-linked recessive
Congenital nephrotic syndrome	Recessive
Polycystic kidney disease	
Adult type	Dominant
Infantile type	Recessive
Medullary cystic disease	Dominant
Nephronophthisis, juvenile, familial	Recessive
Nail-patella syndrome	Dominant
Renal Tubular Dysfunction	
Proximal Tubular Dysfunction	
Cystinuria	Recessive
Cystinosis	Recessive
Fanconi's syndrome	Recessive
Oculo-cerebro-renal (Lowe's syndrome)	X-linked recessive
Hypophasphatemic vitamin D resistant rickets	X-linked dominant
Renal glucosuria	Recessive
Distal Tubular Dysfunction	
Renal tubular acidosis	Dominant and sporadic
Nephrogenic diabetes insipidus	X-linked recessive
Bartter's syndrome	Recessive

plex (Table 3). Evaluation of the hereditary pattern of the disease is not only important for an accurate diagnosis of the disease among symptomatic and asymptomatic patients in the family, but also for the prevention of the disease by genetic counseling.

2.3. Physical examination

Physical examination provides important diagnostic information. All patient complaints, no matter how small or seemingly insignificant, should be thoroughly investigated. The following points are particularly important in patients with renal disease.

The most important and sensitive indication of a disorder in water balance is a change in body weight. All patients with renal disease should be weighed daily, at the same time and on the same scale. The value of having a reliable weight is unfortunately often appreciated only

in retrospect. Daily assessment of other signs of the state of hydration should also be made. Early signs of water loss may be detected by evaluating skin turgor and noting the moistness of mucous membranes.

The usual maneuvers in physical examination apply to the renal patient. Special attention should be paid to signs that relate to the type and severity of renal disease. In addition to water balance, these would include hypertension, eye ground changes, skin changes, neurologic disorders, muscoloskeletal disorders, anemia, cardiac arrhythmias or pericarditis or signs of systemic disease. In examination of dialysis patients, careful examination of the fistula for heat, tenderness or induration is important since this is often a portal entry for infection. In transplant patients, the graft should be examined for tenderness or increase in size which might suggest rejection. A bruit can often be heard over the graft and this correlates with good graft function or occasionally with vascular stenosis. In both dialysis and transplant patients, as well as patients with renal insufficiency, pulmonary infections are common and the lungs should be examined frequently.

2.4. Urinalysis

There are few clinical tests which are at once as simple, powerful and cost-effective as the urinalysis. It is useful in screening, diagnosis and follow-up. Urinalysis, as performed in most hospitals or in the physician's office, is a group of qualitative tests including evaluation of pH, glucose, ketones, hemoglobin, protein, and microscopic examination for formed elements. Tests for bilirubin and urobilinogen are sometimes included and recently a nitrate reduction test for bacteriuria has been made available.

Most of these chemical tests are readily available on a 'dipstick' which is dipped into fresh urine and read by comparing the color changes with the standards on the bottle. Evaluation of the renal concentration mechanism is usually approximated by measuring specific gravity although the measurement of osmolality is becoming more available and provides more specific information. Microscopy is performed to identify cells, casts, crystals or bacteria. In some hospitals, many of these tests are now mechanized.

A large amount of clinical information is available from the urinalysis. However, because of poor performance of the procedure and unreliable results, many physicians ignore or do not utilize fully the results of urinalysis. A properly performed urinalysis can give crucial informa-

tion about the kidneys in less time and at less expense than any other procedure. It is indeed a 'liquid biopsy' of the kidney. Limitations include a high incidence of false positive and false negative reactions, lack of generally accepted standards and performer bias. Improper collection and delay in examining urine are common sources of poor results. Urine should be 'clean catch' and should be examined within one hour of collection. Delay in processing causes not only lysis of cells but also the opportunity for bacterial growth.

2.4.1. Visual inspection

Much information can be gained by simply looking at freshly voided urine in the light. Normal urine has a clear amber-yellow appearance due primarily to the urochrome pigments. High fluid intake results in a colorless, dilute urine while fluid restriction results in a more concentrated, yellower urine. Thus, the yellowness of urine roughly correlates with the degree of concentration but this should be checked as there are exceptions.

Table 4. Urinary Rainbow.

Appearance	Causes
Colorless	Dilute urine, polyuria, diabetes insipidus
Cloudy	Bacteriuria, leukocyturia, phosphates, urates, contrast media, calculi
Milky	Lipiduria (nephrotic syndrome), chyluria (lymphatic obstruction)
Yellow	Nitrofurantoin
Amber	Concentrated urine (dehydration), bilirubin, phenazopyridine
Red	Hemoglobin, red blood cells, myoglobin, porphyrin, aniline dye, beets, menstrual contamination
Red-pink	Phenolphthalein (laxatives), rhubarb, cascara
Red-brown	Red blood cells, hemoglobin on standing
Brown-black	Methemoglobin, homogentisic acid (Alkaptonuria), methyldopa
Blue-green	Methylene blue, pseudomonas infection (blue pus)
Dark brown	Levodopa (high doses)

Table 4 describes the appearance of urine in abnormal states. Cloudy urine is most often normal and due to phosphate precipitation in alkaline urine. Urates cause a white or pink cloud in acid urine. Bacterial growth causes an unpleasant odor in addition to the cloudiness. Turbidity or smokiness may be due to red blood cells, spermatozoa, prostatic fluid, mucin or chyle. Turbidity due solely to chyle can be extracted with ether. Red urine is the most common color abnormality noted.

The term is loosely applied to urine of shades from pink to brown and black. Benign causes include menstrual contamination in the female and beet ingestion in some individuals. A convenient approach is to separate red urine into heme positive and heme negative groups by dipstick. If heme positive, there are three clinical possibilities: hematuria (RBC's), hemoglobinuria (elevated plasma hemoglobin) and myoglobinuria (from skeletal muscle damage). Heme negative red urine may be caused by drug ingestion, beets, acute porphyria or other diseases producing red pigments. If red cells are present in large numbers, they may arise anywhere from the glomeruli to the urethral meatus. Heme positive urine with few or no RBC's contains hemoglobin or myoglobin. These may be distinguished by the fact that myoglobin is associated with clear plasma while hemoglobin colors plasma red.

2.4.2. pH

The kidney's ability to maintain normal hydrogen ion concentration in plasma and extracellular fluid is reflected in the urine pH. Nonvolatile acids such as sulfuric, phosphoric and hydrochloric acids as well as small amounts of pyruvic, lactic and citric acids and some ketone bodies are byproducts of metabolism which cannot be removed by the lungs. These acids reach the distal tubule along with sodium where hydrogen ions are exchanged for sodium and the urine becomes acid. Normal urine pH is about 6 with a range from pH 4.6-8. Normally, the diet is responsible for most swings in urine pH. When protein intake is high, more phosphates and sulfates are produced and this results in a more acid urine. In many non-Western countries where a vegetarian diet is usual, the urine pH is more alkaline.

Acid urine is produced by diets high in protein or cranberries, or by metabolic acidosis and potassium depletion. Alkaline urine is produced by vegetarian diets, citrus fruits, metabolic alkalosis, respiratory alkalosis and renal tubular acidosis. Alkalinization of urine by sodium bicarbonate, potassium citrate or acetazolamide, may be used to aid dissolution of renal calculi (uric acid stones) and in the treatment of salicylate or other drug poisoning. Excretion of amphetamine, morphine and procaine is greater in acid urine, while barbiturates, phenylbutazone, salicylic acid and sulfonamides have greater clearance in alkaline urine.

2.4.3. Osmolality and specific gravity

The concentrating mechanism of the kidney is most frequently tested by measuring osmolality or specific gravity. The kidney maintains homeostasis of body fluid and electrolytes by varying the volume of urine

excreted and the solute concentration. The renal countercurrent mechanism enables the kidney to excrete urine more concentrated than the plasma from which it is derived. The solute concentration of urine varies with water and solute ingestions, the state of the tubular cells and the influence of antidiuretic hormone (ADH) on water reabsorption in the distal tubules and collecting ducts. Concentrating or diluting defects indicate renal disease or hormonal imbalance as detailed in Chapter 2 (disorders of water and electrolyte balance) and Chapter 10 (Acute Renal Failure).

Urine osmolality is a function of volume and solute concentration of urine. Osmolality depends entirely on the number of particles in solution. The normal adult on a normal diet and with normal fluid intake will produce urine of about 500-800 m Osm/kg. The normal kidney can decrease urine osmolality to as low as 40 m Osm/kg during water diuresis and increase urine osmolality to as high as 1400 m Osm/kg during dehydration. After a period of fluid restriction, the kidney should be able to produce urine three to four times as concentrated as plasma. Thus, after 24 hours of fluid restriction, a urine osmolality greater than 900 m Osm/kg indicates a normal renal concentrating mechanism. Urine osmolality is generally measured by an osmometer and is a sensitive measure of overall renal function. It often becomes abnormal before the serum creatinine rises.

Because of the ease of measurement and its linear relation to osmolality over a wide range of urine tonicity, specific gravity is usually substituted for measurement of osmolality. Normal adults with normal diets and normal fluid intake produce a urine specific gravity of 1.016-1.022. A random specimen with a specific gravity greater than 1.026 indicates normal renal concentrating ability. Urine specific gravity after 12 hours of fluid restriction should be 1.022 and after 24 hours 1.026. Specific gravity depends upon the density of the various solute molecules in a solution. It is measured by a urinometer (hydrometer) which should be standardized daily in distilled water and corrections made if the reading varies from 1.000. Attention to detail is important in using the urinometer. Make certain it is floating freely and always read the bottom of the meniscus. Measurement of specific gravity is affected by many variables. Urine should be allowed to come to room temperature before a reading is made. Glucose or protein in urine may falsely elevate values and 0.001 should be subtracted for every 2.7 gm of glucose or 3.9 gm of protein per 1000 ml of urine. A high specific gravity in pale urine should suggest the presence of glucose. Radiographic contrast media will also falsely elevate specific gravity.

2.4.4. Proteinuria

Protein in the urine is a major clinical finding pointing to kidney disease. Both the amount of protein and the pattern of excretion can be of diagnostic value. The first sign of proteinuria usually is discovered by 'dipstick' testing. While the simplicity and ease of performance make this an ideal screening test, any abnormality should be investigated further by quantitative measurement of 24 hour protein excretion. The dipstick is a specific indicator of urinary albumin and is not sensitive to globulin (hemoglobin, myoglobin, Bence-Jones protein). Many nephrologists prefer to test urine with a few drops of 20% sulfosalicylic acid. However, there is little reason to prefer this test over the dipstick test, unless the presence of abnormal protein such a Bence-Jones protein is suspected. In patients who have high urine volumes, these qualitative assays may be normal.

Normal 24-hour protein excretion is between 100-150 mg/day. Small increases in proteinuria (less than 0.5 g/24 h) may be seen with febrile states, exercise and in patients with heart failure in the absence of renal disease. The presence of protein in the urine protein points to some abnormality in the glomerular wall. We now understand that the determinants of filtration of macromolecules across glomerular capillaries include not only molecular size but also molecular charge and renal hemodynamics. Proteinuria may be minimal or absent in urinary tract obstruction, renal tumors, cystic kidney diseases, pyelonephritis and hypokalemic and hypercalcemic nephropathies. Only slight amounts of protein (less than 0.5 g/day) are seen in polycystic kidney disease, tubulo-interstitial nephritis, and nephrosclerosis. Very heavy proteinuria (greater than 3 g/day) is an essential diagnostic criteria of nephrotic syndrome. The clinical significance of proteinuria is described in detail in Chapter 4 (Glomerulonephropathies).

Protein excretion may be continuous, intermittent or postural. A group of patients with abnormal protein excretion in the upright position (orthostatic proteinuria) have been followed longitudinally without progression to renal failure.

2.4.5. Urinary sediment

Examination of the urinary sediment can be most helpful in arriving at a diagnosis. It is important that the physician cultivate the habit of performing urinalyses by him or herself and knows what to look for in the sediment, otherwise it will not be seen. Equally important is attention to detail in preparation of the specimen for microscopy. Urine should of course be fresh. It is valuable to examine one drop of unspun

urine with condensor lowered, for bacteria. Any bacteria seen correlate with a significant bacteriuria (greater than 10^5 bacteria/ml of urine on quantitative culture) and urinary tract infection. The sediment should be prepared by centrifuging 15 ml of urine at 1500 RPM for 5 minutes. The tube is inverted to dispose of the supernatant and the remaining small 'button' is resuspended in the residual urine by tapping the tube sharply. A small amount is pippetted onto a glass slide, covered with a cover slip and then examined with the high dry (44 ×) objective under low light.

2.4.5.1. Cellular elements. Red blood cells may appear either grossly or only on microscopic examination. In either case, the most common causes of hematuria are urologic and include urinary tract infection, tumor, prostatitis, renal stones, obstruction and urethritis. Benign causes include menstrual contamination, fever and exercise. Renal causes of hematuria are discussed in the chapter on Glomerulonephropathies. The mechanism by which red blood cells enter the urine is not known. Normally, the daily urinary excretion of red blood cells is less than 1.5 million. Red blood cells are not seen on microscopic examination unless the daily total excretion exceeds three times this amount, the equivalent of a cubic millimeter of blood lost in the urine. Qualitative microscopic examination should show only an occasional red blood cell per high power field. Any more than this in several fields should be considered as microscopic hematuria. Hematuria of glomerular origin has distinct characteristics. It is never associated with blood clots and, microscopically, it gives rise to a wide range of morphological alterations in red cells. In contrast, hematuria of nonglomerular origin (renal tumors, trauma) or from the urinary tract, is often associated with clots, usually red rather than brown or black, and, microscopically, morphology of red cells is usually normal with some 'ghost' cells. The observation of red-cell casts confirms a renal origin, specifically glomerular origin, of hematuria.

White blood cells in the urine are most commonly a result of specimen contamination. The physician must ensure that the urine was collected by the mid-stream clear-catch technique and that strict attention was paid to cleaning of the external meatus. In females particularly, there should be no vaginal epithelial cells seen. After contamination, the most common cause of pyuria is urinary tract infection. This cause is evaluated best by examining a drop of unspun urine for bacteria. Careful attention must be paid to focusing of the microscope for it is easy to overlook bacteria. Normal urine may have as many as five white

cells per high power field. More than ten white cells per high power field should suggest pyuria. Causes of culture negative pyuria include tubulo-interstitial nephritis, pelvic inflammatory disease, malignancy and genito-urinary tract tuberculosis. The presence of proteinuria, glitter cells (leukocytes with refractile granules which show brownian movement), or the presence of white cell casts may help differentiate actual renal infection (pyelonephritis) from lower urinary tract infection.

Renal tubular epithelial cells are about the same size as a leukocyte and have a large round nucleus. They are seen in acute renal failure. Epithelial cells that undergo fatty degeneration are termed oval fat bodies and are found in the nephrotic syndrome.

Other cells that are diagnostically helpful may be seen in urine. Nuclear inclusions may be found in patients with cytomegalovirus infection. Small lymphocytes may be seen during renal transplant rejection as well as red and white cells. Rarely, tumor cells may be found. The presence of renal papillary tissue indicates papillary necrosis.

2.4.5.2. Casts. Casts are agglutinated masses of cellular or noncellular elements in a matrix of Tamm-Horsfall protein. The presence of cellular casts in increased numbers in urine establishes the existence of renal disease rather than lower urinary tract disease, since they are formed in the nephron. Most casts arise in the distal tubules or upper portions of the collecting ducts. Casts formed in the distal collecting ducts indicate urinary stasis and are wider than most other casts. These are termed broad or renal failure casts, as they are usually seen in chronic renal diseases but also in the recovery phase of acute tubular necrosis.

Hyaline casts are frequently long, have a ground glass appearance and may have cellular or lipid inclusions. They are seen in proteinuric states as well as after exercise and dehydration. Granular casts are seen with exercise, dehydration, fever and cardiac failure.

Leukocyte casts are distinguished from leukocyte clumps by the presence of a border. They are seen with tubulo-interstitial nephritis but may also be seen in acute glomerular diseases. Red blood cell casts are recognized by their characteristic reddish brown color. They are usually found in patients with glomerular disease. Thus, the presence in the urine establishes a renal origin for hematuria.

2.4.5.3. Crystals. Crystals do not carry the diagnostic significance nor prognostic implications of casts. Under ordinary circumstances the positive identification of crystals is not necessary, except in patients with renal stone disease. Cystine crystals are distinctive and should be

sought in patients with unexplained renal function as well as in renal stone disease. Identification of urinary crystals is essential for pathophysiologic evaluation of patients with renal stones. Cystine crystals appear hexagonal, uric acid crystals tetrahedral, triple phosphate crystals have a coffin lid appearance and calcium phosphate crystals are needle shaped.

2.5. The chemical data base

A chemical data base in patients with renal disease may be established by measuring serum sodium, potassium, chloride, CO_2 content, calcium, phosphorus, urea and creatinine clearance.

In most instances, a rapid and reasonably (although not totally) reliable chemical evaluation of renal function may be obtained with a serum creatinine determination (normal values; 0.6-1.5 mg/100 ml or 60-130 μmol/l). Both creatinine production, as determined by the breakdown and metabolism of muscle creatine and the excretion rate of creatine over a wide range of renal function, remain relatively constant (15-25 mg/kg of body weight/day or 0.13-0.22 mmol/kg/day). The increase in creatinine production during the first two decades of life, is accompanied by increased excretion, such that clearance remains unchanged when corrected for body surface area. Similarly, muscular individuals tend to have higher serum creatinines than asthenic ones. As the kidney ages, i.e., beyond the fourth decade of life, its ability to excrete creatinine decreases, clearance falls, but serum creatinine remains unchanged, because muscle mass, and thus endogenous production, decreases. Although a small fraction of urinary creatinine is derived from tubular secretion, creatinine clearance closely correlates with glomerular filtration rate over a wide range of renal function (normal values; 150-180 l/day or 100-125 ml/min per 1.73 m^2 of body surface area).

Blood urea nitrogen (BUN) as well as the urea nitrogen excretion rate (urea clearance) have also been used to assess renal function. Since many non-renal factors influence both the production and renal excretion of urea, it not only less accurately reflects overall renal function but also requires great caution in interpretation. Non-renal factors that may increase BUN include a high protein intake, hypercatabolic states and drugs causing hypercatabolism (corticosteroids, tetracycline), hypovolemia and states associated with renal hypoperfusion (shock and congestive heart failure). Non-renal factors, including protein malnutrition and hepatic dysfunction, may decrease BUN by decreasing urea synthesis.

The renal excretion rate of urea depends on its glomerular filtration and tubular reabsorption. Factors that reduce tubular flow rate, such as hypovolemia, hypotension and congestive heart failure, increase tubular reabsorption and consequently BUN.

In renal diseases, as the glomerular filtration rate decreases, BUN increases proportionally to serum creatinine with an approximately 10-20 : 1 ratio. The BUN : serum creatinine ratio may exceed 20 : 1 when other factors that increase either production or renal tubular reabsorption of urea are superimposed. Similarly, the ratio may be less than 10 : 1 in states accompanied by overhydration (i.e., syndrome of inappropriate ADH secretion).

The significance of the other chemical values mentioned at the beginning of this section are described later in appropriate chapters.

2.6 Radiologic techniques

2.6.1. General comments

Radiologic evaluation plays an important role in the diagnosis and management of patients with renal disease. Renal diagnosis and treatment has benefitted from the rapid advances in diagnostic and therapeutic radiology in the past decade. Techniques such as nephrosonography, computerized tomography and renal scans, have increased our ability to diagnose renal disorders by non-invasive techniques. In addition, the growth of therapeutic radiologic techniques, such as embolization and renal artery balloon dilatation, have moved radiology into the therapeutic arena as well. The rapid growth and complexity of these radiologic techniques has increased more than ever the need for better communication between the nephrologist and radiologist. Frequently, rather than simply ordering a study, the physician might better confer with the radiologist about what he is looking for. In that way, the radiologist might better understand how to approach the problem and can individualize the study. Good communication between physician and radiologist will lead to a better study.

The patient should always be informed about why a particular study is being done and what the risks are of the procedure. This should be done by the patient's physician and not only by the radiologist. Patients will be more cooperative and tolerant when they are convinced a procedure is important for them.

That renal size correlates with renal disease, is a major concept utilized in radiology. The excretory urogram, nephrosonogram, com-

Table 5. Renal diseases associated with abnormal kidney size.

Small Kidneys:

- Chronic parenchymal kidney diseases;
  - Chronic glomerulonephritis
  - Chronic tubulo-interstitial nephritis
  - Hypertensive nephropathy (arterionephrosclerosis)
  - Hereditary nephritis
  - Chronic transplant rejection
  - Cortical necrosis (chronic)
  - Diabetic nephropathy (end-stage)
  - Radiation nephropathy (chronic)
- Renovascular diseases;
  - Renal artery stenosis
  - Renal vein obstruction (chronic)
- Collagen vascular diseases;
  - Systemic lupus erythematosus (end-stage)
  - Polyarteritis nodosa (end-stage)
  - Scleroderma kidney (end-stage)
- Cystic disease;
  - Medullary cystic disease
- Obstructive nephropathy with back pressure atrophy;

Normal to Large Kidneys:

- Acute parenchymal kidney disease;
  - Acute glomerulonephritis
  - Lipoid nephrosis
  - Acute tubular or cortical necrosis
  - Toxic nephropathy
  - Acute tubulo-interstitial nephritis
  - Collagen vascular diseases and vasculitis
  - Acute transplant rejection
- Chronic parenchymal kidney diseases;
  - Amyloidosis
  - Diabetic nephropathy
  - Xanthogranulomatous pyelonephritis
- Renovascular disease;
  - Acute renal vien thrombosis
- Cystic disease;
  - Polycystic kidney disease
  - Simple renal cysts
- Obstructive uropathy;
- Kidney disease secondary to neoplasms;
  - Primary and metastatic kidney tumors
  - Myeloma kidney
  - Lymphoma

puted tomography and scanning techniques, all give information concerning renal size. The simplest approach to assessing renal size is to begin with a plain film of the abdomen or perhaps the nephrosonogram. The plain film may be performed as an isolated study or prior to a more detailed study. From it, one can get information about the size and position of the kidneys and any affect they may have on adjacent viscera, e.g., stomach, liver, spleen and colon. Calcifications can also be evaluated and their relation to the kidney determined by oblique, lateral or tomographic views.

Average values for renal size in the adult are 12-13 cm or $3\frac{1}{2}$ times the height of a lumbar vertebrae. The left kidney is usually slightly larger than the right and position may vary considerably. These values are not absolute and renal size must be interpreted on an individual basis. In particular, the kidneys should be symmetrical in shape, size and thickness, and these facts may be of greater value than absolute size.

Table 5 gives a list of disorders associated with small kidneys and normal or large kidneys.

Some diseases such as cysts and tumors may cause only a localized increase in size.

2.6.2. Plain film

The importance of the plain film for kidney evaluation can not be overemphasized. It should be taken as a preliminary film before the introduction of a contrast medium for the examination of the kidney or other abdominal structures.

For silent urinary calculi, if no preliminary roentgenogram had been made, stones could be missed as the opaque medium obscures them completely. In contrast, areas of increased density in the region of the calyces or where the ureter is kinked on itself may be interpreted erroneously as calculi. Thus, it is important that the plain film be made before the urogram. Since 90% of renal stones are calcified, most of the stone diseases are recognized simply on plain film. Therefore, whenever renal colic is suspected, taking a plain film should be the first diagnostic step.

Besides stone problems, determination of renal size and shape, which is usually provided on plain film, is important in approaching and managing the patient. As an ancillary finding, the plain film gives us valuable information about skeletal and soft tissue structures, which sometimes are also an important clue for evaluating renal disease.

2.6.3. Intravenous pyelography (IVP)

The IVP is the standard renal imaging technique against which all other radiologic studies must be judged. The primacy of the IVP in evaluating the kidney has been challenged in recent years by the sonogram, radionuclide scanning techniques, and computed tomogram. The fear of radio-contrast induced acute renal failure, poor quality studies, and the availability of alternative techniques have led to somewhat less dependence on the IVP, particularly in patients with renal insufficiency. Perhaps the most common cause of an inadequate study is poor patient preparation. This is often given only casual attention by the physician since most hospitals utilize a protocol. Proper attention to the patient's bowel habits and an individualized regimen will help ensure the patient arrives 'cleaned out' for the study.

The IVP should never be considered routine. Many studies have now documented the occurrence of acute renal failure secondary to radiographic contrast agents. Animal experiments have shown a direct nephrotoxic effect of these agents on tubular epithelium. Dehydration, multiple myeloma, diabetes and renal insufficiency have been implicated as risk factors for acute renal failure in patients undergoing these studies. Scheduling of radiologic contrast studies should always be spread out over several days and never be done 'back to back' as this will increase the likelihood of a toxic reaction. Renal function should be monitored routinely after these studies. If these precautions are taken, the occurrence of acute renal failure following contrast studies may be reduced.

Almost any renal disease at any level of renal function may be evaluated by the IVP. In cases of renal failure, suspected mass or in patients over 40 years old, nephrotomography should be included as part of the IVP. Nephrotomography eliminates overlying bowel gas, permits excellent definition of the renal outline, and allows delineation of renal masses. Common indications include acute abdominal or flank pain, recurrent urinary tract infections, hypertension, suspected renal masses, obstructive uropathy, as well as parenchymal kidney diseases.

All patients should be questioned about any previous contrast reactions or history of allergy to iodine. The ability of contrast media to visualize the kidney and collecting system is based on their iodine content. The iodine dose used may vary from 15-60 grams, depending on renal function. Some preparations contain large amounts of sodium and can cause volume overload in patients with renal insufficiency. Iodine accounts for the majority of reactions which can range from mild uricosuria to acute renal failure, hypertensitivity reactions and sudden death. Adverse reactions are seen in 10% of patients undergoing uro-

graphy and the incidence of death ranges from 1 in 13,500 to 1 in 40,000 patients.

2.6.4. Computed tomography (CT)

The place of this newest renal imaging procedure in the diagnostic scheme is controversial. The technique is capable of giving highly accurate information about renal anatomy, masses, carcinoma, calcifications and hydronephrosis. The technique is independent of renal function and thus may be very helpful in patients with renal insufficiency. The literature on applications of computed tomography is rapidly expanding and its definitive indications are still being defined.

The renal CT is better than the IVP in demonstrating the renal outline, however it cannot differentiate cortex from medulla. Quantitative information about radiologic density (relative radiologic absorption coefficient) is of value in differentiating various lesions around and in the kidney. Renal cell carcinoma and benign cysts can be readily differentiated by CT scanning. Small intrarenal masses, however, may be difficult to define. Contrast media is often employed to aid in differentiation of renal masses. The detection and evaluation of perirenal abnormalities by renal CT is superior to the IVP. In particular, the CT scan can visualize abnormalities in the perinephric space or adjacent areas extremely well. The IVP has often been normal in such instances, whereas the CT clearly revealed the abnormality. The renal arteries and veins can be clearly seen leaving the aorta or entering the vena cava. Thus, renal vein thrombosis or invasion of the renal vein by tumor may be diagnosed by noninvasive techniques.

It must be remembered that iodinated contrast media is often used during the CT, particularly to visualize renal masses or the collecting system. Contrast media induced acute renal failure may occur and the same precautions used to minimize contrast related complications during an IVP, also apply to CT of the kidneys.

2.6.5. Angiography

Widespread use of nephrosonography, renal scanning and computerized tomography have reduced the need for renal angiography. If, however, these techniques fail to demonstrate or unequivocally define the nature of a renal lesion, angiography may be necessary. The major uses of angiography today include preoperative assessment of renal masses, demonstration of intravenous tumor extension, preoperative donor transplant evaluation, postoperative transplant evaluation and renal vascular hypertension. Its risks are mainly related to contrast medium reaction and complications of angiographic instrumentation.

2.6.6. Nephrosonography

The last decade has seen the rapid growth of this procedure to the point where it has come to rival the intravenous pyelography as the first procedure in evaluation of renal disease. While the pyelography remains the standard for detailed radiologic examination of renal structure, the sonogram is often the preferred primary study because of its safety, ease of performance and excellent resolution. Because it does not depend on renal function for visualization of structure, the sonogram is particularly helpful in evaluating renal size, contour and architecture in patients with impaired renal function. It is increasingly the initial procedure for evaluation of suspected obstruction, acute renal failure, renal masses and renal transplant complications.

Often the selection between nephrosonography or intravenous pyelography as a first study, must be tempered by the particular skill and interest of the radiologist. The techniques are complementary and selection of the proper initial study should be individualized.

The sonogram has high reliability and sensitivity in excluding urinary obstruction as a cause of renal disease. The degree of obstruction can also be readily seen. Rarely, false positive sonograms may result from normally overdistensible or clubbed calyxes. False negative results are seen with cases of obstruction associated with retroperitoneal fibrosis, vesicoureteral reflux, diabetes insipidus or infection.

Differentiation of solid (malignant) from cystic (benign) masses was one of the earliest uses of sonography. Cysts can be resolved at a diameter of 2 cm. Limitations of the technique must be kept in mind. The acoustic transmission patterns of the sonogram may produce misleading results in cases of carcinoma with liquefaction necrosis, homogenous solid tumors or with highly vascular tumors.

Sonography has become an even more necessary procedure in the evaluation of renal failure. Many of the potential drawbacks of urography, such as contrast toxicity and dependence on function, are avoided.

Renal size, location, morphology and the presence of absence of obstruction can be quickly and noninvasively determined. Renal medullary pyramids, cortical parenchyma and arcuate arteries may be identified and form the basis for sonographic diagnosis of diffuse renal diseases. Such information may well obviate the need for renal biopsy in selected cases.

The proximity of the transplanted kidney to the body surface has made the sonogram extremely useful in evaluating post-transplant complications. Renal transplant rejection may be identified by serial sono-

graphic renal volume determinations. Collections of fluid can be readily identified. Sonographic evaluation of obstruction is complicated by the fact that most transplanted kidneys have variable degrees of pelvocaliceal dilatation due to diuresis or obstruction, may be difficult. If there has been no change in creatinine, one should be cautious in diagnosing obstruction in a renal transplants patient.

2.6.7. Renal scan

Renal scanning consists of three main procedures which may be performed together or independently.

Renal scintiangiography is accomplished by injecting the patient with 99m Tc DTPA or 99m Tc glucoheptinate while serial images are obtained of the aorta, main renal arteries and kidneys. Resolution is not as good as an arteriogram; however, serial studies over time can provide noninvasive information about the arterial supply. This technique is particularly helpful in the evolution of renal transplant.

Renal scintiscanning give a parenchymal image and some indication of morphology and functioning renal tissue.

Renography, using ^{131}I hippuran, which is secreted largely by the tubules, gives information on renal function. Renal scanning is particularly valuable in patients in whom excretory urography is contraindicated.

2.7. Percutaneous renal biopsy

A percutaneous renal biopsy provides important diagnostic and prognostic information in a number of clinical conditions. Properly selected patients undergoing kidney biopsy have a comparable morbidity rate to that from the patients undergoing a liver biopsy.

Clinical situations in which a renal biopsy may be helpful include:

1. Evaluation and follow-up of patients presenting with clinical syndromes suggesting significant glomerular, interstitial, or vascular disease.
2. Evaluation of patients with acute renal failure in which the expected resolution has failed to occur.
3. Evaluation and diagnosis of rejection and recurrent disease in renal transplant recipients.

Patients to undergo a renal biopsy should be screened with a CBC and platelet count, prothrombin time, partial thromboplastin time and urinalysis. In addition, the patient should have a type and cross match for 2 units of blood. Prior evaluation should rule out the presence of

infection and establish that two functioning kidneys are present. In addition to abnormalities in the above, contraindications to closed percutaneous biopsy include: single functioning kidney, uncontrolled hypertension, and when the patient is uncooperative.

Biopsies are performed using local anesthesia after premedication with diazepam and meperidine. Localization of the kidney may be done using either sonography or pyelogram and fluoroscopy. A complete evaluation of the specimen should include light microscopy, including a number of routine stains, immunofluorescence and electron microscopy. On occasion, special stains, such as Congo red for amyloid, may be indicated.

After biopsy the patient should be kept at strict bed rest for 24 hours, monitoring blood pressure, pulse, urine output, and gross hematuria if present. Hydration is maintained with parenteral solutions, and the resumption of a regular diet permitted. Hematocrit is checked at six hour intervals and if the patient is stable for 24 hours, ambulation is permitted and the patient is discharged after 24 hours of further observation.

The most frequent complications seen after renal biopsy include flank pain, perirenal hematoma formation and gross hematuria. Transfusion may be required is less than 1% of patients and nephrectomy in less than a tenth of a percent. Overall mortality is estimated to be less than 0.1%.

2.8. Risks and cost of procedures

In this chapter, we have described a number of ways in which renal disease is currently recognized. Most patients with renal disease have few symptoms. Physical examination may reveal signs of renal involvement, although these are often subtle. The greatest abnormalities are generally found in the laboratory evaluation. Thus, urinalysis, measurement of creatinine and BUN, electrolytes in serum and urine, radiologic assessment and biopsy are all critical in the evaluation of renal disease. In the evaluation of any patient, however, the risk and cost of procedures must be taken into account. The decision to do a renal CT or other radiographic studies should always be considered carefully and should be done only when such information cannot be readily obtained by other techniques. In particular, the risks of renal biopsy must be carefully weighed against its benefits. The crucial question that must be answered is: will the information gained by biopsy change the management of the patient in any significant way?

3. SYNDROMES OF RENAL DISEASE

This section deals with how the diagnostic procedures outlined here are used in the evaluation of selected renal syndromes. Since syndromes are defined as unique constellations of signs and symptoms, some patients are not defined well by any one of these syndromes and may have characteristics of two or even more simultaneously. Thus, while a syndrome may enable us to characterize the nature of the disease, it does not necessarily represent an absolute description of disease in any particular patient. However, classifying a disease process into a syndrome can help us to understand the disease better and leads us to more effective diagnostic and therapeutic approaches.

3.1. Acute renal failure

Acute renal failure (ARF) is a rapid decrease in renal function accompanied by oliguria and progressive azotemia over a period of hours, days or weeks. Occasionally, urine output may gradually decline and oliguria is apparent only by measuring daily urine output. Rarely, there is little or no fall in urine output (non-oliguric renal failure). Similarly, degrees of azotemia and duration of renal failure are variable depending on the cause of ARF and its reversibility.

Major causes of ARF are acute tubular necrosis (toxic nephropathy and vasomotor nephropathy), acute glomerulonephritis (post infectious nephritis, rapidly progressive glomerulonephritis, Goodpasture's syndrome), renovascular disorders (vasculitis, emboli), and acute bilateral obstruction. If decreased kidney function is secondary to pre-renal factors, such as hypotension, hypovolemia or heart failure, it is not considered ARF despite the presence of oliguria and azotemia.

Pathophysiology and diagnosis of ARF and its medical management are discussed in detail in Chapter 10 (Acute Renal Failure).

3.2. Chronic renal failure

Chronic renal failure (CRF) implies a progressive reduction in the glomerular filtration rate due to irreversible nephron loss over an extended period of time. This term has been used clinically in a comprehensive sense that includes all degrees of chronic and irreversible reduction in renal function, with varying degrees of azotemia and uremic symptoms.

To establish a diagnosis of CRF, it is essential to document the

presence of reduced glomerular filtration rate or azotemia over a period of several months. Although laboratory data are not helpful in differentiation of CRF from acute renal failure, the clinical findings such as small kidneys, renal osteodystrophy and uremic peripheral neuropathy are supportive evidence for CRF.

Pathophysiology of CRF and its medical management is discussed in detail in Chapter 11 (Chronic Renal Failure).

3.3. Acute nephritic syndrome

This syndrome is characterized by an acute onset of varying degrees of hematuria, proteinuria, azotemia and impaired salt and water excretion (circulatory congestion, hypertension and oliguria) secondary to acute glomerulitis. Since a major cause of acute nephritic syndrome is post infectious glomerulonephritis including poststreptococcal glomerulonephritis, most patients with the syndrome have a history of infection, such as pharyngitis or impetigo, one to two weeks before onset of the syndrome.

Causes, diagnosis and management of acute nephritic syndrome are discussed in detail in Chapter 4 (Glomerulonephropathies).

3.4. Nephrotic syndrome

The nephrotic syndrome is characterized by severe and sustained proteinuria (3.5 gm/24 hours for adults), associated with hypoalbuminemia, hyperlipidemia, lipiduria and generalized edema. Since most of the biochemical and physical abnormalities of nephrotic syndrome are consequences of proteinuria, these are worse as proteinuria is heavier and is sustained a longer period of time.

The presence of nephrotic syndrome usually indicates a significant glomerular involvement of primary or secondary kidney diseases. The causes, differential diagnosis and its management of nephrotic syndrome are discussed in detail in Chapter 4 (Glomerulonephropathies).

3.5. Urinary tract infection

Infection may occur anywhere from the kidney to the urethral meatus. The diagnosis of urinary tract infection is based on urine culture. Significant bacteriuria is a term used to indicate a bacterial count greater than 100,000/ml of urine and implies the presence of urinary tract

infection. This significant quantitative urine culture correlates with any bacteria seen on examination of one drop of unspun urine from a clean catch specimen.

Infection of renal parenchyma may present as acute pyelonephritis or may be entirely asymptomatic. Symptoms of acute pyelonephritis includes the sudden onset of fever, chills, flank pain and frequent burning urination. Abdominal pain is often a part of this symptom complex. Physical examination reveals exquisite tenderness over the kidney usually noted in the costovertebral angle. Urinalysis shows bacteriuria and usually pyuria. The presence of WBC casts in urine indicates renal parenchymal infection. Uncomplicated urinary tract infection does not impair renal function even when the kidney is directly involved.

The significance of bacteriuria, localization of infections and medical management of urinary tract infection are discussed in detail in Chapter 5 (Urinary Tract Infection and Pyelonephritis).

3.6. Obstructive Nephropathy

Obstruction to urinary flow can result from a number of post renal conditions (Table 6) and causes varying degrees of acute or chronic renal failure.

Clinical manifestations, pathophysiologic changes and therapeutic approaches of obstructive nephropathy vary greatly depending on many factors such as duration of obstruction (acute vs. chronic), severity (partial vs. complete), extension (unilateral vs. bilateral), level (upper vs. lower), nature of the lesion (benign vs. malignant), and origin of the lesion (intraluminal vs. extraluminal). Thus, an acute, bilateral, complete urinary tract obstruction may present clinically as an acute renal failure with back pain, but chronic, unilateral, partial obstruction may produce no symptoms or azotemia at all. Similarly, urinary output may be the anuric range, with alternative periods of oliguria and polyuria or even persistent polyuria. Thus, the possibility of obstructive nephropathy should be evaluated in every patient who presents with unexplained renal failure.

The sonogram, excretory pyelogram (IVP) and retrograde pyelogram are the essential diagnostic tests for this syndrome. The frame of diagnostic work should be designed to obtain all the factors outlined earlier.

Table 6. Causes of obstructive nephropathy

Renal:
Renal carcinoma
Renal stones
Pelvis and Ureter:
Blood clots
Trauma and surgical ligation
Stones
Tuberculosis
Congenital anomalies
Neoplasms
Retroperitoneal fibrosis or neoplasm
Pelvic inflammatory disease
Bladder:
Vesicoureteral reflux
Neurogenic bladder
Neoplasms
Stones
Congenital anomalies
Urethra:
Urethritis
Prostatic diseases (benign hypertrophy and carcinoma)
Neoplasms
Trauma
Foreign body

3.7. Renal tubular dysfunction

There are three groups of kidney diseases which tend to affect, anatomically and/or functionally, renal tubules more than glomeruli. These are cystic diseases (e.g., polycystic kidneys, medullary cystic kidneys, medullary sponge kidneys), tubulo-interstitial diseases (e.g., pyelonephritis, analgesic nephropathy, tubulo-interstitial nephritis, hypercalcemic nephropathy, urate nephropathy) and renal tubular acidosis.

Clinically, these diseases are characterized by varying degrees of impaired renal concentration capacity, electrolyte imbalance, metabolic acidosis, mild or no proteinuria, and lack of nephrotic syndrome and generalized edema. In cystic and tubulo-interstitial diseases, as the diseases progress, azotemia usually develops and may advance to uremia, but it is often mild or absent in renal tubular acidosis. Because of a urinary salt losing tendency, hypertension is rare in most of these diseases except in patients with tubulo-interstitial nephritis or polycystic kidneys. The clinical features, diagnosis and management of renal tubular acidosis, tubulo-interstitial diseases and cystic diseases are discussed

in detail in chapters 3, 6, 7 and 9 (Disorders of Acid-Base Balance, Tubulo-Interstitial Nephritis, Cystic Diseases of the Kidney, and Drug-Related Nephropathy, respectively).

3.8. Nephrolithiasis

Virtually all renal calculi are composed of one or more of the following substances; calcium oxalate, struvite (magnesium ammonium phosphate), uric acid or cystine. Calcium oxalate stones with or without calcium phosphate are the most common type of renal stones in North America, and next in descending order of frequency are struvite stones, uric acid stones and cystine stones. Diseases that are often associated with renal stones are:

Calcium stones; hyperparathyroidism, Cushing syndrome, immobilization, sarcoidosis, milk-alkali syndrome, renal tubular acidosis, medullary sponge kidney, chronic small bowel disease, hypervitaminosis D and idiopathic hypercalciuria

Struvite stones; chronic and recurrent urinary tract infection with urea-splitting organisms

Urate stones; hyperuricemia

Cystine stones; cystinuria.

Clinically, renal stones may be silent or produce varying combinations of acute or chronic obstructive nephropathy, tubulo-interstitial disease with tubular dysfunction, urinary tract infection and hematuria. The clinical significance and management of renal stones are greatly dependent on the composition, causes, size, location (upper vs. lower and unilateral vs. bilateral) and associated symptoms and signs of the renal stones. Thus, the clinical evaluation of patients with renal stones should be designed to obtain all of this information. The clinical features, diagnosis and management of renal stone disease are discussed in detail in Chapter 8 (Urolithiasis).

3.9. Accelerated hypertension

The cardinal features of accelerated hypertension are (1) severe hypertension, with diastolic blood pressure over 120 mm Hg, (2) progressive retinopathy with exudates, hemorrhages and papiledema (Keith-Wagner grade III-IV retinopathy), (3) rapidly declining kidney function with azotemia and hematuria, and (4) encephalopathy manifested by headache, convulsion, stupor and coma.

Essential hypertension and glomerulonephritis are the most common diseases causing accelerated hypertension, but chronic pyelonephritis, radiation nephritis, scleroderma, pheochromocytoma, and renovascular hypertension may cause accelerated hypertension.

Accelerated hypertension is a clinical syndrome, not a pathological entity. Pathological changes are, however, unique and characterized by widespread necrotizing vasculitis. This is especially severe in the kidneys, brain, pancreas and adrenal glands.

Accelerated hypertension is a serious medical emergency. Potential irreversible damage to the vital organs, and severe complications of uremia, intracranial hemorrhage and pulmonary edema, may occur at any time. Immediate and efficient control of blood pressure is, therefore, essential and may reverse the clinical course.

The clinical significance of hypertension and its management are discussed in detail in Chapter 12 (Renal Hypertension).

4. CONCLUSION

Renal disease may be studied at several different levels. A patient presents to his physician with a symptom. The physician must then correlate this symptom with other data from the history, physical examination and laboratory tests and attempt to make a diagnosis. The diagnosis may be based upon the patient's symptom (e.g., hematuria or renal colic), upon the pathology at the time (e.g., membranous glomerulopathy), pathogenesis, clinical syndrome (e.g., nephritic), or on the behavior of the disease over time (acute or chronic renal failure). It is evident then that diagnosis in nephrology is based upon observed correlations between different kinds of data.

A review of the history of renal nomenclature leads to an appreciation of the shifting nature of the terms used today. Nephrologic diagnosis is constantly changing as new information is uncovered, and one must be cautious in placing too much emphasis on a specific diagnosis. It must be recalled that in spite of attempts to predict the course of renal disease, the physician has only a limited number of therapeutic maneuvers available. Diagnostic terms mean little to a patients, and he is mainly looking for relief from the symptoms which brought him to the physician. The physician should never lose sight of his main task which is to lessen the impact of illness upon that individual. Thus, diagnosis should be understood for what it is: an attempt to explain a

disease process at one point in time utilizing current terminology. Diagnosis should therefore be only one step in the physician's total task in alleviating the burden of illness and should not be viewed as an end in itself.

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2. DISORDERS OF WATER, SODIUM AND POTASSIUM METABOLISM

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1. MAINTENANCE OF OSMOTIC HOMEOSTASIS

1.1. General considerations

Normal cellular function depends upon a carefully regulated osmotic environment. Plasma osmolality is normally maintained between 280 and 295 mOsm/l. Any deviation from this range stimulates a complex array of physiologic responses that tend to return plasma osmolality toward normal.

Osmolality of a solution is determined in the clinical laboratory by freezing point depression. The freezing point of water decreases by 1.87 °C for each increase in total solute concentration of 1 mole per liter (i.e., 1000 mOsm/l). The osmometer rapidly cools the sample and determines the freezing point from a sudden change in the electrical conductivity of the solution during ice crystal formation.

Plasma osmolality can, however, be accurately estimated by determining the concentrations of the main solutes of plasma. The following calculation can be used:

$$\text{Plasma osmolality (mOsm/l)} = 2 \times \text{Na}^+ \text{ (mEq/l)} + \frac{\text{Glucose (mg/dl)}}{18} + \frac{\text{BUN (mg/dl)}}{2.8}$$

Serum sodium accounts for more than 90% of the cationic solute in plasma. The multiplicative factor of two is required to account for the approximately equal concentration of anions (mostly chloride and bicarbonate) that accompany sodium in solution. Glucose and urea also present modest additions to total plasma solute concentration. An estimate of the contribution of glucose to plasma osmolality can be obtained by dividing the measured serum glucose in mg/dl by its molecular weight (180 mg/mmol). Conversion from mOsm/dl to the more conventional mOsm/l requires multiplication by a factor of ten.

Hence, a net division by 18 of the serum glucose (mg/dl) results in the osmotic concentration in mOsm/l.

The osmotic load of urea is calculated by using a denominator (2.8), derived by a similar method. The major difference is that serum urea is determined by measurement of blood urea nitrogen (not urea *per se*) in mg/dl. The urea molecule contains 2 nitrogen atoms (14 daltons each). Therefore, the conversion of BUN in mg/dl to urea in mOsm/l is achieved by dividing by 28/10, i.e., 2.8.

Unfortunately, no simple calculation is acceptable for estimation of urinary osmolality. Total urinary solute is made up primarily of urea and other solutes that are not routinely measured. Urine sodium concentration is usually inversely related to osmolality and is therefore not helpful. As with plasma, urine osmolality can be measured by freezing point depression.

Determination of urine specific gravity provides a more available means of estimating urine osmolality. The two commonly used bedside methods employ the use of either a hydrometer or a refractometer. These two techniques are both useful, but several precautions should be observed in the interpretation of urinary specific gravity measurements. Refrigeration of the urine, or excretion of large quantities of glucose, protein, or radiocontrast agents may result in significant increases of urine specific gravity in excess of corresponding increases in osmolality. The glassware must be kept clean and detergent-free. Finally, these instruments should be calibrated at frequent intervals with distilled water.

A urine specific gravity of 1.020 corresponds to a urine osmolality of about 800 mOsm/l; a specific gravity of 1.010 is equivalent to 300 mOsm/l, while a specific gravity of 1.001 is equivalent to approximately 50 mOsm/l.

1.2. Free-water clearance

Theoretically, abnormal plasma osmolality could result from disorders in either water or solute balance. For example, hyponatremia (hypo-osmolality) might arise from either a gain in total body water or a loss of extracellular solute. Conversely, hyperosmolar states might occur secondary to either loss of water or net gain in solute.

However, it is distinctly unusual for alterations in solute (i.e., sodium) balance to be directly responsible for changes in plasma osmolality. In almost every instance, the net external balance of water is the final determinant of plasma osmolality.

Net urinary water excretion in excess of solute can be quantitated by determining the 'free-water clearance' (C_{H_2O}). Urine volume may be divided into two parts. One fraction contains the volume needed to excrete the total solute load at the same osmolality as plasma. This isotonic component is termed the 'osmolar clearance' (Cosm). The remaining component is the so-called 'free-water clearance' (C_{H_2O}), and is the *theoretical volume* of solute-free water that has been added to (positive C_{H_2O}) or reabsorbed from (negative C_{H_2O}) the isotonic portion of urine (Cosm) to result in either hypotonic or hypertonic urine respectively. These relationships may be arranged as follows:

$$V(\text{urine flow}) = \text{Cosm} + C_{H_2O}$$

$$\text{Cosm} = \frac{(\text{Uosm}) \times \text{urine flow (V)}}{\text{Plasma osmolality (Posm)}} = \frac{\text{Uosm}}{\text{Posm}} \times V$$

$$C_{H_2O} = V - \text{Cosm}$$

Inspection of these relationships will allow several general conclusions to be drawn. When Uosm is less than Posm (hypotonic urine), V is greater than Cosm; therefore C_{H_2O} will be positive. On the other hand, when Uosm is greater than Posm (hypertonic urine), V is less than Cosm; the resultant C_{H_2O} will be negative. Finally, when Uosm equals Posm (isotonic urine), V equals Cosm; therefore C_{H_2O} is zero.

Excretion of a hypertonic urine (negative C_{H_2O}) has the net effect of returning solute-free water to the organism, thereby diluting body fluids. Conversely, the excretion of a hypotonic urine (positive C_{H_2O}) has the effect of removing solute-free water from the body and thus concentrating body fluids [39].

1.3. Renal concentrating and diluting mechanisms

In the final analysis, plasma osmolality is governed primarily by the ability of the kidney to excrete concentrated or dilute urine (negative or positive C_{H_2O}) in the appropriate quantities and circumstances. The important functional and morphological characteristics enabling the kidney to perform this subtle but all-important homeostatic operation will be outlined. It is recognized that this function of the kidney is dependent upon a number of intra- and extrarenal hemodynamic factors as well as hormonal mechanisms.

1.3.1. Proximal tubule

Approximately 60-85% of filtered sodium is actively reabsorbed in the proximal tubule. Because this early component of the nephron is freely

permeable to water, a similar percentage of filtered water is reabsorbed passively (and isotonically) with sodium. An important property of this site is the inverse relationship between renal blood flow (i.e., effective blood volume) and sodium and water reabsorption [2].

1.3.2. Ascending limb of the loop of Henle and the early distal tubule (diluting segment)

This segment maintains permeability to sodium and chloride, but is almost totally impermeable to water. With active reabsorption of NaCl, the urinary filtrate becomes progressively less hypertonic. As the urine approaches the tip of the cortical diluting segment (early to mid distal tubule), it becomes hypotonic to plasma [24].

Reabsorption of electrolytes without water from the 'diluting segment' serves two major functions. First, removal of solute from the tubular lumen creates urine which eventually reaches a minimal osmolality of about 60 mOsm/l. It is here that 'free water' is made. It is important to note that all urine that reaches the end of the diluting segment has developed this low osmolality. Second, entrance of solute into the interstitial space causes local tonicity to increase dramatically, reaching a maximum osmolality of approximately 1200 mOsm/l near the tip of the loop of Henle [27]. As described below, generation of interstitial hypertonicity serves as the main driving force for reabsorption of solute-free water from the collecting duct during states of antidiuresis.

1.3.3. Late distal tubule and collecting duct

When ADH is not present, this segment is only slightly permeable to water. As a result, final urine retains the hypotonic character that is generated by electrolyte removal in the diluting segment. However, in states with reduced urinary flow, transit time through this segment may be prolonged sufficiently to allow the final urine osmolality to approach isotonicity.

Under the influence of ADH, the tubular epithelia of the late distal tubule and collecting duct become highly permeable to water. A progressive increase in water resorption takes place along the length of the collecting duct as it reaches the deeper medullary portions of the kidney. Here, water transport is induced by the hypertonic nature of the interstitium, which has in turn been produced by solute resorption along the diluting segment. All urine arriving at this ADH-responsive site has a tonicity of approximately 60 mOsm/l but may reach as high as 1200 mOsm/l in the terminal medullary portion of the collecting sys-

tem. Thus, 'free water' may be removed from the urine and returned to the body during states of antidiuresis, thereby helping to preserve normal plasma osmolality [2, 24, 27].

1.4. Antidiuretic hormone

1.4.1. Structure and storage

ADH is a cyclic octapeptide. Synthesis occurs primarily in neurons of the supraoptic and paraventricular nuclei of the hypothalamus. The peptide is bound to one of a group of transport proteins, neurophysins, and transported along the axon in neurosecretory granules. The axons terminate within the posterior pituitary gland where the hormone is stored [35].

1.4.2. Site of action

Antidiuretic hormone action is initiated by binding to specific receptor sites along the basolateral (capillary) surface of the late distal tubule and collecting duct. Membrane-associated adenyl cyclase is activated, resulting in generation of cyclic AMP from ATP [24].

Perhaps via activation of protein kinases, intracellular cyclic AMP increases permeability of the luminal surface membrane to water, urea, and sodium. Calcium ion is known to interfere with both ADH-receptor binding and adenyl cyclase activation. Prostaglandin E_1 may also inhibit adenyl cyclase activation. In contrast, adrenal steroids enhance the permeability response to ADH, perhaps by inhibition of intracellular phosphodiesterase [27, 35].

1.4.3. Stimuli for release of ADH

Release of vasopressin from the posterior hypophysis is most sensitive to changes in the plasma osmolality. This is apparently mediated by intracellular dehydration of osmoreceptors within the central nervous system. Increments in plasma osmolality of as little as 1% within the normal range of 280–290 mOsm/l result in measurable elevations of plasma ADH.

Plasma volume depletion (i.e., extracellular dehydration) is another important stimulus for ADH release. Small decreases in plasma volume are less potent than corresponding increases in osmolality. However, large decreases in blood volume lead to ADH levels that exceed those caused by similar but opposite changes in osmolality.

There are a number of other stimuli for ADH secretion that may be clinically important. These include pain, emotional stress, cholinergic

agents, beta-adrenergic agents, nicotine, barbiturates, narcotics, tricyclic antidepressants, several chemotherapeutic agents, prostaglandins, and perhaps sulfonylureas. Ethanol, diphenylhydantoin, narcotic antagonists, and glucocorticoids have been shown to inhibit ADH release [35].

1.5. Summary of requirements for maximum water diuresis (C_{H_2O})

The following conditions must be met to ensure optimal free-water clearance [24].

1. Normal glomerular filtration.
2. An adequate volume of filtrate must escape reabsorption in the proximal tubule to be delivered to the diluting region of the nephron.
3. The tubular epithelial cells of the diluting segment must be functionally intact in their capability to reabsorb solute while remaining impermeable to water.
4. Free water, which is generated in the diluting site, must escape reabsorption in the late distal tubule and collecting duct. Thus, these areas must also remain impermeable to water.

2. CLINICAL STATES ASSOCIATED WITH HYPO-OSMOLALITY

2.1. True dilutional hyponatremia

2.1.1. Primary polydipsia

Excessive water intake as a cause of hyponatremia is by itself a distinctly uncommon phenomenon. Normal metabolic processes produce about 600 mOsm of solute to be excreted by the kidneys each day. Since the diluting capability of the nephron is to approximately 60 mOsm/l, an intake of greater than 10 liters/day would be necessary to cause dilution of body solutes. It is clear that only serious disorders of hypothalamic thirst regulation or profound psychiatric disturbances would result in such abnormal drinking behavior [24].

A possible exception is that of so-called beer-drinker's hyponatremia. This is occasionally seen in patients who have chronically ingested large quantities of beer, often to the exclusion of food. Since beer itself is quite low in solute, the net obligatory solute excretion may decline to as little as 300 mOsm/day. Thus, a total beer intake of only about 5 liters/day could result in hyponatremia [2].

Treatment would include reduction of beer intake or, failing that, increased solute intake (e.g., salted beer).

2.2. Renal failure

Mild to moderate levels of renal insufficiency interfere with optimal free-water clearance by decreasing the amount of filtrate presented to the diluting segment of the nephron. Such a defect does not usually become apparent until excessive quantities of water are ingested.

However, in the presence of more severe renal failure, especially if oliguric, maximum free-water clearance may be zero or actually negative. In this setting, even otherwise normal fluid intake could result in hyponatremia. This phenomenon is most likely to occur during acute oliguric renal failure, since recognition of limited fluid tolerance may often be delayed.

Treatment should be directed to restriction of the patient's fluid intake commensurate with his limitation of free-water clearance. It is usually safe to limit such intake to about 600 ml/day plus urine output. With severe or symptomatic hyponatremia it may be necessary to add dialysis therapy as a life-saving measure.

2.3. Decreased delivery of filtrate to diluting segment of the nephron

2.3.1. Depletion of plasma volume

The proximal tubule responds to reduction of renal blood flow by a proportionately greater reabsorption of sodium and water. This phenomenon may be considered an attempt by the body to preserve plasma volume. Therefore, less than the usual amount of urine escapes the proximal tubule to arrive at the diluting segment. The quantity of free water generated at this site is dependent on both the functional integrity of the tubular epithelium and the amount of filtrate delivered. Hence, clinical states resulting in plasma volume depletion impair maximal free-water clearance. As a result, a normal intake of fluid may lead to hyponatremia [2, 24].

Clues to this form of hyponatremia may often be found by physical examination. Dry mucus membranes, poor skin turgor, orthostatic hypotension, and tachycardia are evidence of plasma volume depletion. In most instances, urine sodium concentration is <20 mEq/l. Exceptions include sodium and volume depletion secondary to increased renal losses (diuretics, mineralocorticoid deficiency, renal salt-wasting syndromes).

Initial management requires replacement of losses with isotonic saline. In addition, procedures should be initiated to identify and treat the primary cause of plasma volume depletion. Such measures are usually simple, such as cessation of diuretics, but may require an intensive search for the endocrine, renal, or gastrointestinal disorders listed in Table 1. Chronic dehydration is easy to treat in the acute in-hospital setting. Prevention of future episodes, however, may necessitate careful psychosocial evaluation and follow-up.

Table 1. Causes of plasma volume depletion that may lead to hyponatremia

Urine sodium less than 20 mEq/l (extrarenal losses)
1. Chronic dehydration
2. Vomiting or diarrhea
3. Burns
4. 'Third-space' losses
Urine sodium greater than 20 mEq/l (renal losses)
1. Diuretic therapy
2. Salt wasting nephropathies
3. Mineralocorticoid deficiency

2.3.2. Volume expansion

As in states of volume depletion, decreased renal blood flow also characterize the edema-forming disorders, such as congestive heart failure, hepatic insufficiency and nephrotic syndrome. Paradoxically, these edema-forming conditions are accompanied by a measurable elevation of extracellular fluid volume and total body sodium. Hence, a state of decreased 'effective' plasma volume is said to exist.

The major immediate cause of sodium retention and edema in these disorders is an increase in proximal tubular sodium and water reabsorption. As in those conditions with 'true' volume depletion (Table 1), the proximal tubular response of these patients serves as a mechanism to increase plasma volume and improve renal perfusion [23].

As proximal tubular fractional reabsorption of sodium and water increases, less filtrate is available to the diluting segment for generation of free water. Hence, maximum free-water clearance is blunted, putting the patient at risk to develop hyponatremia following an otherwise normal fluid intake.

Physical examination may reveal some or all of the following clinical findings: edema, ascites, hypertension, neck vein distention, pulmonary rales, or a third heart sound. As in most cases of 'true' plasma volume

depletion, patients with edema excrete urine that usually has a sodium concentration <20 mEq/l.

Management of hyponatremia in any of these settings may be difficult. However, fluid restriction is a key element in any such treatment. Congestive heart failure may require judicious use of diuretics or inotropic agents. The renal and hepatic causes listed may require protein supplementation in addition to nutritional and diuretic therapies. Steroids or cytotoxic agents may be indicated in several forms of nephrotic syndrome.

2.4. Syndrome of inappropriate ADH (SIADH)

As described above, ADH acts on the epithelial lining of the late distal tubule and the collecting duct to increase permeability to water. In the presence of ADH, free water generated by the more proximal diluting segment is passively reabsorbed. Normally, this sequence of events takes place only when plasma osmolality is elevated or plasma volume is decreased. The syndrome of inappropriate ADH is characterized by continuous ADH secretion despite plasma osmolality that is subnormal and plasma volume that is normal or increased [8]. The disorders associated with this syndrome are listed in Table 2.

Table 2. Disorders associated with SIADH.

1. Neoplasm – lung, duodenum, pancreas, prostate, lymphoma, thymoma
2. Pulmonary Disease – tuberculosis, pneumonia, abscess, aspergillosis, chronic infection
3. Central Nervous System Disorders
   - Encephalitis, meningitis
   - Cerebralvascular accident
   - Space-occupying lesions
   - Head trauma
   - Guillain-Barré syndrome
4. Miscellaneous
   - Acute intermittent porphyria
   - Hypokalemia
   - Systemic lupus erythematosis
5. Idiopathic

2.4.1. Criteria for diagnosis of SIADH

No firm diagnosis of SIADH can be made in the absence of any of the findings listed in Table 3 [24, 27, 35]. However, problems in interpretation may arise. For example, there is no consensus about what consti-

Table 3. Criteria for the diagnosis of SIADH

1. Serum hypo-osmolality – Rule out Pseudohyponatremia
2. Inappropriately concentrated urine
3. Normal plasma volume – No Evidence of edema or volume depletion
4. Normal renal, adrenal and thyroid function
5. Urine sodium approximately equivalent to intake
6. Correction by water restriction alone
7. Hypouricemia

tutes an inappropriately concentrated urine. A urine osmolality greater than 60 mOsm/l indicates that water has been reabsorbed distal to the diluting segment of the nephron and might therefore represent inappropriate ADH activity. However, some residual permeability to water does exist in the collecting duct despite the absence of ADH. In clinical states with low urine flows (renal insufficiency, decreased effective plasma volume) a significant fraction of glomerular filtrate may be reabsorbed distally even with suppressed ADH. Urine osmolality may be isotonic or mildly hypertonic in those settings, and does not necessarily represent abnormal ADH activity. Therefore, before invoking SIADH as the cause of hyponatremia in any patient, it is most important to demonstrate a normal plasma volume and glomerular filtration rate.

Urine sodium concentration is usually greater than 30 mEq/l, which is a reflection of the normal or slightly increased plasma volume in patients with SIADH. However, these patients are capable of reducing U_{Na} to lower levels in the presence of rigid salt restriction [2].

2.4.2. Treatment of SIADH

2.4.2.1. Water restriction. Reduction of free-water intake is an important aspect of the diagnosis and management of hyponatremia secondary to SIADH. While rigid fluid restriction is effective and practical during acute, inhospital care, it is often difficult to achieve on a chronic, out-patient basis.

2.4.2.2. Hypertonic saline and diuretic therapy. Occasionally, rapid development of hyponatremia may result in severe alterations in brain function accompanied by stupor, convulsions, or coma. A potent diuretic such as ethacrynic acid or furosemide may be administered intravenously to induce a rapid increase in free-water clearance. Urinary electrolyte losses are exactly replaced by an equivalent infusion of a small volume of hypertonic (3%) saline [22]. Hypertonic saline may be used without a diuretic for this purpose but is only transiently effective since, in the presence of the volume expansion of SIADH, sodium is

rapidly excreted. Furthermore, in an elderly patient, hypertonic saline alone may precipitate pulmonary edema.

2.4.2.3. Pharmacologic agents. Both lithium and demeclocycline have been found to antagonize the effect of ADH on renal tubular epithelium. While lithium is now thought to be too toxic for use, studies of demeclocycline therapy are more promising [17]. In addition, investigations are now underway with a variety of other agents including diphenylhydantoin, narcotic antagonists, and ADH analogues [44]. Some or all of these drugs may prove to be especially useful in managing patients with chronic SIADH who find it difficult to maintain the strict fluid limitation necessary to avoid serious hyponatremia.

2.5. Drugs associated with impaired free-water clearance

Table 4 contains a list of agents that have been shown to interfere with urinary dilution. Although the classification is according to mechanism, there is not total consensus in every case [18, 24, 39].

Table 4. Drug-related hyponatremia

a.	Stimulation of ADH release
	1. Nicotine
	2. Narcotics
	3. Barbiturates
	4. Tricyclic antidepressants
	5. General anesthetics
	6. Antineoplastic agents – Vincristine, Cyclophosphamide
	7. Carbamazepine
	8. Clofibrate
	9. Chlorpropamide
	10. Prostaglandin E
b.	Simulation of renal ADH effect
	1. ADH analogues
	2. Oxytocin
	3. Chlorpropamide
	4. Prostaglandin synthetase inhibitors
c.	Multifactorial
	1. Diuretics

Diuretics are the most common cause of drug-induced hyponatremia. Plasma volume depletion, leading to increased proximal tubular reabsorption of sodium and water, with decreased delivery of filtrate to the diluting segment, has already been cited. Furthermore, both plasma volume depletion and hypokalemia have been shown to enhance ADH

secretion [16]. Finally, distal-acting diuretics, including thiazide and loop-acting agents, interfere directly with the ability of the diluting segment to reabsorb electrolytes, thereby limiting generation of free water within the tubular lumen.

2.6. Endocrine deficiencies

2.6.1. Hypothyroidism

Hyponatremia has occasionally been described with severe degrees of hypothyroidism. It is probable that several factors may interfere with maximum urinary dilution. There is evidence that the normal functional integrity of the diluting segment may be impaired in the absence of thyroid hormone. In some patients, overt or covert heart failure may exist, creating a state of effective volume depletion. Also, ADH levels have been reported to be elevated in a large fraction of myxedematous patients [40]. Whether this latter effect is directly caused by thyroid deficiency *per se* or by cardiac insufficiency is not clear at this time.

Therapy is directed toward appropriate thyroid hormone replacement and treatment of coexisting heart failure.

2.6.2. Adrenal insufficiency

Mineralocorticoid deficiency has already been cited as a cause of renal salt wasting, resulting in 'true' plasma-volume depletion and subsequent interference with maximum free-water clearance. Deficient mineralocorticoid production is most likely to accompany glucocorticoid deficiency as seen in disorders of primary adrenal insufficiency. However, isolated defects of aldosterone production have also been described. Suspicion of inadequate mineralocorticoid production should be aroused by the simultaneous presence of hyperkalemia, hyponatremia, and high urine sodium in the setting of normal or only mildly impaired renal function.

Glucocorticoid deficiencies may also limit maximum free-water clearance. There is recent evidence that glucocorticoid deficiency has a deleterious effect on cardiac function, thereby resulting in 'ineffective' plasma volume as well as ADH stimulation [4]. Furthermore, glucocorticoids may be necessary to achieve minimal water permeability of the collecting duct when ADH is absent. Deficient glucocorticoid production may either be seen as an isolated phenomenon with disorders of the hypothalamic-pituitary-adrenal axis or together with mineralocorticoid deficiency when primary disease of the adrenal gland exists.

2.7. Reset osmostat

This phenomenon probably represents what was formerly referred to as the 'sick cell syndrome'. Hyponatremia has occasionally been described in patients with certain chronic, debilitating diseases such as tuberculosis, cirrhosis, or malabsorption syndrome. As in SIADH, these patients can excrete whatever sodium is ingested, as well as concentrate their urine normally. In contrast to those with SIADH, such patients are capable of normal urine dilution and excretion of a water load when their plasma osmolality reaches a certain lower set point. In true SIADH, normal urine dilution following a water load is never achieved because of continued ADH excretion despite lowered plasma osmolality [10].

2.8. Summary of the diagnostic approach to hyponatremia

2.8.1. Rule out non Hypo-osmolar states

Significant elevations of serum proteins or lipids displace some water from the plasma compartment. Since sodium is only in aqueous solution, measured sodium concentration in plasma (which includes water and nonaqueous substances) may be reduced.

Hyperglycemia can cause hyponatremia because of the osmotic effect of glucose in the extracellular space. Water shifts out of the intracellular space diluting extracellular solutes. For each increment of serum glucose of 100 mg/dl, serum sodium should decline by about 1.6 mEq/l.

Therefore, it is important early in the evaluation of hyponatremia to determine levels of the patients' serum lipids, proteins, and glucose.

2.8.2. History

Emphasis should be placed on a careful search for underlying problems and unusual eating and drinking habits, as well as drug history.

2.8.3. Physical examination

Physical examination is probably the single most useful procedure for evaluation of hyponatremia. Of greatest importance is an estimate of the patient's extracellular fluid volume.

A clinically normal extracellular volume suggests several possibilities, chiefly: SIADH, drugs, pain, emotion, hypothyroidism, and isolated glucocorticoid deficiency. Evidence of plasma volume depletion implies that one of the renal or extra-renal disorders listed in Table 1 is the likely etiology. Finally, the presence of edema or other evidence of volume expansion points towards cardiac, hepatic or renal disease as the underlying etiology.

Careful physical examination is also likely to yield clues about the precise nature of the underlying process.

2.8.4. Urine sodium concentration

As described above, urine sodium of less than 20 mEq/l is consistent with either 'true' or 'effective' plasma volume depletion. Clinical states with normal plasma volume occasionally may also be accompanied by U_{Na} less than 20 mEq/l if dietary intake is low. Interpretation of U_{Na} greater than 20 mEq/l is dependent upon the plasma volume status of the patient. On one hand, this level is consistent with any of the aforementioned disorders known to be associated with normal plasma volume. However, in the setting of plasma volume depletion, a U_{Na} greater than 20 mEq/l indicates renal losses as the cause of volume depletion (see Table 1).

3. HYPERNATREMIA AND DISORDERS OF URINE CONCENTRATION

In contrast to hypo-osmolar states, hypernatremia is characterized by water loss in excess of solute [14]. Commonly, hypernatremia occurs with normal renal concentrating function in the setting of severe, acute hypotonic fluid losses. Some hypernatremic patients however, are unable to achieve maximum urinary concentration; hence, free-water clearance is abnormally high. Concentrating defects can be attributed either to low levels of circulating ADH or to an impaired response of the kidney to appropriate levels of ADH.

3.1. Low circulating levels of ADH

3.1.1. Central diabetes insipidus

3.1.1.1. Pathophysiology. As described earlier, ADH acts on the late distal tubule and collecting duct to increase epithelial permeability to water. The interstitium surrounding the collecting duct has been made hypertonic by solute reabsorption in the diluting segment. Hence, in the presence of ADH, water will be reabsorbed, thereby concentrating the urine.

Defects in the synthesis or release of ADH will lead to a marked concentrating defect and, therefore, an inappropriately elevated free-water clearance with polyuria. Urinary osmolality usually varies from 50 to 200 mOsm/l and specific gravity from 1.001 to 1.005. An intact thirst

and drinking mechanism will result in polydipsia which maintains net water balance, keeping serum sodium in the normal range [35].

The exact nature of defective regulation of ADH secretion has not been thoroughly elucidated. However, there appear to be several different types and levels of ADH insufficiency [33]. ADH levels may be either partially or completely deficient, thereby resulting in concentrating defects that may range from mild to severe. In some settings, ADH levels may be absent or subnormal until a certain high 'set point' of plasma osmolality is achieved, above which normal regulation occurs. Another type of defect is characterized by ADH levels which rise in proportion to plasma osmolality, but always to a subnormal degree. Some patients may have no ADH response to osmotic stimuli but a normal elevation when challenged with volume depletion [21].

It is important to note that hypernatremia does not occur in any of these disorders as long as normal thirst and drinking behavior are present. The small initial rise in plasma osmolality resulting from water losses will usually stimulate thirst and sufficient fluid ingestion to maintain plasma osmolality in at least the high-normal range. There are, however, occasional circumstances in which patients are not able to drink sufficient fluid to avoid hypernatremia. This might occur during states of disturbed consciousness, or when free water is not available, such as on a desert or open sea. Another disorder termed 'essential hypernatremia' is characterized by deficient thirst in the setting of inadequate ADH release. Interestingly, patients with this condition may be remarkably asymptomatic despite very high plasma sodium concentrations [21].

3.1.1.2. Causes and clinical features of central diabetes insipidus. Table 5 presents a classification of disorders that may lead to insufficient ADH release [14]. Surgery in the area of the hypothalamus or pituitary, together with head trauma, now represent the majority of cases of central diabetes insipidus. Following neurosurgical procedures, a classic

Table 5. Causes of central diabetes insipidus

Head trauma
Hypophysectomy
Supra – or intrasellar tumors
Idiopathic and familial
Cysts
Granulomatous disorders
Cerebral vascular disease
CNS infections

triphasic pattern of water metabolism may occur. Immediately postoperatively, the patient may experience polyuria and polydipsia which is thought to represent acute damage to the hypothalamic center involved in ADH release. After four or five days, a period of profound antidiuresis may occur that is ascribed to release of stored ADH from the denervated neurohypophysis. Finally, after several more days, polyuria returns, this time as permanent central diabetes insipidus [24].

A number of characteristic clinical features may be seen regardless of the specific etiology of central diabetes insipidus. The onset of central diabetes insipidus is often abrupt. Some patients are able to recall the exact time that polyuria began. The severity of polyuria frequently reaches its peak in the first few days after onset. In contrast to psychogenic polydipsia, patients with central diabetes insipidus usually must void and drink large volumes of fluid both day and night. These patients often insist that only ice water will quench their otherwise relentless thirst [39].

3.1.1.3. Treatment of central diabetes insipidus. Patients with a mild partial defect of ADH secretion may be content to continue their increased drinking habits and, therefore, prefer to avoid replacement therapy. Usually, however, therapy with one of several available forms of vasopressin is indicated. In the acute in-hospital setting, aqueous vasopressin is the preparation of choice. This is administered intramuscularly or subcutaneously in doses (usually 5–10 units) and frequencies (often every 4–6 hours) necessary to control polyuria.

For chronic therapy, vasopressin tannate in oil has a duration of action of 24–72 hours when given intramuscularly. Several intranasal preparations are also available. Lysine vasopressin is well tolerated but has the disadvantage of a short duration of action lasting only three to four hours. Recently, another intranasal preparation has been synthesized that has greater potency than endogenous arginine vasopressin. The analogue l-deamino-8-D-arginine vasopressin (DDAVP), when given intranasally at a dose of 10–20 mg, has a duration of action of 12–24 hours [36]. In addition, there is a complete loss of the pressor activity normally seen with other derivatives of ADH.

Chlorpropamide, in doses of 250–500 mg/day, enhances the effect of endogenous ADH on the renal concentrating mechanism. Hence, this drug may be useful in managing patients with partial defects of ADH release. Clofibrate at a dose of 500 mg q.i.d. stimulates release of endogenous ADH and may, therefore, be useful in treating partial central diabetes insipidus. Occasionally, clofibrate has been used at full doses in

combination with low doses of chlorpropamide to reduce the risk of hypoglycemia from the latter drug [27].

3.1.1.4. Psychogenic polydipsia. This syndrome of compulsive water drinking mimics central diabetes insipidus since both are associated with polyuria, polydipsia and low circulating levels of ADH. In contrast to central diabetes insipidus, ADH release in psychogenic polydipsia is inhibited appropriately by the mild hypo-osmolality and volume expansion of body fluids resulting from the primary increase in water intake.

There are several clinical features of compulsive water drinking that are helpful in distinguishing it from central diabetes insipidus. Compulsive water drinking is often seen in females, frequently in menopause, with a history of psychiatric disturbances. The history of onset of polyuria is often vague with greater variations in fluid intake than is usually seen in central diabetes insipidus. Severe nocturia is more variable in this functional disorder. While in diabetes insipidus plasma osmolality is typically in the high-normal range (290–300 mOsm/l), compulsive water drinkers usually have plasma osmolality in the low-normal range (270–280 mOsm/l) [39]. Definitive physiological tests involving either dehydration, administration of exogenous vasopressin or hypertonic saline will serve to distinguish these two entities.

Management is directed at the primary psychiatric disorder.

3.2. Renal tubular hyporesponsiveness to ADH (nephrogenic diabetes insipidus)

3.2.1. Causes and pathophysiology

There are a number of factors that may impair the ability of the kidney to concentrate urine maximally in the presence of adequate levels of ADH [11]. The causes listed in Table 6 are mediated by several of these mechanisms.

Table 6. Causes of nephrogenic diabetes insipidus

Hypercalcemia
Hypokalemia
Interstitial nephritis
Urinary tract obstruction
Polycystic and medullary cystic kidney disease
Dysproteinemias-amyloidosis, multiple myeloma, Sjögren's syndrome
Drugs-lithium, demeclocycline, methoxyflurane
Sickle cell disease
Hereditary

Acute hypercalcemia may interfere with receptor-binding of ADH, in addition to inhibiting renal tubular adenyl cyclase. Chronic hypercalcemia often results in nephrocalcinosis, which probably interferes with tubular function elsewhere, including the ability of the diluting segment to generate interstitial hypertonicity. Impaired ability of the ascending limb of Henle to produce a hypertonic interstitium plays a major role in the concentrating defects seen with a number of conditions, including hypokalemia, interstitial, obstructive, and cystic renal diseases, as well as dysproteinemias. Both lithium and demeclocycline are known to interfere with response to ADH by impairment of both cyclic AMP generation and action. The specific mechanism of the concentration defect induced by methoxyflurane is not well understood but may relate to its toxic metabolites which include fluoride and oxalate. Concentrating defects are frequently seen in sickle cell disease. This has been ascribed to intravascular sickling and occlusion of the medullary vasa recta, with resultant inhibition of solute transport in the ascending limb of Henle [27].

Hereditary nephrogenic diabetes insipidus is a rare disease that is apparently transmitted in a sex-linked pattern with variable penetrance in female heterozygotes. There are data which suggest that the concentrating abnormality is a result of tubular resistance to the action of ADH, perhaps secondary to renal tubular adenyl cyclase deficiency [46].

3.2.2. Treatment of nephrogenic diabetes insipidus

Unfortunately, management of patients with this form of diabetes insipidus can be quite difficult. With the exception of electrolyte abnormalities, obstructive uropathy, and drugs, most primary causes of nephrogenic diabetes insipidus are not reversible.

Therapy includes ensuring that patients have free access to water at all times. Polyuria can be diminished somewhat by reducing the solute load. Hence, a low protein and salt diet may be a useful adjunct. Finally, thiazide diuretics have also been shown to be useful in this setting. The effectiveness of this class of drugs appears to be the result of contraction of extracellular volume and subsequent increased proximal tubule reabsorption of glomerular filtrate. Hence, distal water delivery and eventual excretion will be reduced. Consistent with this mechanism of action is the fact that salt restriction must be maintained to avoid return of polyuria.

3.3. Diagnostic approach to the patient with a disorder of urinary concentration

3.3.1. General considerations

Attention to the clinical features as outlined earlier in this chapter will usually provide enough information to make an accurate diagnosis of the underlying causes of most polyuric states. However, patients with milder or functional types of polyuria may require extensive physiological testing to evaluate all aspects of the concentrating mechanism.

3.3.2. Dehydration test [39]

A carefully done water deprivation test usually enables one to recognize ADH deficiency of all degrees, as well as to differentiate these patients from those with polyuria of other etiologies. It is carried out by withholding fluid until urine osmolality becomes stable during hourly collections. In persons with severe polyuria, fluid restriction is advised to begin early in the day to avoid the risk of severe volume depletion in the middle of the night. Those with milder forms of polyuria may require 12–18 hours before urine osmolality becomes stabilized and may therefore begin fluid deprivation in the evening. Plasma osmolality is measured prior to the initiation of fluid restriction and again at the time of reaching the plateau of urine osmolality. At the end of the fluid deprivation period, aqueous vasopressin, 5 units, is administered subcutaneously. Urine osmolality is again measured 1 hour later.

At the termination of dehydration, a normal subject will have increased his urine osmolality to greater than 800 mOsm/l. Patients with partial central diabetes insipidus as well as those with compulsive water drinking may achieve urine osmolalities in the 400–600 mOsm/l range. Submaximal urine concentration in psychogenic polydipsia is probably related to a medullary washout phenomenon. After several more days of avoidance of high fluid intake, urine osmolality can reach normal levels on re-testing. Complete central or nephrogenic diabetes insipidus will typically result in maximum urine osmolalities of less than 200 mOsm/l at the end of dehydration.

Following ADH administration, patients with severe central diabetes insipidus will show at least a 50% increase in urine osmolality above that obtained by fluid deprivation alone. It is common for the absolute value of urine osmolality to remain subnormal, secondary to medullary interstitial dilution that may occur with any polyuric-polydipsic state. Patients with partial defects in ADH release will show a modest increase in urine osmolality of greater than 9% but less than 50%.

Urine osmolality will show little change in either the normal state or in those with a nephrogenic form of diabetes insipidus.

An alternative method of increasing plasma osmolality is to infuse hypertonic saline. As plasma osmolality rises, a sudden sharp decline in measurable free-water clearance can be detected when the ADH release mechanism reaches its osmotic threshold [33]. In normal individuals, or in those with compulsive water drinking, this threshold is generally less than 290 mOsm/l. Some patients with partial central diabetes insipidus will have normal release but at an abnormally high threshold. Patients with complete central or nephrogenic diabetes insipidus will not respond at all to the osmotic stimulus.

Eventually, as accurate, sensitive ADH assays become available, levels of ADH will be of utmost help in distinguishing among total and partial diabetes insipidus, nephrogenic diabetes insipidus and psychogenic polydipsia.

4. DISORDERS OF SODIUM METABOLISM

Extracellular osmolality is a function of water balance. Extracellular fluid volume, however, is primarily dependent on total body sodium content. Since sodium is the major osmotically active element in the extracellular space, it serves as the main determinant of the distribution of water in various body fluid compartments. Total body sodium is in turn regulated primarily by urinary excretion.

Each day, the kidneys filter about 160 liters of plasma water with a sodium concentration of 140 mEq/l. Hence, the total filtered load of sodium is about 23,000 mEq per day. The final urine content of sodium is only about 100 to 200 mEq per day—less than 1% of the filtered load. About 60 to 75% of filtered sodium is reabsorbed by an energy dependent process in the proximal tubule. Chloride reabsorption occurs passively down its electrical gradient [19]. In the thin ascending limb of the loop of Henle, sodium and chloride are further reabsorbed passively down their respective concentration gradients. In the thick portion of the ascending limb, chloride reabsorption is an active process. Sodium follows passively out of the tubular lumen along the electrical gradient that has been created by chloride removal [6]. In the late distal tubule and collecting duct, sodium is once again actively reabsorbed, under the influence of aldosterone. The intraluminal electronegative potential that is generated serves as the driving force for potassium and hydrogen ion secretion at this site [19].

4.1. Determinants of renal sodium excretion

4.1.1. Filtered load

As noted above, the daily filtered load of sodium greatly exceeds excretion. In order to avoid potentially fatal variations in urine flow and sodium excretion, some form of coupling of filtration and reabsorption of sodium must exist. This poorly understood phenomenon, termed glomerulo-tubular balance, is quantitatively the most important determinant of tubular handling of sodium [29]. A large number of mechanisms have been put forth to explain this feedback system. Among the factors that have been thought to play a role are the renin-angiotensin system, 'natiuretic hormone' [20], the renal neural system and the physical properties of the peritubular interstitium (colloid and hydrostatic pressures) and capillaries (hematocrit and blood viscosity).

4.1.2. Aldosterone

Sodium reabsorption in the late distal tubule and collecting duct is highly dependent on the presence of mineralocorticoids. Aldosterone apparently acts by inducing the synthesis of a protein that either serves as a permease, a carrier, or as a source of energy for the active sodium transport system [12]. Since the late nephron segment is the final site of sodium reabsorption, the influence of aldosterone on the 'fine-tuning' of sodium homeostasis is clearly of great importance.

4.1.3. Third factors

It has been conclusively shown that factors in addition to aldosterone and filtered load have a potent influence on tubular sodium reabsorption. This so-called 'third factor' probably consists of multiple variables.

One such factor may be renal plasma flow (RPF). Renal blood flow is influenced in turn by effective arterial blood volume in addition to various humoral agents including catecholamines, angiotensin II and prostaglandins. Glomerular filtration rate (GFR) and renal plasma flow may be decreased to a moderate extent, with a disproportionate fall in RPF leading to an increased filtration fraction (GFR/RPF). An elevation in filtration fraction indicates that a higher than normal fraction of renal plasma flow is being filtered. The protein concentration in postglomerular peritubular capillaries will be increased since a higher proportion of protein-free fluid has been removed by filtration. The resultant higher peritubular oncotic pressure may induce a greater quantity of filtrate to leave the tubular lumen [28].

It is also possible that urinary excretion of sodium may be influenced by the distribution of intrarenal blood flow [38]. Normally, about 90% of total renal blood flow is cortical and 10% medullary. Morphologically, cortical nephrons are characterized by short thick loops of Henle that only reach to the outer medulla. The loops of Henle of the juxtamedullary nephrons are longer and reach deep into the medullary and papillary regions of the kidney. These nephrons may have a greater sodium reabsorptive capacity than cortical nephrons. It has been postulated that a number of conditions such as cirrhosis, congestive heart failure and hypovolemia lead to salt retention because blood flow is directed away from the cortex and into juxtamedullary nephrons.

4.2. Sodium retaining states (edema)

Edema is a sign that indicates the abnormal accumulation of salt and water in the interstitial space. Development of generalized edema indicates that abnormal retention of sodium and water by the kidney has occurred irrespective of underlying disease process.

4.2.1. Congestive heart failure

Myocardial failure is one of the most common causes of generalized edema. Heart failure is defined as inadequate cardiac output, either in absolute terms (low output failure) or in relative terms (high output failure). In either case, total renal blood flow is generally reduced. However, because of renal autoregulatory mechanisms, glomerular filtration rate is usually better preserved. Thus, filtration fraction tends to increase, leading to changes in peritubular physical factors that promote sodium reabsorption [32]. Normal blood pressure is maintained in heart failure in part by increased activity of the sympathetic nervous system. As a result, renal vascular resistance increases, causing a further decline in total renal blood flow. Furthermore, greater sympathetic tone may also shunt blood flow away from the cortical nephrons and into the medulla where greater sodium reabsorption is thought to occur [41].

Decreased renal perfusion may also stimulate biosynthesis and release of renin from the juxtaglomerular apparatus, resulting in an increased formation of angiotensin II, which acts as both a renal vasoconstrictor and a potent inducer of aldosterone production and release. Aldosterone serves as a powerful stimulant of sodium reabsorption in the distal tubules. Plasma levels of aldosterone may also be elevated as a result of impaired hepatic metabolism in heart failure [43]. Finally, there is con-

tinued speculation that the absence of some as yet unidentified natriuretic substance may also contribute to renal salt retention.

4.2.2. Hepatic cirrhosis

Cardiac output is often normal or elevated in cirrhotic patients. Total peripheral resistance is, however, usually diminished in cirrhotic patients with edema. Vascular resistance is probably altered as a result of anatomical arteriovenus shunts that arise as a consequence of hepatic insufficiency. It has also been proposed that metabolic clearance of some undefined vasodilator may be impaired.

Most patients with liver cirrhosis have reduced renal blood flow. Causes of this change are multifactorial, including decreased peripheral vascular resistance, increased adrenergic tone and angiotensin II activity as well as shunting of renal blood flow to the medullary region. Renal perfusion may be further impaired by the presence of hypoalbuminemia in some patients [13].

Aldosterone levels are more frequently elevated in patients with liver cirrhosis than with heart failure. This is probably a result of increased angiotensin II-induced release as well as impaired hepatic clearance. Nevertheless, the clinical significance of hyperaldosteronism in the edema formation of liver disease has not been determined [37].

4.2.3. Renal disease

The filtered load of sodium provides the quantitatively most important determinant of tubular handling of sodium. As the glomerular filtration rate declines in either acute or chronic renal failure, the ability to maintain sodium homeostasis becomes progressively limited. Thus, unless sodium intake is reduced in proportion to the diminished renal function, edema may ensue.

In the nephrotic syndrome, the situation is more complex. Glomerular filtration rate may be low, normal or even elevated. Glomerular leakage of plasma protein leads to hypoalbuminemia and diminished plasma oncotic pressure. As a result, altered Starling's forces will allow plasma water to leak out of the vascular bed and into the interstitial space. Consequently, true plasma volume will often be depleted. All or most of the humoral and hemodynamic mechanisms proposed for congestive heart failure and hepatic disease may then come into play to contribute to the generalized edema of the nephrotic syndrome [26].

4.2.4. Miscellaneous causes of edema

Edema often arises during the course of normal pregnancy. Most commonly, this is confined to the legs and results probably from compres-

sion of the inferior vena cava by the enlarging uterus. Elevated estrogen and aldosterone levels may also contribute to sodium retention. Edema in association with toxemia of pregnancy may be a consequence of several factors, including renal vasoconstriction, decreased glomerular filtration rate and proteinuria [15].

The edema seen in hypothyroid patients has been shown to be partially related to increased capillary permeability to plasma albumin in addition to impaired lymphatic drainage of the interstitial space [34]. Overt or covert myocardial dysfunction may also be a consequence of hypothyroidism.

Idiopathic cyclic edema is a common, but poorly understood, phenomenon seen usually in women of child-bearing age. A number of abnormalities have been demonstrated in these patients including excessive venous stasis in the legs, exaggerated aldosterone response to the upright posture, and abnormal regulation of antidiuretic hormone [45].

Localized edema can be a result of several factors. Tissue damage of almost any cause may lead to increased capillary permeability with resultant extravasation of protein and fluid into the interstitial space. Obstructive lesions of the venous system can lead to increased capillary hydrostatic pressure that will also tend to drive fluid out of the vascular space [38]. Lymphatic obstruction, on the other hand, may interfere with normal drainage of the interstitial fluid.

4.3. Diuretic therapy

4.3.1. General principles in the treatment of edema

Most causes of generalized edema are mediated by a decrease in effective arterial blood volume. It is therefore imperative that initial management be directed at the underlying disorder [26]. With cardiac disease, adequacy of digitalization, control of blood pressure and arrhythmias should be evaluated. In cirrhosis, good nutrition and abstinence from alcohol may improve hepatic function and its accompanying humoral and hemodynamic derangements. Certain types of nephrotic syndrome may respond to steroids or cytotoxic agents. Several nonspecific modalities such as salt restriction, bed rest and supportive stockings may aid in the management of edema. In hypoalbuminemic states, infusion of colloid may be transiently effective in mobilizing edema fluid.

Even if all else fails, the presence of edema alone is not a definite indication for diuretic therapy. Any cosmetic value must be weighed against potential toxic effects of these drugs. Situations in which fluid accumulation impairs cardiac or respiratory function, or causes signifi-

cant physical discomfort, are clear indications for diuretic treatment [26]. Occasionally, patients will find a low-salt diet unpalatable; diuretics can be used to allow them to add some salt to their food.

4.3.2. Proximal tubular diuretics

Table 7 contains a classification of currently used diuretics, according to site of action along the nephron.

Table 7. Classification of diuretics by site of action.

Chief site of action	Agents	Potency	Dose
Proximal tubule	Acetazolamide	low	250–500 mg PO* or IV per day
	Mannitol	moderate	50–200 ml IV** infusion
Loop of Henle	Furosemide	high	20-200 mg PO or IV per day
	Ethacrynic acid	high	50–200 mg PO or IV per day
Early distal tubule	Hydrochlorothiazide	moderate	25–50 mg PO once or twice per day
	Chlorthalidone	moderate	25–100 mg PO once per day
	Ticrynafen	moderate	250–500 mg PO once per day
Late distal tubule	Spironolactone	low-moderate	25–75 mg PO two or three times daily
	Triamterene	low	100 mg PO twice daily

* PO = by mouth.
** IV = intravenously.

Osmotic agents such as mannitol are freely filtered but not reabsorbed. As a result, osmolality of tubular fluid reaches high levels, thereby inhibiting fluid reabsorption from the tubular lumen. Acetazolamide inhibits the enzyme carbonic anhydrase, and in turn slows bicarbonate reabsorption. Since bicarbonate reabsorption is indirectly coupled to sodium, interference with carbonic anhydrase activity partially blunts sodium reabsorption in this segment. However, the more distal nephron segments have the capacity to increase reabsorption of salt when faced with a greater load. Therefore, depression of proximal reabsorption of sodium may not be associated with a significant diuresis. Proximal tubular diuretics are most effective when used in conjunction with distally acting agents [38].

4.3.3. Loop of Henle diuretics

Furosemide and ethacrynic acid are the two most potent diuretic agents available at this time. It should be recalled that sodium reabsorption in the loop of Henle is dependent on active chloride reabsorption. The loop acting drugs owe their potency to their virtually complete inhibition of chloride transport in this segment [5]. Massive diuresis can result from the fact that approximately 20 to 25% of the filtered load of sodium is normally reabsorbed in the ascending limb of the loop of Henle. In addition, there is evidence that furosemide administration causes an intrarenal shift in blood flow toward the presumably less sodium-avid cortical nephrons. Part of the acute beneficial effect of furosemide on pulmonary edema may be explained by a veno-dilatory action causing a reduction in venous return and thereby relieving pulmonary congestion even before diuresis has occurred.

Because of their potency as diuretics, therapy with both furosemide and ethacrynic acid is more likely to result in some of the complications listed in Table 9. Ototoxicity has been especially associated with these drugs. Although usually reversible, there are reported cases of irreversible deafness associated with both agents, especially when administered to patients with renal insufficiency. Ethacrynic acid may be more dangerous in this respect; it is, however, the preferred agent for individuals with sulfonamide allergy.

4.3.4. Early distal tubular diuretics

Hydrochlorothiazide, chlorthalidon and ticrynafen are chemically distinct, but have a similar inhibitory action on active chloride transport in the cortical diluting segment of the nephron. Normally, net passive sodium reabsorption at this site is quantitatively less important than in the loop of Henle [26]. Hence, the complications of these agents are less frequent and generally less severe than from the loop-acting drugs.

Ticrynafen has the unique property of blocking tubular reabsorption of uric acid [42]. Hyperuricemia is a common side effect of both the loop-acting and early distal acting diuretics. Besides gout, there is some evidence that hyperuricemia may predispose to early cardiovascular disease. Hence, the plasma uric acid lowering property of this new agent may prove to be of great importance.

4.3.5. Potassium sparing diuretics

Both spironolactone and triamterene act on the late distal tubule and collecting duct to inhibit active sodium reabsorption and its dependent potassium secretion. Spironolactone has a direct antagonistic effect on

aldosterone action, whereas the mechanism of triamterene is less clear [26]. Because sodium reabsorption in this site represents only a small fraction of the total filtered load, these agents are not potent diuretics. Nevertheless, they may play a useful role in combination with more proximally acting diuretics, supplementing the diuretic effect and preventing hypokalemia.

4.3.6. Use of diuretics in non-edematous states

Diuretics are useful in a number of disorders (Table 8) in which there is no clinical evidence of sodium and fluid retention [31].

Table 8. Use of diuretics in nonedematous conditions

Hypertension
Diabetes insipidus
Proximal renal tubular acidosis
Hypercalciuria
Hypercalcemia
Hyponatremia
Halide intoxication
Salicylate and barbiturate intoxication
Hyperuricemia
Cystinuria

As discussed above, decreased effective arterial blood volume provides a potent stimulus for proximal reabsorption of fluid and electrolytes. The distal-acting thiazides cause a mild state of hypovolemia. This property can be employed in the management of several disorders including diabetes insipidus, proximal renal tubular acidosis and hypercalciuria. In each condition, the thiazide-induced hypovolemic state can stimulate the proximal tubule to increase reabsorption of sodium, water, bicarbonate or calcium respectively. Hypertension also often responds to diuretics even though clinical hypervolemia may not exist. Hypercalcemia may respond to the combination of isotonic fluids and loop acting diuretics. Life threatening hyponatremia may be treated with a combination of a loop diuretic and hypertonic saline. Loop diuretics can also be useful in the management of halide intoxication from fluoride, bromide or iodide.

The urine alkalinizing effect of acetazolamide has been utilized successfully to increase the excretion of salicylates and barbiturates. Alkalinization of the urine may also prevent the urolithiasis of hyperuricemia and cystinuria.

4.3.7. Complications of diuretic use

Volume depletion is the most common and often the most serious complication of diuretic therapy [26]. Further volume loss superimposed on the decreased effective blood volume that underlies most cases of edema, may cause cardiac output to fall, possibly resulting in shock or renal failure. Mechanisms of diuretic-induced hypokalemia and hyponatremia are discussed elsewhere in this chapter. Hyperchloremic acidosis is often seen with acetazolamide therapy and is a result of proximal bicarbonate wasting. Alkalosis is more frequently seen with loop or early distal-acting diuretics and is presumably secondary to a combination of volume, chloride and potassium deficiency. Hypercalcemia and hyperuricemia are most probably related to hypovolemia-induced tubular avidity for these substances. An increased rate of cardiovascular death has been associated with long-term thiazide treatment. This may be secondary in part to carbohydrate intolerance, hyperuricemia, or stimulation of the renin-angiotensin system. Carbohydrate intolerance itself is best explained by diuretic-induced potassium deficiency. The various hypersensitivity reactions have been most commonly associated with the sulfonimide derivatives. Acute renal failure may complicate diuretic therapy as a result of several factors, including volume depletion, interstitial nephritis, electrolyte disorders (hypokalemia, hypercalcemia and uric acid nephrolithiasis).

Table 9. Complications of diuretic use

Volume depletion
Hypokalemia
Hyperkalemia — potassium-sparring diuretics
Hyperchloremic acidosis — acetazolamide
Alkalosis
Hyponatremia
Hyperuricemia — *all* except *ticrynafen*
Hypercalcemia
Carbohydrate intolerance
Deafness — loop-acting diuretics
Hypersensitivity reactions — skin rash, thrombocytopenia, fever, interstitial nephritis, pancreatitis
Cardiovascular?
Acute Renal Failure

5. DISORDERS OF POTASSIUM METABOLISM

5.1. Internal potassium balance

Approximately 98% of total body potassium (about 50 mEq/kg) is located in the intracellular space. As listed in Table 10, a number of clinically important factors can influence the transcellular distribution of potassium. Alteration of extracellular pH causes hydrogen ion to move into or out of cells along its concentration gradient. The resultant change of transcellular potential difference leads to a flux of cationic potassium in the opposite direction [25].

The role of hormonal factors in the distribution of potassium remains to be fully clarified. Insulin enhances tissue uptake of potassium, independently of glucose. Furthermore, increase in potassium concentration within the physiological range stimulates insulin secretion. Insulin may play a key role in the adaptive response to acute potassium loads. Aldosterone acts primarily on the distal nephron. Nevertheless, this hormone may also play an important role in extrarenal adaptation to chronic potassium loads [9].

Sudden increases in extracellular osmolality cause a porportional outward shift of cellular water. Potassium also leaves the cell by a 'solvent drag' effect. Succinylcholine, which acts as a depolarizing agent, and cardiac glycosides by inhibition of Na-K dependent ATPase, may cause cellular egress of potassium.

Factors that increase cellular metabolic rate, or cause cellular breakdown, can result in massive efflux of potassium into the extracellular space without affecting total body potassium content [25].

5.2. External potassium balance

5.2.1. Intake

The average American diet contains approximately 60 to 100 mEq of potassium per day. In the hospitalized patient, intravenous solutions,

Table 10. Factors affecting transcellular distribution of potassium

Extracellular fluid pH
Endocrine factors
Insulin
Aldosterone
Extracellular fluid osmolality
Drugs – Succinylcholine, digitalis overdose, beta adrenergic inhibitors
Cellular metabolism – Fever, exercise, infection, hypoxemia
Cellular necrosis – Hemolysis, rhabdomyolysis, hematological malignancy

including potassium salts of drugs (such as penicillin G which contains 1.7 of potassium per 10^6 units) can also contribute significantly to the daily intake of this ion.

5.2.2. Output

5.2.2.1. Renal potassium handling. Since potassium freely permeates the glomerular barrier, approximately 600–900 mEq are filtered daily. This large filtered load is virtually completely reabsorbed by the proximal tubule and the ascending limb of the loop of Henle.

Urinary potassium is ultimately dependent on secretion by the distal tubule. Both potassium and hydrogen ion secretion are enhanced by the negative intraluminal electrical potential that is generated by active sodium reabsorption along this site [30].

There are several clinically important factors that affect the secretory function of the distal segment of the nephron. First, potassium secretion is proportional to the urine flow rate. Hence, oliguric states may impair potassium secretory capacity. Secondly, tubular secretion of potassium is directly related to intracellular levels of ths ion. Thus, factors that cause redistribution of potassium into the cellular space may also enhance renal excretion. Finally, electronegativity of the tubular lumen also directly influences potassium secretion. This potential can be amplified in several ways. Aldosterone and volume depletion stimulate sodium reabsorption in the distal nephron. Also, a large filtered load of poorly resorbable anions such as phosphate, sulfate, bicarbonate and citrate will result in greater negativity of intraluminal space [25].

5.2.2.2. Extrarenal output. Under normal circumstances, combined fecal and sweat losses of potassium are about 10 to 15 mEq per day. This may increase markedly in the presence of diarrhea or exfoliative dermatitis. Nasogastric suction may contribute an additional 5 to 10 mEq per liter to these losses.

5.3. Hyperkalemia

Table 11 presents a list of disorders that have been associated with elevated serum potassium concentrations.

5.3.1. Pseudohyperkalemia

Forearm exercise prior to blood drawing, can result in spuriously high serum potassium levels. In addition, serum from patients with marked thrombocytosis or leukocytosis may contain high levels of potassium.

Table 11. Conditions associated with hyperkalemia

a. Pseudohyperkalemia
Improper blood collection
Thrombocytosis, leukocytosis
b. Cellular efflux (normal body potassium)
Acidosis
Diabetes mellitus
Hypoaldosteronism
Hyperosmolar states
Drugs – Succinylcholine, digitalis overdose
Fever, exercise, infection, hypoxia
Hemolysis, rhabdomyolysis, hematological malignancy
c. Increased total body potassium
1. Exogenous load
Oral or I.V. potassium
Potassium containing drugs
Transfusion
Geophagia
2. Decreased renal excretion
Acute and chronic renal failure
Potassium sparing diuretics
Mineralocorticoid deficiency
Addison's disease
Selective hypoaldosteronism
Tubular unresponsiveness to aldosterone

This is presumed to result from release during in vitro clotting. Determination of plasma potassium should prevent this error [25].

5.3.2. Normal total body potassium (cellular efflux)
Clinical states leading to hyperkalemia in the setting of normal body potassium stores are outlined in section 4.1.

5.3.3. Increased total body potassium
5.3.3.1. Exogenous potassium load. Human adaptive responses to exogenous loads of potassium are such that intake by itself would be a rare cause of hyperkalemia. However, in the presence of disordered renal function, oral or intravenous solutions and potassium-containing drugs may contribute importantly to hyperkalemia. There are also a number of reported cases of hyperkalemia induced by stored-blood transfusion, as well as clay ingestion (geophagia).

5.3.3.2. Impaired renal potassium excretion. In view of the importance of renal mechanisms in the homeostatic control of serum potassium, it is remarkable that serious hyperkalemia is not present in all or even most patients with renal failure.

In chronic renal insufficiency, a number of adaptive responses can occur. These might include a relatively greater single nephron glomerular filtration rate with resultant rapid tubular flow rate in addition to increased distal delivery of sodium and nonresorbable anions, all of which might lead to enhanced single nephron potassium secretory capacity. Also, there is evidence for increased distal tubular and intestinal epithelial Na-K dependent ATPase activity that may further contribute to improved transport and secretion at these sites. Therefore, life threatening hyperkalemic episodes are unlikely to occur in renal failure unless one or more of the following is present: severe oliguria, large exogenous or endogenous potassium loads, systemic acidosis, plasma volume depletion [25], shock or hypoxemia [19].

5.3.4. Clinical consequences of hyperkalemia

The most serious effects of hyperkalemia probably result from reduction (less negative) of the resting transmembrane potential of skeletal and cardiac muscle. This change slows conductivity (a function of the total amplitude of the action potential) and simultaneously increases excitability (inversely related to the difference between the resting membrane potential and the threshold potential). These cellular events are manifested in part by muscle weakness or paralysis. Mortality in hyperkalemic patients is usually due to heart block or ventricular arrhythmias.

The electrocardiographic changes begin with peaking of the T wave at serum potassium levels of 5.5 mEq/l. As serum potassium exceeds 6.5 mEq/l, slowed intraventricular conduction results in widening of the QRS complex and above 7.0 mEq/l, P waves may be lost [11].

Serum potassium levels less than 6.5 mEq/l, in the absence of significant electrocardiographic changes, may respond well to simple potassium restriction and liberalization of sodium intake. If the serum potassium is greater than 6.5 mEq/l, or the above measures fail, then a cation exchange resin such as sodium polystyrene sulfonate (Kayexalate®) 15 to 20 grams orally, three or four times daily in water or 70% sorbitol, may be used.

Major electrocardiographic changes almost always accompany serum potassium levels greater than 7.0 mEq/l. These changes in cardiac conductivity constitute a medical emergency regardless of the precise serum potassium level. Treatment should be initiated with one to three ampules of 10% calcium gluconate, infused intravenously over three to five minutes for each ampule, during constant electrocardiographic monitoring. Calcium acts rapidly by raising (makes less negative) the threshold potential, thereby decreasing excitability. Sodium bicarbonate causes

a rapid intracellular shift in potassium and can be administered either as a bolus or by drip infusion, depending on the urgency of the situation. Insulin, 10 units, plus 50 gms of glucose, either in bolus form (50 ml of 50% glucose) or by infusion of a 10% glucose solution, will also drive potassium into the cellular space. The onset of action of glucose and insulin is somewhat slower than $NaHCO_3$, but may last for several hours [25].

Since these measures are only temporarily useful, it may be necessary to initiate or intensify a hemodialysis or peritoneal dialysis regimen to reduce the total body load of potassium.

5.4. Hypokalemia

Clinical disorders associated with hypokalemia are classified in Table 12.

Table 12. Disorders associated with hypokalemia

- a. Normal body stores
  - Alkalosis
  - Insulin therapy
  - Periodic paralysis
- b. Depletion of total body potassium stores
  1. Gastrointestinal losses
     - Vomiting
     - Nasogastric suctioning
     - Diarrhea
     - Villous adenoma
     - Laxative abuse
  2. Renal losses
     - Diuretics
     - Metabolic alkalosis
     - Ureterosigmoidostomy
     - Antibiotics: Carbenicillin, amphotericin, gentamicin
     - Diabetic ketoacidosis
     - Acute leukemia
     - Mineralocorticoid excess
       - Low plasma renin activity
         - Primary hyperaldosteronism
         - Cushing's syndrome
         - Adrenogenital syndromes
         - Licorice excess
       - High plasma renin activity
         - Accelerated hypertension
         - Renal vascular hypertension
         - Renin-producing tumor
         - Bartter's syndrome

5.4.1. Normal total body potassium (cellular shift)
As previously discussed, a rise in extracellular pH results in hypokalemia acutely by causing an inward flux of potassium in exchange for outward-moving hydrogen ion. It should also be emphasized that alkalosis also causes increased urinary losses of potassium. This is probably on the basis of higher intracellular levels available for secretion by the renal tubular epithelium.

Periodic paralysis is a familial and sporadic disorder associated with episodes of paresis and hypokalemia. Curiously, these spells are best prevented by the daily administration of Acetazolamide 375 to 500 mg per day [25].

5.4.2. Depletion of body potassium stores
5.4.2.1. Gastrointestinal losses. Vomiting and nasogastric suctioning are among the most common causes of hypokalemia. This is unlikely to result entirely from the loss of potassium in the enteric fluid. The potassium concentration of gastric and small bowel secretions is rarely greater than 5 to 10 mEq/l. Hypokalemia in this setting is primarily related to the associated alkalosis, causing both intracellular shifts and increased renal epithelial secretion of potassium.

On the other hand, diarrheal fluid often contains potassium levels of 50 to 100 mEq/l. Thus, it is possible to develop diarrhea-induced hypokalemia even in the presence of accompanying acidosis. Hypokalemia may be particularly severe in patients with villous adenoma or those with laxative abuse.

5.4.2.2. Renal losses. Diuretics remain the most common cause of hypokalemia. Potassium secretion is enhanced by increased flow rate along the distal tubule. Also, increased sodium presentation to this site amplifies luminal electronegativity, thereby promoting further potassium secretion. Finally, potassium reabsorption in the ascending limb is indirectly inhibited by the action of the loop acting diuretics (furosemide and ethacrynic acid) [25].

Hypokalemia is frequently seen in both the proximal and distal forms of renal tubular acidosis (RTA). In the former type, impaired proximal resorption of bicarbonate results in flooding of the distal nephron with this poorly resorbable anion. The resultant increase in luminal electronegativity enhances potassium secretion. In the distal form of RTA, renal potassium loss may arise from a reduction in distal tubular Na^+–H^+ exchange due to a limitation in the hydrogen ion gradient that can be achieved [25].

Hypokalemia has been repeatedly observed in patients receiving certain antibiotics. Carbenicillin probably acts as a poorly resorbable anion, whereas gentamicin and amphotericin are direct tubular toxins. In acute leukemias, there is evidence that lysozyme released by myeloid cells may cause renal tubular dysfunction; but this issue remains unresolved.

Hypermineralocorticoidism leads to hypokalemia by its direct stimulating effect on the distal tubular sodium reabsorption-potassium secretory mechanism. The primary forms are distinguished by suppressed plasma renin activity resulting from increased salt retention. In the secondary forms, excessive renin release with formation of Angiotensin II acts to stimulate adrenal production and release of aldosterone. The precise mechanisms of renin release in these disorders is still a matter of active investigation [3].

5.4.3. Clinical consequences of potassium depletion

The most serious effects of potassium depletion are on the myocardium and the neuromuscular system. Cardiac abnormalities include ventricular and atrial irritability, A-V conduction abnormalities and predisposition to digitalis toxicity. Electrocardiographic changes begin with depression of the S–T segment and the amplitude of the T wave. Subsequently, a U wave may be seen. With severe hypokalemeia, the amplitude of both the P wave and QRS complex may increase [25].

Neuromuscular alterations may be dramatic with profound weakness of skeletal and smooth muscle that can lead to quadrapligia, respiratory paralysis and ileus. In addition, rhabdomyolysis leading to myoglobinuria may ensue [7].

Hypokalemia may also result in renal dysfunction, with a concentrating defect and impaired glomerular filtration rate. Potassium depletion also interferes with normal insulin release leading to glucose intolerance. Finally, metabolic alkalosis may be worsened by potassium deficits in part because of transcellular shifts of hydrogen ion and increased proximal tubular bicarbonate reabsorption [1].

5.4.4. Management of hypokalemia

Unfortunately, because only 2% of body potassium is extracellular, serum potassium levels can only provide a crude index of the magnitude of body potassium deficits. As noted earlier, a number of factors, especially pH, affect the transcellular distribution of potassium. A patient with metabolic acidosis and a serum potassium of 2 mEq/l may have a potassium deficit in excess of 1000 mEq. However, in the pre-

sence of alkalosis, the corresponding deficit would be considerably less.

Modest degrees of potassium depletion can generally be corrected with oral supplements. This is most conveniently given in the form of KCl elixir or the newer tablet Slo–K®. The chloride salt is generally the preferred form since chloride deficiency is commonly associated with hypokalemia. Non-chloride salts of potassium, such as bicarbonate or gluconate, should be used in patients with renal tubular acidosis or with other forms of hyperchloremic acidosis.

Patients with serious neuromuscular or cardiac alterations of hypokalemia, or who cannot take potassium by mouth, should be treated intravenously. Depending on the urgency of the clinical situation, potassium can be given up to a rate of 10 mEq/l per hour. More rapid replacement should be given only with appropriate electrocardiographic monitoring.

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3. ACID-BASE DISTURBANCES

KURT H. STENZEL

1. INTRODUCTION

The pH of body fluids is maintained within narrow limits by physiologic buffers, by respiratory regulation of pCO_2, and by renal control of H^+ excretion. The pH is defined as the negative logarithm of the hydrogen ion concentration and is related to hydrogen ion concentration as shown in Table 1.

Table 1. Relationship between pH and $[H^+]$

pH	$[H^+]$(nEq/l)
6.90	120
7.00	100
7.05	90
7.10	80
7.15	70
7.22	60
7.30	50
7.40	40
7.52	30
7.70	20
8.00	10

1.1. Physiologic buffers

Buffering occurs in all body fluids, both extracellular and intracellular. The major buffer systems are bicarbonate-carbonic acid, phosphate, tissue proteins (including bone) and hemoglobin. The major extracellular buffer is $NaHCO_3$. The pH of blood is a function of the equilibrium between $[HCO_3^-]$ and $[H_2CO_3]$. This buffer is unique in that its acid is volatile and can be removed via respiration.

$$H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons H_2O + CO_2 \uparrow$$

Normally, the ratio of bicarbonate [HCO_3^-] to carbonic acid [H_2CO_3] is 20/1. pH is related to the ratios of these components by the following (Henderson-Hasselbalch) equation:

$$pH = 6.1 + \log \frac{[HCO_3^-]}{[H_2CO_3] + [CO_2]}.$$

HCO_3^- or total CO_2 combining power measurements are readily available in most clinical laboratories and can be used as the numerator of this equation. Carbonic acid measurements are not generally available, but [H_2CO_3] is related to pCO_2 so that the equation may be rewritten:

$$pH = 6.1 + \log \frac{[HCO_3^-]\text{(Metabolic)}}{.03\ pCO_2\ \text{(Respiratory)}}$$

In terms of [H^+] the relationship becomes:

$$[H^+]\text{(nEq/l)} = 24 \frac{pCO_2}{[HCO_3^-]}$$

Thus, given any two of the three unknowns in these equations the third can be calculated. In serious acid-base disorders, however, all three should be measured directly and their accuracy checked by fitting them into the Henderson-Hasselbalch equation. It is clear from these considerations that pH depends on the ratio of [HCO_3^-] to [H_2CO_3] or pCO_2 rather than their absolute values. With alterations in [HCO_3^-] or pCO_2, various compensatory mechanisms occur that tend to restore their ratio to 20/1. The numerator of the Henderson-Hasselbalch equation is termed the metabolic component, since it is metabolically controlled, and the denominator the respiratory component, since it is controlled by respiration.

1.2. Respiratory control of pH

Respiratory rate is sensitive to changes in [H^+]. Decreases in pH stimulate respiration, pCO_2 drops, and the ratio of [HCO_3^-]/.03 pCO_2 tends toward normal. Increases in pH have the opposite effect.

1.3. Renal control of H^+ excretion

Normal metabolic processes result in the production of approximately 1 mEq of acid/kg of body weight per day. The kidneys have the ultimate task of ridding the body of this excess acid. HCO_3^- is freely filtered at the glomerulus and at normal plasma levels is completely reclaimed. There is a bicarbonate threshold, however, and HCO_3^-

appears in the urine when blood levels exceed 28 mM/l. Excess H^+ is excreted by buffering various bases, especially Na_2HPO_4.

$$Na_2HPO_4 + H^+ \leftrightharpoons Na^+ + NaH_2PO_4$$

H^+ excreted in this manner is termed titratable acidity. Net loss of H^+ is also accomplished by renal production of NH_3 from glutamine. NH_3 combines with H^+ in the tubular lumen to form NH_4^+, an ion that is impermeable to the tubular epithelium.

1.4. Clinical definitions

Acidemia or alkalemia refer to actual changes in blood pH or $[H^+]$ whereas acidosis and alkalosis refer to those physiologic processes that tend to alter pH. A metabolic acid-base disturbance is one that is initiated by a primary change in $[HCO_3^-]$, whereas a respiratory disturbance is one initiated by a primary alteration in pCO_2. Respiratory disturbances can occur in acute or chronic form. Acid-base disorders may be simple, that is consisting of only one of the four possible disturbances (see Table 2), or mixed, consisting of the superimposition of several of these processes in the same patient. Mixed disorders are quite common in many serious clinical conditions. Compensatory mechanisms are those biochemical or physiological processes that tend to restore the ratio of $[HCO_3^-]/.03\ pCO_2$ towards 20/1 and thus tend to return the pH toward normal. The types and kinetics of compensatory mechanisms include: extracellular buffering (instantaneous), respiratory control of pCO_2 (minutes), diffusion into cells and intramuscular buffering (several hours) and finally renal control of $[H^+]$ (hours to days).

Table 2. Simple acid-base disorders.

	pH	HCO_3^-	pCO_2
Metabolic Acidosis	↓	↓ (primary)	↓ (compensatory)
Respiratory Acidosis	↓	↑ (compensatory)	↑ (primary)
Metabolic Alkalosis	↑	↑ (primary)	↑ (compensatory)
Respiratory Alkalosis	↑	↓ (compensatory)	↓ (primary)

1.5. Diagnostic approach

It is important to approach acid-base problems with the same thoroughness that is applied to other diagnostic problems in clinical medicine and not rely on laboratory data alone. A systematic approach is manda-

tory, with the background knowledge of the kinds of acid-base disturbances often associated with particular clinical conditions. The history must be carefully analyzed to evaluate processes that could potentially result in acid-base problems, such as a history of diabetes, renal, hepatic, or pulmonary disease, gastro-intestinal abnormalities, and so on. The physical examination often yields information useful to the analysis of acid-base problems. Is the patient on a respirator? Is he losing enteric fluids? Are there physical signs of diabetes, renal, pulmonary or hepatic disease? Are there signs of acute intoxication? The laboratory data is, of course, critical in the analysis, and most importantly initially are the CO_2 combining power (or HCO_3^-), the level of undetermined anions (see below) and the K^+. Other laboratory data should be scanned for clues to acid-base disorders (eg blood sugar, BUN, bilirubin, transaminase). If a significant acid-base problem is suspected, arterial blood gases and pH should be obtained. Urine pH and urinary electrolytes may also be necessary. Finally, the data must be explained. Only through this kind of synthesis can a rational strategy for therapy be developed. Nomograms are in common use to analyze these problems, but they sometimes prevent the clinician from thinking clearly about the problem at hand. Nomograms simply define the predictable pH changes in *normal* individuals for given changes in $[HCO_3^-]$ and pCO_2. The ability to compensate for an acid-base disturbance can, of course, be severely altered by associated clinical problems especially those involving the lungs and kidneys.

2. METABOLIC ACIDOSIS

Metabolic acidosis is initiated by a primary decrease in $[HCO_3^-]$ without an adequate compensatory decrease in pCO_2. It may be caused by either a loss of $[HCO_3^-]$ (renal or extrarenal) or a gain in acid (endogenous or exogenous). It is characterized biochemically be a decrease in plasma pH, a decrease in plasma $[HCO_3^-]$ (or CO_2 content) and a decrease in pCO_2 (see Table 2). Serum K^+ is often, but not always, elevated secondary to shifts from the intracellular to the extracellular space. This probably occurs as an exchange of intracellular K^+ for extracellular H^+, which is then buffered by intracellular proteins. Cl^- may be increased or normal, and this is an important diagnostic aid (see below under anion gap). The compensatory mechanisms that modify changes in pH in metabolic acidosis are primarily respiratory. Each 1.0 mEq/l decrease in $[HCO_3^-]$ leads to approximately a 1.0–1.3 mm Hg decrease in pCO_2.

Finally, resolution of the acidosis depends on renal excretion of excess H^+ and regeneration of HCO_3^-. In renal failure this function is served by dialysis. Mild metabolic acidosis may be symptomless, but as the $[HCO_3^-]$ falls below 15–18 mEq/l patients may complain of weakness, malaise, headache, nausea, abdominal pain and vomiting. Respirations become deep and usually more rapid (Kussmaul breathing) as the HCO_3^- and pH decrease further. The pH is generally <7.2 when this sign appears. Restlessness and mild to moderate confusion may be apparent and vasodilation may occur. Severity of the symptoms depends on both the acuteness of their development as well as the absolute biochemical changes. Often the clinical picture is dominated by the cause of the acidosis.

Causes of metabolic acidosis can be conveniently grouped into two major categories. In one, the acidosis is primarily secondary to retention of the anion of a non-volatile endogenous or exogenous acid. This anion is generally not measured in the usual electrolytes, and thus there is an anion gap. The second category is related to a loss of HCO_3^- or to a gain of a Cl^- containing acid, thus leading to an increase in serum Cl^-, and a hyperchloremic or normal anion gap acidosis. Thus, the anion gap is an important concept in the differential diagnosis among the various causes of metabolic acidosis.

2.1. Anion gap

Figure 1A illustrates the acid-base composition of normal blood plasma. In analyzing an acid-base problem in terms of anion gap, usually only Na^+, Cl^- and HCO_3^- are considered, and the anion gap is defined as the difference between these cationic and anionic components:

$$\text{Anion gap} = [Na^+] - ([Cl^-] + [HCO_3^-])$$

In reality, of course, the electrical neutrality of blood is maintained and there is no anion gap. The unmeasured anions and cations are indicated in Table 3. Thus the difference in the unmeasured anions (23 mEq/l) and the unmeasured cations (11 mEq/l) accounts for the normal anion gap (23–11 = 12 mEq/l). When other unmeasured anions (such as $SO_4^=$, $PO_4^=$, organic acids, lactate or ketone bodies) accumulate, the normal gap is increased (see Figure 1).

An increased anion gap, once laboratory error has been excluded, might theoretically also be caused by a decrease in unmeasured cations (K^+, Ca^{++}, Mg^{++}). It would be unusual, however, in clinical condi-

Table 3. Anion gap.

Unmeasured cations			*Unmeasured anions*	
K^+	4.5 mEq/l		Protein	15 mEq/l
Ca^{++}	5.0 mEq/l		PO_4^-, SO_4^-	3 mEq/l
Mg^{++}	1.5 mEq/l		Organic acids	5 mEq/l
Total	11.0 mEq/l	(Anion Gap 23-11 = 12)		23 mEq/l
Measured cations			*Measured anions*	
$+Na^+$	140.0 mEq/l		$+Cl^-$	103 mEq/l
			$+HCO_3^-$	25 mEq/l
Grand total	151.0 mEq/l			151 mEq/l

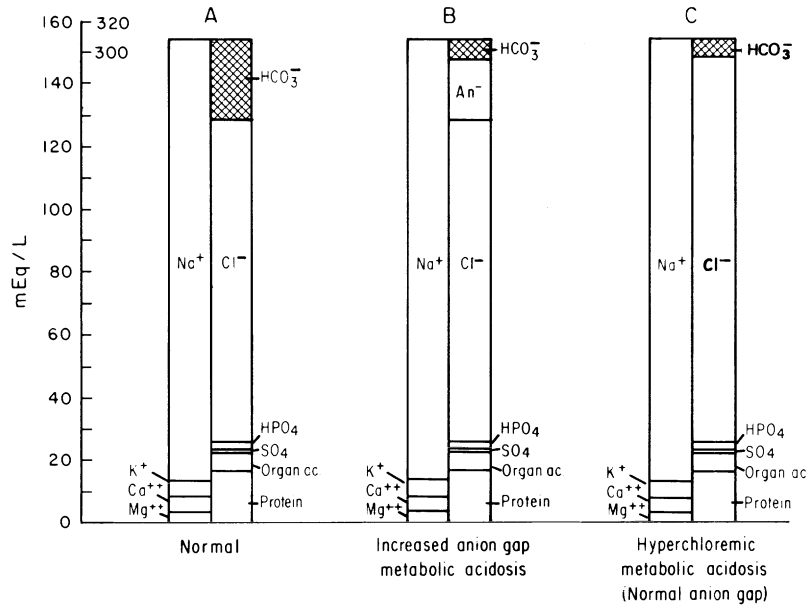

Fig. 1. Electrolyte alterations in acidosis.

tions to have all of these cations depressed enough to result in a significant anion gap.

A decreased anion gap (less than 8 mEq/l) can also occasionally occur. This may be caused by an increase in unmeasured cations, a decrease in unmeasured anions or a random or systematic error in measurement. An increase in unmeasured cations may result from increases in the normal cations (K^+, Ca^{++}, Mg^{++}) or from retention of abnormal

cations. Gamma globulin is a cationic protein, and large increases as might occur in multiple myeloma can result in a decreased anion gap. Similarly, accumulations of lithium or tromethamine (THAM) can occur. A decrease in unmeasured anions could occur in severe hypoalbuminemia. Systematic errors in measurement can account for extremes in decreased anion gap and even a negative anion gap. Br^- and I^- are both measured as Cl^- in most clinical laboratories. There is a fairly linear relationship between increases in Br^- and measured increases in Cl^- in mEq/l. In the case of I^-, however, 1 mEq/l of I^- may be measured as several mEq/l Cl^-, thus accounting for extremely high reports of Cl^- levels.

Clinically, the anion gap in its simple form $[Na^+]-([Cl^-]+[HCO^-])$, is used to differentiate among various causes of metabolic acidosis.

2.2. Metabolic acidosis with an increased anion gap

Metabolic acidosis accompanied by an increased anion gap occurs when anions of acids that titrate HCO_3^- are retained.

For example: $H^+Lac^- + Na^+HCO_3^- \leftrightharpoons Na^+Lac^- + H_2CO_3$
(Lactic acid) $H_2O + CO_2$

It should be noted that acidosis results from depletion of HCO_3^- and not retention of the anion. Table 4 lists common causes of metabolic acidosis associated with an increased anion gap (normochloremic).

Table 4. Metabolic acidosis with increased anion gap (>12 mEq/l) – (Normochloremic)

Uremia
Diabetic ketoacidosis
Ketoacidosis with alcoholism or starvation
Lactic acidosis
Toxins: Salicylate
Methanol
Paraldehyde
Ethylene glycol

2.2.1. Renal failure

Increased anion gap acidosis may occur either in acute or chronic renal failure. In acute renal failure it may be severe, occur rapidly and be associated with significant hyperkalemia. Acidosis in chronic renal fai-

lure is usually better tolerated and often moderate and not progressive. Acidosis in chronic renal failure is apparently related to an inability to excrete the normal metabolic acid load, and retention of $PO_4^=$, $SO_4^=$ and organic acids, leading to an increased anion gap. However, in less severe renal failure, hyperchloremic acidosis may also occur. This may be due to a decreased HCO_3^- reabsorption (and a HCO_3^- leak at normal plasma HCO_3^- concentrations), a decrease in NH_3 production, and finally a hyporeninemic state (see below). It is a common clinical impression that hyperchloremic acidosis in renal failure is more commonly associated with interstitial diseases of the kidney. Laboratory data in uremic acidosis reveal a depressed HCO_3^- and pCO_2, a normal or increased Cl^-, usually an elevated K^+ and a creatinine usually >4.0 mg% and BUN >40 mg%.

2.2.2. Lactic acidosis

Lactic acidosis is recognized with increasing frequency as a major cause of acidosis in patients with a variety of life threatening illnesses. It is often accompanied by other acid-base disorders and thus presents as a mixed disorder. Some clinical conditions associated with lactic acidosis are listed in Table 5.

Table 5. Lactic acidosis.

Tissue Hypoxia
Ingestion of drugs and toxins
ethanol, methanol, phenformin and other biguanides, salicylates, fructose, sorbitol, catecholamines
Miscellaneous
neoplasia, hepatic failure, diabetes, sepsis, rare congenital metabolic defects

Lactate is formed from the reduction of pyruvate with $NADH_2$ and converted back to pyruvate by oxidation with the oxidized form of the dinucleotide NAD^+. The reaction is catalyzed by lactic dehydrogenase. The amount of lactate formed is thus a function of the ratio of $NADH_2/NAD^+$ and the pyruvate concentration. The ratio of $NADH_2/NAD^+$ is related to the oxidation-reduction state of the cytosol, and the availability of NAD^+ is impaired in states of tissue hypoxia. As noted above, H^+ formed with accumulation of Lac^-H^+ is titrated with HCO_3^- and other buffer systems. The magnitude of the accumulation of H^+ may be much greater than the ability of the kidney to regenerate bicarbonate, without the concomitent consumption of lactate and regeneration of HCO_3^- by the liver.

The diagnosis of lactic acidosis should be considered in patients with metabolic acidosis and a large anion gap in the absence of uremia or ketonemia, and it should be confirmed by blood lactate determinations. Resting lactate levels are normally less than 2 mM/1, and levels above 4 mM/1 denote severe abnormalities in lactate metabolism. Some plasma amino acids are often elevated in lactic acidosis, including alanine, proline, valine, lysine and leucine. Serum PO_4^- and urate are also frequently elevated.

In addition to tissue hypoxia, drugs, hepatic failure, neoplasia and diabetes, a variety of congenital defects in hepatic gluconeogenesis may result in increased blood lactate. These are usually discovered in childhood and associated with severe hepatic and neurological defects that preclude survival to adult life. The abnormalities so far delineated include defects in gluconeogenesis (deficiencies in glucose-6-phosphatase — Type I glycogen storage disease, in fructose 1,6-diphosphatase, and in pyruvate carboxylase) and in the oxidation of pyruvate (deficiencies in pyruvate dehydrogenase and in oxidative phosphorylation).

The therapy of lactic acidosis must be directed at the underlying or precipitating cause. Correction of shock and sepsis are obvious needs. When lactic acidosis occurs in low cardiac output states associated with normal or elevated pulmonary wedge pressures, reduction of afterload with vasodilators may improve tissue perfusion and acidosis. Acidemia requires bicarbonate therapy and large amounts may be required. (see below – therapy of metabolic acidosis.)

2.2.3. Ketoacidosis

Diabetic ketoacidosis can be recognized by a high anion gap acidosis in a diabetic patient with a positive plasma nitroprusside test. It can also be associated with lactic acidosis and an accumulation of β-hydroxybutyric acid. In this case, plasma will give a negative nitroprusside test, since nitroprusside does not react with β-hydroxybutyric acid, but rather with acetoacetic acid. Although the need for HCO_3^- therapy has been questioned in diabetic ketoacidosis, patients with severe acidemia ($pH < 7.15$) and severe depletion of HCO_3^- reserves (≤ 8 mEq/l) should probably be given the benefit of alkali therapy. Nausea, vomiting, myocardial depression, hypotension and increased lactate production may all be corrected by improving acidemia.

Ketoacidosis may also occur in alcoholic patients with liver disease and during starvation. Again, if associated with a decreased oxidation potential, the serum nitroprusside test may be negative due to the preferential accumulation of β-hydroxybutyric acid.

2.2.4. Toxins

Salicylate poisoning results in a complex acid-base problem. Initially, there is a stage of respiratory alkalosis with marked hyperventilation. Metabolic acidosis then supervenes and may be associated with hyperpyrexia, hypothrombinemia, thrombocytopenia, convulsions, coma and acute renal failure.

Methanol poisoning is associated with the accumulation of formic as well as lactic acid, and the development of severe acidosis. Associated symptoms include vertigo, headache, impaired vision, cyanosis, restlessness, coma and convulsions. Hemodialysis should be considered early in patients with methanol intoxication since blindness may be prevented by prompt removal of the toxin. Indications include ingestion of 30 ml or more of methanol, blood methanol level of ≥ 100 mg%, severe acidosis and impaired vision. Peritoneal dialysis is not as effective as hemodialysis.

The mechanism of development of paraldehyde acidosis is not clear, but is probably related to acid metabolic products of paraldehyde. In the absence of acute renal failure, treatment of the acidosis can usually be successfully accomplished with alkali therapy.

Ethylene glycol, a component of anti-freeze, is metabolized to oxalic acid and various aldehydes, and frequently results in acute renal failure. Hemodialysis may prevent acute renal failure by removing both ethylene glycol and oxalate.

2.3. Metabolic acidosis associated with a normal anion gap (hyperchloremic)

Metabolic acidosis associated with a normal anion gap occurs primarily when there is a loss of HCO_3^- (as in diarrhea or renal tubular acidosis — RTA) or a gain of Cl^- containing acid (such as HCl, NH_4Cl, arginine HCl or lysine HCl) (Figure 1C). Occasionally, hyperchloremic acidosis occurs with the gain of an acid with an anion other than Cl^-, if the anion is rapidly cleared by the kidney (ie, ketone bodies in diabetic ketoacidosis). Dilution of body fluids by intravenous administration of HCO_3^- free solutions may lead to a dilutional hyperchloremic acidosis, especially in infants or when renal acidification is impaired. Table 6 lists some of the common causes of hyperchloremic metabolic acidosis.

2.3.1. Extrarenal losses of HCO_3^-

The concentration of HCO_3^- in bile is approximately 38 mEq/l, in pancreatic juice 110 mEq/l and in small bowel secretions 30 mEq/l.

Table 6. Metabolic acidosis with a normal anion gap – (Hyperchloremic)

Extrarenal Loss of HCO_3^-
Diarrhea
Pancreatic, biliary or small bowel drainage
Ureterosigmoidostomies or Ileal conduits
$CaCl_2$, cholestyramine
Renal Acidosis
Distal
Proximal
Mineralocorticoid Deficiency
Primary or Secondary
Renal failure
Gain of Cl^- Containing Acid
NH_2Cl, HCl, arginine or lysine HCl, hyperalimentation
Dilutional

Thus, significant losses of HCO_3^-, as well as of water, Na^+ and K^+ can occur with diarrhea or surgical drainage of biliary, pancreatic or small bowel secretions. Metabolic acidosis in these situations is often complicated by dehydration and hypo, rather than hyperkalemia. Careful attention to replacement of electrolytes, especially K^+, must be given when HCO_3^- is administered, since with correction of acidosis, K^+ may decrease further.

Uretero-sigmoidostomies are no longer commonly created. They lead to a hyperchloremic acidosis secondary to reabsorption of Cl^- in the sigmoid in exchange for HCO_3^-, and loss of HCO_3^- in the stool. They are often complicated by the development of interstitial nephritis. Ileal conduits for urinary diversion are better tolerated and because of the relatively small surface area, do not usually result in hyperchloremic acidosis. Infection is also minimal. However, if the conduit is excessively large, hyperchloremic acidosis develops by a mechanism similar to that occurring in patients with uretero-sigmoidostomies.

Oral administration of substances that bind HCO_3^- in exchange for Cl^- also may lead to hyperchloremic acidosis. $CaCl_2$ has been implicated in this process as follows:

$$CaCl_2 + 2NaHCO_3 \rightleftharpoons CaCO_3 + CO_2 + H_2O$$

Cholestyramine might also exchange Cl^- for HCO_3^- and has been reported to cause hyperchloremic acidosis in patients with renal insufficiency.

2.3.2. Renal acidosis

Acid-base ballance is maintained by the kidney by reclaiming virtually all filtered HCO_3^- (5,000 mEq/24 hr) and excreting a net acid load as titratable acid and NH_4^+ to eliminate acid produced by metabolism (70 mEq/24 hr). HCO_3^- reabsorption or regeneration is thought to depend on a H^+ secretory process. 85% of HCO_3^- is reabsorbed or regenerated in the proximal tubule and the remainder in the distal. Tubular diseases that decrease the net secretion of H^+ (either reabsorption of HCO_3^- or decreased production of titratable acid and NH_4^+) at normal plasma [HCO_3^-] result in hyperchloremic acidosis.

Renal tubular acidosis (RTA) can conveniently, although somewhat artificially, be grouped into four major categories. These are distal RTA, proximal RTA, mineralocortocoid deficiency and chronic renal insufficiency. Mineralocortocoid deficiency is often grouped with proximal defects, and metabolic acidosis of renal insufficiency is a complex function of loss of renal mass.

Distal (Type 1) RTA is characterized by an inappropriately high urinary pH even during severe metabolic acidosis. H^+ ion generation in the distal tubule is apparently impaired leading to an inability to excrete H^+ ion produced during metabolism. This in turn results in a positive H^+ ion ballance, and titration of body buffers to a new steady state characterized by a hyperchloremic acidosis. There is an incomplete form of this disorder that may not be apparent until the patient is challenged with an acid load. Distal RTA may be associated with bicarbonate wasting, and in such cases termed Type 3 RTA. Patients with distal, but not proximal, RTA are prone to hypercalciuria, nephrocalcinosis, nephrolithiasis and bone disease. Hypokalemia may be severe.

Proximal (Type 2) RTA is characterized by HCO_3^- wasting secondary to an inability to secret enough H^+ in the proximal tubule to regenerate and then reabsorb filtered HCO_3^- loads at normal plasma HCO_3^- levels. The increased HCO_3^- load delivered to the distal tubule overwhelms its ability to regenerate HCO_3^- and there is a net loss of HCO_3^-. As plasma levels decrease, the filtered load of HCO_3^- decreases to a point where all the filtered HCO_3^- can be regenerated. A new steady state then develops at a decreased plasma HCO_3^- level associated with a hyperchloremic acidosis. Patients with proximal RTA usually have associated defects in proximal tubular function such as glycosuria, uricosuria, phosphaturia and aminoaciduria.

Both types of RTA are associated with losses of salt and water, increased secretion of aldosterone and loss of K^+ in the urine, leading to hypokalemia. K^+ wasting in proximal RTA is proportional to the

degree of bicarbonaturia. Thus administration of HCO_3^-, since its proximal reabsorption is impaired, leads to an exacerbation of K^+ wasting in proximal RTA. HCO_3^- therapy and volume repletion in patients with distal RTA, on the other hand, usually normalizes serum K^+ by decreasing aldosterone production as well as by direct tubular effects on K^+ secretion.

Many clinical conditions may be associated with distal RTA (Table 7). The secondary causes are more prominent in the adult population and may be seen in various immunologic disorders characterized by hyperglobulinemia or round cell infiltration in the renal interstitium. Nephrocalcinosis can result from distal RTA, but distal RTA can also be caused by interstitial and functional changes secondary to increased levels of parathyroid hormone and consequent nephrocalcinosis. Drugs also affect acid secretion by the distal tubule, notably amphotericin B, lithium and toluene (a component of glue). Amphotericin B increases tubular epithilial permeability to H^+ and allows tubular H^+ to leak back into the peritubular blood. Lithium appears to impair generation of H^+ in the distal tubule. A variety of other conditions may also be associated with distal RTA (see Table 7).

Table 7. Clinical conditions associated with distal RTA.

1.	Primary Distal RTA Hereditary or Sporadic
2.	Secondary Distal RTA
	A. Immunologic Disorders hyperglobulinemias, cryoglobulinemias, Sjörgren's syndrome, biliary cirrhosis, SLE, transplanted kidneys
	B. Nephrocalcinosis (disorder of Ca^{++} metabolism) primary hyperparathyroidism, Vitamin D intoxication, hyperthyroidism
	C. Drugs amphotericin B, toluene, lithium
	D. Miscellaneous Sickle cell anemia, medullary sponge kidney, edema forming states (especially cirrhosis), hydronephrosis, Wilson's disease-copper toxicity

Proximal RTA is also associated with multiple clinical conditions (Table 8), many of them similar to conditions associated with distal RTA.

Treatment of distal RTA depends on the severity of presenting symptoms and biochemical values. Patients with severe K^+ depletion and muscle weakness present a medical emergency, since respiratory failure, worsening acidosis and death may rapidly occur. Parenteral K^+ must be given either before or along with HCO_3^- replacement. Chronic therapy

Table 8. Clinical conditions associated with proximal RTA.

1. Primary
   A. Unassociated with multiple dysfunction of proximal tubule (transient disorder in infancy, carbonic anhydrase deficiency)
   B. Associate with multiple defects of proximal tubular function (Fanconi syndrome)
      Inborn errors of metabolism (cystinosis, tyrosinosis, galactosemia, hereditary fructose intolerance)
2. Secondary (all associated with variable degrees of proximal tubular defects)
   A. Immunologic and Neoplastic Disorders (multiple myeloma, Sjögren's syndrome, transplanted kidneys)
   B. Drugs and toxins (lead, mercury, out-dated tetracycline, streptozotocin, 6-mercaptopurine)
   C. Disorders of calcium metabolism (hypervitamosis D, hyperparathyroidism)
   D. Miscellaneous
      Pyruvate carboxylase deficiency, nephrotic syndrome

requires daily HCO_3^- for the rest of the patient's life, usually in doses of 0.5–3.0 mEq/kg/day in divided doses, with some given as $KHCO_3$. Persistent Ca^{++} wasting and bone disease may require a Vitamin D preparation, but this is usually unnecessary. Proximal RTA may not require treatment in adults if the plasma HCO_3^- is greater than 18 mEq/l or if there is no bone disease. Children always require alkali since acidosis is related to growth retardation. At least half of the alkali given should be in the form of $KHCO_3^-$.

Mineralocorticoid deficiency leads to a diminished capacity for H^+ secretion, hence HCO_3^- regeneration in the distal tubule is impaired, and up to 15% of the filtered HCO_3^- may be lost (the amount normally regenerated in the distal tubule). Aldosterone deficiency also impairs NH_3 production, perhaps secondary to hyperkalemia. Mineralocorticoid deficiency may be either primary (Addison's Disease and adrenal enzyme defects) or secondary (usually to renal interstitial disease—hyporeninemic hypoaldosteronism).

Hyporeninemic hypoaldosteronism is being recognized with increasing frequency. The syndrome appears to be secondary to diminished renal secretion of renin leading to decreased angiotensin II production and decreased aldosterone secretion. Hypoaldosteronism leads to a decreased distal reabsorption of Na^+ and impaired ability to excrete K^+ and H^+. Thus metabolic acidosis with hyperkalemia results. Most, if not all, affected patients have some degree of renal insufficiency, often associated with diabetes mellitis or tubular interstitial diseases. This type of RTA differs from both distal and proximal RTA and has therefore been designated Type 4. Therapy with mineralocorticoid generally corrects hyperkalemia and acidosis. In hypertensive patients with fluid overload,

Table 9. Renal tubular acidosis.

	Type 1 (Distal)	Type 2 (Proximal)	Mineralocorticoid Deficiency (Hyporeninemic)	Renal Insufficiency
Acidemia	Present	Present	Present	Present
Bicarbonaturinia at normal plasma HCO_3^-	Approximately normal	Increased	Tends to be increased	Normal to increased
Titratable acid + NH_4^+ excretion at normal plasma HCO_3^-	Reduced	Reduced	Reduced	Reduced
Urinary pH during acidosis	Not appropriately decreased	Appropriately low	Appropriately low	Appropriately low
Bicarbonaturia at ↓ plasma HCO_3^-	Negligable	Negligable	Negligable	Negligable
Titratable acid + NH_4^+ excretion at ↓ plasma HCO_3^-	Subnormal	May be normal or reduced	May be normal or reduced	Reduced
Serum K^+	Normal or ↓ (severe depletion common)	Normal or ↓ (severe depletion rare)	↑	Normal or ↑
Aminoacidemia, uricosuria, glycosuria	Unusual	Common	Unusual	Unusual
Nephrocalinosis, renal calculi	Common	Rare	Rare	Rare
Urinary pH following acid load	>5.5	<5.5	Should not be done	Should not be done

however, such therapy may be hazardous. Furosemide in these situations has been reported to increase K^+ and H^+ secretion.

Rare syndromes of renal tubular resistance to mineralocorticoid have also been reported, leading to hyperkalemia and metabolic acidosis, but with elevated renin and aldosterone levels and hypovolemia.

Finally, renal insufficiency, in addition to producing an increased anion gap acidosis, may be associated with a hyperchloremic acidosis, with normal or elevated renin and aldosterone levels. This is characterized by tubular defects in HCO_3^- reabsorption and a diminished NH_3 production, secondary to loss of renal mass.

The features outlined in Table 9 can serve to differentiate among the various causes of RTA. Incomplete distal RTA can be diagnosed by changes in urinary pH following administration of NH_4Cl (Table 10). This test should not be done in patients with acidosis or with hepatic or renal failure. It may be helpful in some patients with unexplained radio-opaque nephrolithiasis.

Table 10. NH_4Cl test for urinary acidification.

1. NH_4Cl (capsule or liquid form) by mouth (0.1 Gm/kg) over 30–60 minutes
2. Hourly urine samples × 6 hrs in containers with mineral oil for pH
3. Serum electrolytes (blood drawn without stasis) before and 3 hrs after dose of NH_4Cl
4. Normal response: decrease in urine pH to 5.3 or less decrease in serum HCO_3^- 2–5 mEq/l
5. Major contraindications: Acidosis, liver disease, renal insufficiency

2.3.3. Metabolic acidosis secondary to administration of Cl^- containing acids

NH_4Cl or acidic salts of amino acids may all lead to hyperchloremic acidosis. Occasionally, this type of acidosis occurs in patients with diabetic ketoacidosis as noted above. As the ketone bodies are excreted in the urine the anion may be replaced by Cl^- leading to a hyperchloremic acidosis.

2.4. Treatment of metabolic acidosis

Since metabolic acidosis occurs in a wide variety of settings, treatment varies depending upon the underlying condition. Some aspects of treatment of particular kinds of metabolic acidosis have been indicated above. The basic process must always receive appropriate therapy. HCO_3^- deficits may be calculated assuming a volume of distribution

of HCO_3^- as 50% of body weight. In general, estimates based on a correction of plasma HCO_3^- to 15 mEq/l should be used. Calculation is as follows: HCO_3^- deficit (mEq/l) = (desired HCO_3^-) (50% of body weight) – (observed HCO_3^-) (50% body weight) = (desired HCO_3^- – observed HCO_3^-) (50% body weight). In severe acidosis ($HCO_3^- \leq 5$ mEq/l) the volume of distribution of HCO_3^- apparently increases and may be as much as 100% of body weight. Frequent HCO_3^-, K^+, pH and pCO_2 determinations are required to monitor therapy. Overcorrection should be avoided, since metabolic alkalosis could then be induced. Rapid correction may lead to worsening of encenphalopathy, but this should not delay replacement of HCO_3^- stores in life threatening acidosis.

3. METABOLIC ALKALOSIS

Metabolic alkalosis is initiated by a primary decrease in HCO_3^- without an adequate compensatory increase in pCO_2. It may be caused by either a loss of acid or a gain of base. The respiratory compensation for metabolic alkalosis (hypoventilation) is limited somewhat by the toxicity of CO_2, although high pCO_2 levels can occur in patients with severe metabolic alkalosis. Normally, for each mEq/l increase in HCO_3^- there is a 0.4–0.7 mm Hg increase in pCO_2. The increase in HCO_3^- leads to a reciprocal decrease in Cl^- and is usually associated with a decreased K^+. Thus serum electrolytes usually reveal a hypochloremic, hypokalemic alkalosis with increased plasma pH and pCO_2. Many of the dangers of metabolic alkalosis are related to hypokalemia. These include ileus, motor paralysis, cardiac arrythmias, decreased GFR and isosthenuria. Tetany can also occur secondary to an increased plasma pH or decreased ionized calcium.

Since there is a renal tubular maximum reabsorption for HCO_3^-, one might expect increased plasma HCO_3^- to be rapidly corrected by renal losses. Thus, persistance of metabolic alkalosis means that HCO_3^- reabsorption is increased. Since HCO_3^- reabsorption is catalyzed by H^+ secretion and H^+ secretion is associated with Na^+ reabsorption, both H^+ secretion and Na^+ reabsorption are increased. The increased Na^+–H^+ exchange and resultant increased generation of HCO_3^- may be due to either of two factors: 1) Cl^- depletion or 2) direct stimulation of the distal tubule to increase Na^+–H^+ exchange. Metabolic alkalosis can therefore be grouped into two major categories, those associated with a depletion of Cl^- and thus a decreased urinary [Cl^-] and those asso-

ciated with direct tubular stimulation of Na^+–H^+ exchange and are thus associated with a normal or high urinary [Cl^-]. The former generally respond to NaCl therapy and are called salt responsive, and the latter do not and are termed salt resistant forms (Table 11).

Table 11. Metabolic alkalosis.

Low urine Cl^- (<10 mEq/l) (Salt responsive)	High urine Cl^- (>10 mEq/l) (Salt resistant)
Loss of gastric juice	Excess mineralocorticoid
Post-hypercapneic	Aldosteronism
Diuretic therapy (after diuretic discontinued)	Cushing's syndrome
	Bartter's syndrome
	Severe K^+ deficiency
	Licorice (glycyrrhizic acid)
	Carbinoxolone

3.1. Metabolic alkalosis associated with low urinary Cl^-

The most common type of metabolic alkalosis is that associated with loss of gastric contents by vomiting or nasogastric suction. In this situation, the increase in HCO_3^- is associated with a loss of Cl^- as well as of salt and water. HCO_3^- excretion is thus limited by volume depletion and lack of Cl^-. Correction, therefore, depends on adequate replacement of volume and Cl^- deficits. Associated K^+ losses must also be replaced. Renal loss of Cl^- secondary to diuretic therapy may also lead to this type of alkalosis. Loss of salt and water have been reported to lead to contraction alkalosis.

Post hypercapneic metabolic alkalosis results from the sudden relief of chronic respiratory acidosis, without replacement of Cl^-. The compensatory change in chronic respiratory asidosis (the primary change is an increase in pCO_2) is an increase in plasma HCO_3^- and urinary loss of Cl^-. As the pCO_2 diminishes with treatment of the respiratory disease, bicarbonaturia cannot occur until Cl^- is replaced.

3.2. Metabolic alkalosis associated with normal or increased urinary Cl^-

Agents that directly increase Na^+–H^+ exchange in the distal tubule lead to an increased reabsorption of $NaHCO_3$. One of the major causes of this type of alkalosis is mineralocorticoid excess. Urinary excretion of K^+ is also an effect of mineralocorticoids, and the alkalosis is almost always associated with hypokalemia. Chronic K^+ depletion itself exacerbates metabolic alkalosis and can lead to decreased renal concentrat-

ing ability, increased thirst, polyuria and impaired reabsorption of Cl^-. In addition to increased mineralocorticoid, certain agents mimic the effect of these hormones on the renal tubule. These include a component of licorice (glycyrrhicic acid) and carbonoxolone. The increased Na^+ reabsortion results in expanded intravascular volume in these types of metabolic alkalosis.

Bartter's syndrome is an unusual disorder characterized by metabolic alkalosis, hypokalemia, hypovolemia, and a normal blood pressure with increased secretion of renin and aldosterone. The disorder usually becomes apparent in childhood and is associated wih abnormalities in neuromuscular, urinary and gastrointestinal systems, and often with mental retardation. The syndrome may be due to a primary defect in Cl^- reabsorption leading to chronic hypovolemia, stimulation of renin and aldosterone secretion, and hypokalemia and metabolic alkalosis secondary to increased mineralocorticoid. Pathologic changes include hyperplasia of the juxtalglomerular apparatus.

Severe K^+ deficiency itself can apparently cause metabolic alkalosis, largely because of associated depletion of Cl^-. K^+ deficiency results in a decreased intracellular pH and favors H^+ secretion by the renal tubule. It also results in enhanced NH_3 formation. The latter can cause hepatic encephalopathy in cirrhotic patients with even modest degrees of hypokalemia.

3.3 Treatment of metabolic alkalosis

Treatment of metabolic alkalosis should be directed toward both correcting the disturbance initiating the alkalosis and correcting alkalemia. Salt responsive metabolic alkalosis reponds to volume replacement with NaCl and correction of hypokalemia with KCl in patients with normal renal function. These measures are slow, however, and patients with severe alkalemia may need, in addition to NaCl and KCl, therapy with acidic solutions. Dilute HCl (.1 – .2 N) can be administered cautiously via a large central vein. NH_4Cl can also be used but may result in encephalopathy. Both arginine and lysine HCl are effective. The calculation of Cl^- requirements can be done by again assuming a volume of distribution for HCO_3^- of 50%. Thus mEq Cl^- required = desired decriment in $HCO_3^- \times 50\%$ of body weight. Metabolic alkalosis of the salt resistant variety is usually treated by correcting the underlying disorder. Alkalemia is usually not severe and can often be managed with KCl. NaCl is of no value in these conditions and may exacerbate hypokalemia.

4. RESPIRATORY ALKALOSIS

Respiratory alkalosis is initiated by a primary decrease in pCO_2. In the acute form [HCO_3^-] decreases secondary to buffering of tissue proteins. Chronically, respiratory alkalosis results in decreased renal H^+ secretion and decreased HCO_3^- reabsorption. This further decreases plasma [HCO_3^-] and tends to normalize pH. Conditions usually associated with respiratory alkalosis are indicated in Table 12. Treatment depends largely on correction of the underlying problem. Complications of respiratory alkalosis include hypoxia, lactic acidosis, severe depletion of HCO_3^- reserves, and finally metabolic acidosis may supervene. Overbreathing can also lead to pneumonia and the dry lung syndrome. Tetany, convulsions and coma can occur.

Table 12. Conditions associated with respiratory alkalosis.

Acute	Chronic
Pulmonary edema, mild	Hepatic insufficiency
Pulmonary emboli	CNS disease
Fever	Gram negative sepsis
Hysteria	
Salicylates	
Mechanical ventilation	

5. RESPIRATORY ACIDOSIS

Respiratory acidosis is initiated by a primary increase in pCO_2. In the acute form there is an abrupt elevation in pCO_2 with very slight increments in plasma [HCO_3^-]. Conditions associate with acute respiratory acidosis include airway obstruction, sedative overdosage, severe pulmonary edema and cardiac arrest. Chronic respiratory acidosis is compensated for by renal mechanisms. These include an increased secretion of H^+, stimulation of NH_3 formation, increased HCO_3^- reabsorption, and increased Cl^- excretion. K^+ is also usually lost. Thus, chronic respiratory acidosis results in a hypochloremic, hypokalemic acidosis. Chronic respiratory acidosis is usually associated with severe chronic obstructive pulmonary disease such as pulmonary fibrosis, emphysema, bronchiectasis, multiple pulmonary emboli, bronchial asthma, and in severe obesity where hypoventilation may occur as part of the Pickwickian syndrome. Treatment of respiratory acidosis is concerned mainly with correction of the respiratory disturbance and prevention of post-

hypercapneic metabolic alkalosis. The latter can be achieved by providing adequate amounts of KCl during correction of chronic respiratory acidosis.

6. MIXED ACID-BASE DISORDERS

Mixed acid-base disorders occur in many clinical situations and are perhaps even more common than the simple acid-base disorders. Use of a systematic approach outlined above usually provides the correct diagnosis of these mixtures. It must be recognized that in mixed disorders, a normal CO_2 content does not mean that there is no acid-base emergency, and on the other hand a grossly abnormal CO_2 content is not necessarily an indication for immediate therapy. Disorders that have an additive effect on pH result in minimally altered CO_2 content. Disorders that have opposite effects on pH may result in severely disturbed CO_2 content.

Several clinical situations are commonly associated with mixed metabolic and respiratory acid-base disturbances. Combined respiratory acidosis and metabolic acidosis usually occurs during cardiac arrest. Combined respiratory alkalosis and metabolic acidosis may occur during septic shock, salicylate intoxication and with hepatic and renal failure. The common association of metabolic alkalosis and respiratory acidosis following partial correction of chronic respiratory acidosis has been noted above. The treatment of mixed acid-base disturbances is, of course, directed towards the initiating insult. The treatment of the combination of respiratory acidosis and metabolic alkalosis has already been mentioned and includes primarily avoiding Cl^- deficiency by replacing KCl in hypokalemic patients and those with edema, and replacing NaCl if the patient is sodium depleted. The combination of respiratory acidosis and metabolic acidosis as may occur during cardiac arrest can lead to severe and progressive acidemia with a relatively normal plama [HCO_3^-]. Both acid-base problems must be treated in such patients. The pulmonary problem must be improved and adequate amounts of alkali must be administered to return pH into a safe range. The combination of respiratory alkalosis and metabolic acidosis can occur during septic shock and in people with both hepatic and renal damage. Typically such patients have a moderate hypokalemia, a pH that is near normal or slightly alkaline and a severely depressed [HCO_3^-]. Since pH is close to normal, no immediate alkali therapy is required. Therapy is directed at the primary disease states initiating

these mixed disorders. The combination of respiratory alkalosis and metabolic alkalosis is unusual, but can be serious. It is sometimes seen in post-surgical patients who have large amounts of gastric drainage and are treated with mechanical respiratory support. Again, both problems must be approached together and severe alkalemia requires treatment with some form of mineral acid.

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4. GLOMERULONEPHROPATHIES

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1. INTRODUCTION

The glomerulonephritides comprise a group of diseases in which there is a primary abnormality in glomerular structure. The abnormality may be toxic, degenerative or inflammatory in origin and may appear to affect only the kidney (primary glomerulonephritis) or may occur in a setting of systemic disease (secondary glomerulonephritis). Other entities affecting the kidney also alter glomerular structure secondarily, i.e., interstitial nephritis, obstructive uropathy, etc., but have their primary pathogenesis directed at nonglomerular structures.

Glomerulonephritis has been approached and classified on a number of different levels. These include pathological description (light microscopy), pathogenesis (immunofluorescence and electron microscopy) and clinical presentation and course. The latter approach, although overlapping the former two, is the way the clinician observes the disease. As a result, clinical evaluation alone determines the early steps of patient evaluation, as well as often later therapeutic intervention.

Developing an approach to patients with the various glomerulonephritides may be greatly aided by recognizing a variety of clinical syndromes that have been associated with different glomerular abnormalities. These syndromes may then be used to develop guidelines for a thorough evaluation, biopsy and follow-up of the patient. In the following sections, discussion of the primary glomerulopathies has been based on such a classification: asymptomatic urinary abnormalities (hematuria, proteinuria); acute nephritic syndrome; nephrotic syndrome; rapidly progressive glomerulonephritis; chronic renal failure [29]. Secondary glomerulonephritides are associated with the same syndromes, but are discussed separately.

2. ASYMPTOMATIC URINARY ABNORMALITIES

2.1. Hematuria

2.1.1. Definition

Patients with asymptomatic hematuria have red blood cells in their urine without apparent cause (i.e., no evidence of either systemic illness or localizing genitourinary tract pathology). The hematuria, especially when gross, may occur as either an isolated event of variable duration or be episodic. If episodic, it may be followed by persistent microscopic hematuria. In addition, the hematuria may be entirely and continuously microscopic (>5 RBC/HPF in females, >3 RBC/HPF in males).

Proteinuria in the presence of gross hematuria is difficult to evaluate. A grossly bloody urine may be produced by adding 1 ml of whole blood to 100 ml of urine and, without hemolysis, causes a 1+qualitative protein reaction. Without gross hematuria, proteinuria should not exceed 1 gm/day.

2.1.2. Patient evaluation

Evaluation of patients with asymptomatic hematuria begins with documentation of the hematuria. Especially when a history suggests dark urine, the presence of RBC's as the source of this color must be established. Other causes of dark urine to be excluded include: hemoglobin, myoglobin, melanin, beet ingestion (betacyanin, especially if G-6-PD deficiency is present and much less common in normals), and phenolphthalein ingestion.

Red blood cells may enter the urine anywhere along the genitourinary tract, and as a result, a thorough evaluation of the entire system is necessary. Red blood cell casts in association with hematuria indicate glomerular origin, whereas bright red blood, especially with passage of clots, suggests a nonglomerular source.

A thorough history and physical examination may uncover a source of hematuria (see Table 1). Evidence of systemic disease should be looked for, including collagen vascular disease, atherosclerosis (embolic source), coagulopathy, and infection (may include tuberculosis). A painful kidney may be due to pyelonephritis, a calculus, passage of a clot or papilla or a recent infarct. Evaluation of renal size may suggest a cyst or mass. Bladder examination may reveal tenderness suggestive of cystitis or enlargement suggestive of prostatic obstruction. A vaginal examination may reveal an invasive source of hematuria (neoplasm) and testi-

Table 1. Clinical considerations in investigating asymptomatic hematuria.

1)	Family history
	deafness, visual impairment, renal failure (Alport's syndrome)
	cystic disease (polycystic, medullary cystic and medullary sponge variants)
	sickle cell anemia
	bleeding diathesis
	hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)
2)	Renal and bladder calculi
3)	Trauma and injury
	renal: includes vigorous exercise prior to examination ('jogging')
	bladder: includes foreign bodies, radiation and sudden decompression after chronic obstruction
	urethra: foreign body
4)	Genitourinary tract infection
	renal: pyelonephritis (especially with papillary necrosis), tuberculosis, cystitis, prostatitis
5)	Neoplasm (throughout the genitourinary tract)
6)	Vascular lesions
	kidney: arteriovenous malformations, fistulas and aneurysms, 'essential hematuria'
	Bladder: varicosity
7)	Drug toxicity
	renal toxicity: sulfonamides (crystallization); analgesic nephropathy, especially with papillary necrosis
	bladder: cyclophosphamide (hemorrhagic cystitis)
8)	Glomerulonephritis
	primary
	associated with systemic disease
9)	Systemic disease
	contiguous organ involvement: direct spread to genitourinary organs of inflammatory or malignant disease
	atheroembolic sources

cular examination may reveal an epididymitis suggestive of tuberculosis.

2.1.3. Diagnostic procedures and laboratory examination

The diagnostic and laboratory procedures suggested attempt to eliminate an obvious source of hematuria. Initial evaluation should include the following:

— urinalysis to confirm hematuria is source of pigment; look for red cell casts indicating glomerular origin;

— CBC and platelet count to indicate anemia (suggest extent of blood loss, chronic renal failure, hemoglobinopathy) and thrombocytopenia;

— serum creatinine, creatinine clearance, electrolytes (including calcium, phosphorus) to suggest underlying renal disease, stone predisposition;

— twenty-four-hour urine protein—in absence of gross hematuria protein excretion should be less than 1 gm/24 hours.

An IVP at this time will be helpful to rule out structural disease, as well as providing evidence of chronicity (i.e., shrunken kidneys, scarring). If a mass is seen, tomography and a sonogram may determine cystic versus solid consistency and suggest a possible neoplasm. This may be further evaluated by an arteriogram. If no red cell casts are seen, then cystoscopy and retrograde studies are indicated to complete the structural evaluation. This may be especially helpful during an episode of hematuria to better localize the source, i.e., unilateral vs. bilateral. If structural disease is still not evident at this time, then a serological evaluation to better define an underlying systemic disease or primary glomerulopathy should be performed. This includes an ASLO titre (or streptozyme), antinuclear antibody, complement determination, immunoglobulin electrophoresis, serum for cryoglobulins and hepatitis B antigen. If all of these are unrevealing and the clinical nature of the bleeding suggests a vascular lesion, an arteriogram may be warranted, depending on the severity of bleeding.

If the above evaluation has been completed and the original definition fulfilled, the diagnosis by exclusion is benign essential hematuria. Although a biopsy at this point allows a pathological classification, it has little therapeutic value and a patient may be reassured that without it, his prognosis is excellent with the likelihood of progressive renal dysfunction approximately 10%. At the same time, particularly for the first follow-up year, repeat evaluations at 3-month intervals are suggested. During these visits, attention is directed at changes in physical examination, renal function, sediment and proteinuria, any of which may suggest a progressive disease and one in which a biopsy may be helpful. Subsequent follow-up may be carried out at progressively longer intervals.

2.1.4. Clinicopathological correlation of primary hematuria

The clinical spectrum of primary hematuria includes a number of pathological entities. Although there is no clinical feature to clearly distinguish them, the presence of significant proteinuria (>1 gm in 24 hours) in the absence of macroscopic hematuria, suggests more significant underlying disease.

Primary hematuria commonly presents in childhood or early adulthood, and 50–60% of the patients are under 25 at discovery [50, 65]. Males tend to predominate and if gross hematuria is evident, it occurs within one to two days of fever, infection, innoculation or strenuous

exercise. It tends to last for one to two days (occasionally longer) and then subsides [38, 50, 65]. This short latency period is significant in that a similar observation may be made in a number of chronic glomerulonephritides, including Alport's syndrome, whereas the latency period between infection and gross hematuria in acute poststreptococcal glomerulonephritis tends to approach one week or longer. As already indicated, the rest of the physical and laboratory evaluations are unremarkable, although patients may complain of loin pain, possibly due to blood clot passage.

Kidney biopsy of these patients reveals varying abnormalities [50, 58, 65]. Twenty percent of the patients have a normal biopsy and an additional 50% will have a focal proliferative glomerulonephritis. Immunofluorescence and electron microscopy of the latter generally reveals mesangial immunoglobulin deposition, including IgA, IgG and IgM. An additional 20% of patients have a diffuse proliferative glomerulonephritis, in which mesangial deposition is more extensive and some endothelial deposits may be present. Rarely, linear immunofluorescence, suggesting the presence of anti-GBM antibody disease, is found [50]. The remaining group of patients are found for the most part to have chronic glomerulonephritis or interstitial nephritis [65, 68].

Follow-up of these groups of patients reveals loss of hematuria and normal renal function in one third to one half in two to five years [65, 68]. If hematuria persists and no other clinical change is evident, renal histology will probably be unchanged and prognosis remains good [65]. Patients with evidence of glomerular sclerosis or crescent formation may develop progressive renal failure [50]. In any event, there is no clear therapy for the underlying process.

2.1.5. Berger's disease (IgA–IgG nephropathy)

Berger's disease is a type of mesangial or focal proliferative glomerulonephritis that may cause benign, intermittent gross or microscopic hematuria. It has been singled out as an entity because of the abundant IgA deposits in the glomerular mesangium [8]. Pathogenetic significance of the IgA is, however, unknown.

Berger's disease accounts for about 5% of renal biopsy specimens [55]. It occurs most commonly in children and young adults, with males predominating. The lesion may draw attention to itself clinically, by causing gross hematuria several days after the onset of an upper respiratory tract infection or fever, or may present as asymptomatic microscopic hematuria. Physical examination is otherwise unremarkable. Hypertension is uncommon and protein excretion usually does not

exceed 2 grams per day. Patients are generally normocomplementemic and (some about 20%) have elevated serum IgA levels [55, 83]. A skin biopsy may reveal perivascular IgA deposition.

Renal biopsy frequently reveals mesangial proliferation and/or a focal proliferative glomerulonephritis. In addition, sclerotic lesions, localized crescents, interstitial scarring and diffuse proliferative lesions may occasionally be seen [55, 83]. Abundant deposition of IgA, as in biopsies of patients with lupus nephritis and Henoch-Schoenlein purpura [44], along with IgG and complement is frequently seen in the mesangium and less frequently subepithelially and subendothelially.

Berger's disease was originally thought to represent a benign lesion. More recently progression into renal failure has been noted when persistent proteinuria in excess of 2 grams per day, hypertension and a biopsy revealing glomerular sclerosis and tubular destruction, have been present [55, 83]. No specific therapy has proven to be beneficial and the lesion may recur in a transplanted kidney.

2.2. Asymptomatic proteinuria

2.2.1. Definition

Asymptomatic proteinuria refers to an abnormal urinary excretion of protein in the absence of signs or symptoms suggestive of renal or systemic disease. The proteinuria is in the non-nephrotic range (usually less than 2.5 gm/24 hours) and is unaccompanied by either elements of the nephrotic syndrome or an active urine sediment (red blood cells, white blood cells and casts).

Asymptomatic proteinuria has been further classified according to its relation to posture (fixed or orthostatic proteinuria) and the reproducibility of its presence (persistent or intermittent).

2.2.2. Patient evaluation

Asymptomatic proteinuria generally reveals itself as an incidental finding. This means that the determination has been qualitative and not quantitative. A trace to 1+ reaction thus, may or may not be significant depending on urine concentration. Similarly, a negative reaction in a dilute urine, may miss significant excretion.

After proteinuria has been detected, a thorough history and physical examination may reveal evidence of systemic illness as a cause of proteinuria. Transient fever or prior exercise may also be associated with intermittent proteinuria. The specific causes of proteinuria to be considered during patient evaluation have been outlined in Table 2.

Table 2. Consideration in evaluating asymptomatic proteinuria.

Orthostatic proteinuria
Benign persistent proteinuria
Forme fruste of nephrotic syndrome (glomerulonephritis)
Nil Disease
membranous glomerulonephritis
membranoproliferative glomerulonephritis
focal and segmental sclerosis
rapidly progressive glomerulonephritis
chronic pyelonephritis
Interstitial nephritis
Congenital abnormalities (hypoplasia, polycystic disease)
Neoplasms (including genitourinary tract and systemic)
Systemic disease
Metabolic and inherited disease (diabetes mellitus, amyloidosis)
Collagen vascular disease (lupus nephritis, Sjogren's syndrome)
Allergens
Drug toxicity
Infectious disease
Neoplasia
Fever
Exercise
Renal vein thrombosis
Pregnancy
Massive obesity

In older children and young adults, the proteinuria may be orthostatic in nature and further evaluation will be unrevealing. Proteinuria may also be the first indication of the nephrotic syndrome and will manifest itself more fully upon subsequent examination. In addition, a form of benign persistent proteinuria exists in which the proteinuria is not orthostatic, does not progress to nephrotic syndrome and is associated with no apparent abnormality in renal histology.

Glomerulonephritis, especially membranous and membranoproliferative disease, may present as asymptomatic proteinuria. In the vast majority of these cases, however, hematuria is also present. Scarring due to chronic pyelonephritis or interstitial nephritis, may also cause proteinuria, although it is usually mild and accompanied by leukocyturia. Congenital abnormalities causing proteinuria include renal hypoplasia or polycystic disease, and systemic causes of proteinuria include diabetes mellitus, lupus nephritis, amyloidosis and multiple myeloma.

At the time of initial evaluation, urinalysis is important. Several morning specimens should be examined for abnormal urinary sediments and thus, the hint of more significant underlying disease.

The next step in evaluating patients with asymptomatic proteinuria includes routine chemical and hematological studies and a 24-hour

urine protein and creatinine clearance. The variety of inflammatory, neoplastic processes or congenital deformities being considered, may be further evaluated by an intravenous pyelogram. Renal proteinuria originates in the glomeruli or tubules and may be evaluated by a urinary protein electrophoresis. Glomerular diseases show predominantly albuminuria, whereas tubular diseases show a predominance of low molecular weight proteins that migrate as globulins. The latter are not detected by routine dipstick analysis.

Further evaluation at this time includes serology for collagen vascular disease, complement levels, serum protein electrophoresis to detect multiple myeloma and a 2-hour post-prandial glucose to evaluate diabetes mellitus. A rectal biopsy may be performed if amyloidosis is seriously considered. Evaluation for orthostatic proteinuria may be done as outlined below.

Adhering to the definition of asymptomatic proteinuria, there is probably no indication for renal biopsy at this point. Having ruled out all evidence of systemic disease, no specific treatment is warranted and thus there are no therapeutic implications of a biopsy. Furthermore and equally important, a biopsy at this point is often non-informative.

2.2.3. Clinicopathological correlations

It is useful to observe whether proteinuria is fixed or orthostatic, and if it is persistent or intermittent.

Orthostatic proteinuria is generally considered an exaggeration of a normal process, in which albuminuria increases in an upright or lordotic position, when renal blood flow is decreased [74]. Actually, albuminuria is increased above normal in a lying position in these patients as well. It is usually seen in older children or young adults. A random urine yields a trace to 2+ reaction, although occasionally more [88]. Abnormal urinary sediments, although usually considered atypical, may appear in as many as 45% of patients on a 5-year follow-up [82]. Total protein excretion is generally less than 2 grams per 24 hours.

A review of renal biopsies from these patients reported that 45% were normal, 45% showed minor changes consisting of glomerular capillary thickening and mild hypercellularity, and 10% showed more definitive abnormalities [73].

Although orthostatic proteinuria often persists for a long time, it rarely progresses into renal failure [72, 82].

Evaluation to determine the orthostatic nature of proteinuria may be done by instructing the patient to void prior to retiring and then one hour after retiring. In the morning, the patient is then instructed to void

while still in bed or immediately after rising. Not even a trace amount of protein should be detected in this specimen. A specimen examined after the patient is up and around will reveal demonstrable proteinuria. The proteinuria may be exaggerated and red blood cells and casts produced by lordotic positioning.

Asymptomatic fixed proteinuria refers to patients in whom detectable proteinuria is seen both after recumbency and after standing. This is also more common in young adults. In contrast to orthostatic proteinuria, a significant histological abnormality is more often seen in this group of patients. Less clear, however, is its clinical significance. Even with persistent proteinuria and pathological changes, few patients show progressive renal failure [64].

2.2.4. Prognosis and follow-up

After the initial evaluation, which, except for the proteinuria, has been found to be normal, follow-up at three-month intervals including clinical examination, urinalysis, quantitative urine protein and creatinine clearance, is necessary. The clinical course may then be more clearly defined. A decline in creatinine clearance or an increase in proteinuria are generally accepted as indications for a renal biopsy. If repeat evaluations are unchanged, further follow-up at extended intervals is acceptable. It is important at the outset, to explain the nature of the patient's condition and especially its excellent prognosis.

2.3. Asymptomatic proteinuria and hematuria

2.3.1. Definition

Patients included under this category have proteinuria continuously in excess of 1 gram per 24 hours, and accompanying microscopic hematuria. Transient gross hematuria may occur, especially during intercurrent infection, but even during periods of clearing, microscopic hematuria persists and proteinuria does not decline to levels associated with benign essential hematuria. Proteinuria may often be in the range of 1–3 gm/24 hours, with neither lipid abnormalities nor edema.

This group of patients is an important subgroup to identify. It includes a considerable number of patients who have conventionally identifiable renal lesions and who, despite a benign presentation, may go on to develop progressive renal failure.

2.3.2. Patient evaluation

The evaluation here is essentially the same as that described for benign essential hematuria. With the discovery of significant proteinuria, how-

ever, in addition to the other studies performed, a renal biopsy should be done. The types of pathological changes uncovered in this evaluation include lesions compatible with focal and segmental sclerosis, membranous, membranoproliferative and chronic glomerulonephritis, and anti-GBM antibody nephritis. In addition, other nonspecific lesions, compatible with resolving post-streptococcal glomerulonephritis, may be discovered.

The type of lesion will determine prognosis and possible therapeutic intervention, as discussed in further sections.

3. NEPHROTIC SYNDROME

3.1. Definition

The nephrotic syndrome has been defined by five components. These include proteinuria (≥ 3.5 gm/24 hours), hypoalbuminemia, lipiduria, hypercholesterolemia and edema. Patients with protein excretion ≥ 3.5 gm/hours but lacking one or more of the other criteria, are nevertheless considered to have nephrotic range proteinuria and there is no particular significance to the presence or absence of the complete syndrome. In fact, some diseases characterized by nephrotic range proteinuria seem less likely to show hypercholesterolemia (SLE, amyloid), and others show a greater tendency towards edema formation (diabetes). With increasing amounts of protein excretion (sometimes as high as 20–30 gm/24 hours), the rest of the syndrome is more likely to be present.

3.2. Pathogenesis of proteinuria

Normal individuals excrete less than 150 mg of protein in a 24-hour period [70]. If the protein in a normal urine is examined electrophoretically, 2/3 to 3/4 of it migrates with the globulin fraction and the rest migrates as albumin. The globulin fraction in urine is antigenically similar to circulating globulins in normal plasma, but is of much lower molecular weight (10,000–20,000) and readily filtered by the glomerulus. They represent, in some cases, light chains of circulating globulins (behaving the same way on heating as Bence Jones proteins), or possible metabolic precursors or derivatives of these globulins [70]. The albumin that is present in urine is identical to that found in serum. With a molecular weight of 40,000, it is a polyanion of sufficient size to meet

considerable filtration resistance by the normal glomerular barrier. Tamm-Horsfall macroprotein is the major protein found in urinary casts. Not found circulating in plasma, it is produced in the loop of Henle and distal tubules and migrates electrophoretically as an α globulin.

Normal handling of circulating proteins by the kidney seems to involve selective glomerular filtration of suitably sized and charged molecules, followed by a considerable amount of proximal tubule active metabolism and return to the systemic circulation. Less than 5% of filtered protein appears in the final urine. Pathological proteinuria results from a defect in the glomerular barrier, a defect in the tubular reabsorptive and metabolic capacity or an overproduction of normally filtered protein, so that the tubular capacity is supersaturated and overflow results [70].

The glomerular barrier to filtration is made up of the fenestrated endothelium, the glomerular epithelium with its podocytes and slit pore membrane between them and the glomerular basement membrane. No pores reaching from one end to the other have been identified and the actual barrier for different molecules may differ. Two characteristics that may determine penetrability are molecular size and net charge. Alterations of the glomerular barrier, as caused by immunological injury or toxins, may lead to a loss of negatively charged proteins in the glomerular barrier, that in turn, permits increased penetration of relatively large molecular weight, anionic proteins such as albumin, that then appear in increased amounts in the urine [10]. In fact, in a glomerular proteinuria, 60 – 90% of the urinary protein is albumin. Attempts have been made to relate the underlying pathological process and steroid reponsiveness to differential protein clearances. Relative clearances of substances with molecular weights similar to albumin (transferrin) and higher molecular weight substances IgG or α2-macroglobulin, enable one to calculate a 'selectivity index'. The overlap that exists between different pathological entities has made this of limited usefulness.

Tubular proteinuria occurs in diseases that either structurally or metabolically affect renal tubules. Normal transport and metabolic processes are interrupted and the normally filtered low molecular weight globulins appear in increased amounts in the urine. Proteinuria in these instances does not usually exceed several grams per day. Of note, also, is that the tetrabromphenol used as a dip stick indicator for proteinuria is specific for albumin and will be negative in these states. Total quantitative protein determination by, for example, sulfasalicylic acid precipitation, will detect the discrepancy [70].

Overproduction of low molecular weight globulins, for instance in multiple myeloma or certain leukemias, may result in proteinuria with an electrophoretic pattern characteristic of tubular proteinuria. Amyloidosis, when superimposed on multiple myeloma, causes a glomerular type proteinuria [70].

3.3. Patient presentation and evaluation

Edema is the most common symptom that brings patients with nephrotic syndrome to a physician's attention, although evaluations for newly discovered hypertension hematuria, or asymptomatic proteinuria, may also uncover evidence of nephrotic syndrome. In addition, while evaluating systemic conditions that may involve the kidney, nephrotic range proteinuria may be discovered. Clinical considerations in evaluating cases of primary and secondary nephrotic syndrome should be directed at those entities listed in Table 3.

Evaluation of the patient with nephrotic syndrome proceeds as described in asymptomatic proteinuria. The quantity of protein excreted in these cases, however, points to its glomerular origin. An intravenous

Table 3. Clinical considerations in evaluating the nephrotic syndrome.

Primary glomerulonephropathies
Lipoid nephrosis
Membranous glomerulonephritis
Mesangiocapillary glomerulonephritis
Focal and segmental glomerulosclerosis
Secondary glomerulonephropathies
Inherited and metabolic diseases
Diabetes, amyloidosis, Alport's syndrome, myxedema, sickle cell disease, Fabry's disease
Infectious diseases
Post-streptococcal, infectious endocarditis, shunt nephritis, leprosy, congenital and secondary syphilis, hepatitis B, malaria, schistosomiasis (hepatic)
Neoplastic diseases
Gastrointestinal solid tumors, lung, breast, kidney, ovary, Hodgkin's and non-Hodgkin's lymphomas
Toxins and allergens
Heavy metals (gold, mercury), street heroin, pencillamine, probenecid, insect and snake venoms
Systemic and immune mediated diseases
Lupus erythrematosus, vasculitic syndromes (polyarteritis, hypersensitivity angiitis, Henoch-Schoenlein purpura, cryoglobulinemia, serum sickness, etc.), sarcoid, dermatitis herpetiformus
Other
Toxemia, transplant rejection

pyelogram, as suggested, may give clues as to chronicity of disease, and serological studies may point to a particular primary glomerulonephropathy or aid in the evaluation of systemic disease. A renal biopsy is usually indicated, in order to make a more precise diagnosis.

3.4. Clinicopathological correlation

3.4.1. Lipoid nephrosis (minimal change disease, Nil Disease)

The variety of terms used to describe this clinicopathological entity, all allude to the fact that there are no specific pathological findings on renal biopsy.

Lipoid nephrosis, generally thought of as a major cause (60–80%) of childhood nephrotic syndrome, accounts for between 10 and 30% of adult nephrotics [45]. Patients generally present with all the features of the nephrotic syndrome and renal function is usually normal or supranormal with severe hypoalbuminemia [14, 45]. On occasion, however, hypoalbuminemia is accompanied by a progressive decline in renal function and irreversible renal failure has been described [71]. Urine sediment is usually unremarkable, except for lipiduria, as is the rest of the physical and laboratory evaluation [14, 45]. An attempt has been made to identify this particular glomerular capillary alteration using the urine protein 'selectivity index'. Whereas in children, protein excretion tends to be selective, this is less of a feature in adult minimal change disease.

Renal biopsy in this group of patients reveals normal appearing glomeruli with nonspecific epithelial foot process fusion and normal tubules with proteinuria-induced hyaline vacuolization. Immunofluorescent studies reveal an absence of immunoglobulins and complement [42, 45].

The nephrotic syndrome attributed to lipoid nephrosis, may occur or exacerbate following an infection, inoculation or insect sting. Causal relationships, however, have not been established and the etiology of this lesion remains obscure. Altered immunological responses have been reported in patients with minimal change disease and the occurrence of this lesion in patients with Hodgkin's disease, a disorder associated with defects in cellular immune function, suggest that cellular immune mechanisms may play a role in its pathogenesis.

Patients with unequivocal minimal change disease have an excellent response to therapy and long term prognosis [42, 45]. A four-week course of prednisone at a dosage of 1 mg/kg/day results in a complete remission in protein excretion in at least 80% of adults. This remission may be permanent and sustained, may be followed by a relapse at some

future time, or may be dependent on maintaining steroid administration. Institution of steroid therapy may be elected after biopsy results are available in adults, whereas children with nephrotic syndrome often receive steroid therapy empirically. The dose of 1 mg/kg is continued for 4 to 6 weeks or until the urine is protein free for 10 days, whichever comes first. Patients are then switched to alternate day administration at the same dosage for 4 to 6 weeks and then the dose is gradually reduced to zero. If relapses are infrequent, the same regimen may be repeated. If relapses occur frequently, or if patients are steroid dependent, the addition of cyclophosphamide [14] or chlorambucil [33] may be considered with the possibility of achieving a longer remission. Patients who are steroid unresponsive or only partially responsive, often do not respond to these added measures and the toxicity of the cytotoxic drugs often precludes their use. Adjunctive measures for symptomatic management of nephrotic syndrome, appropriate in either case, are outlined in a later section. Relapses may continue to occur for 10 or more years, although appearing with diminishing frequency as time elapses [80]. Patients who are initially steroid responsive, usually maintain this responsiveness throughout their course.

3.4.2. Focal and segmental glomerulosclerosis (focal glomerulosclerosis)

Focal and segmental glomerulosclerosis, may be confused with minimal change disease. Characteristic pathological changes seem to originate in juxtamedullary glomeruli and biopsy specimens lacking these may be compatible with minimal change disease [35, 46].

The majority (75%) of adults presenting with this lesion, are under the age of 40, with a peak incidence between 20–30. The ages of children with this lesion clearly overlap those with minimal change disease. There is some male predominance. Most patients with focal sclerosis have proteinuria at presentation and approximately 75% have nephrotic syndrome. In addition, abnormal urine sediments are the rule and a significant percentage have microscopic hematuria (60–80%), and occasionally gross hematuria. Pyruria may also be present and possibly results from interstitial involvement. Upper respiratory infection, as well as other infectious processes and immunizations, often increase the formed elements found in the urine, but no etiological relationship has been shown. Azotemia is also present in some patients at presentation and mild to moderate hypertension is common. Both azotemia and hypertension increase in frequency as the disease progresses. The serological and other laboratory studies are nondiagnostic.

Light microscopic evaluation reveals focal (only some glomeruli

affected) and segmental (parts of glomerular tuft but not entire tuft) sclerosis. Subendothelial hyaline deposits are found in sclerotic areas, and capillary loops are collapsed. These areas contain intracapillary hyaline and foam cells derived from endothelial cells. Additional findings include local capsular adhesions, focal tubular atrophy and interstitial fibrosis. A variant of this lesion has also been described in which scattered glomeruli are found to be entirely fibrotic, so-called focal and global glomerulosclerosis [35]. The significance of this lesion is that it apparently has a better prognosis than the segmental lesion. Electron microscopy reveals foot process fusion and folded, wrinkled basement membranes in involved areas. Electron dense subendothelial and paramesangial deposits are seen [35]. Immunofluorescence reveals a predominance of IgM and complement in affected glomeruli. This is thought to represent nonspecific trapping and not to be indicative of an immunologic origin for the lesion [46].

Although discussed as a separate entity, the lesion of focal glomerulosclerosis is not unique. Similar lesions may be seen in patients with hypertension, vesicoureteral reflux, pyelonephritis, Alport's syndrome, heroin addiction and transplant rejection. It thus appears that a variety of disease processes may lead to the same pathological change. What leads to the establishment of this apparent clinicopathological entity and indeed if it represents a single entity, is unclear.

Patients with focal glomerulosclerosis generally show a gradual decline in renal function. Azotemia at diagnosis, hypertension and persistent fixed proteinuria, suggest a poorer prognosis and adults with the lesion fare worse than children. No specific therapy is known to be effective and thus, none is indicated [46, 59]. The lesion may progress in a setting of apparent improvement in proteinuria. It is interesting to note that focal glomerulosclerosis tends to recur in transplanted kidneys.

3.4.3. Membranoproliferative glomerulonephritis (mesangiocapillary glomerulonephritis)

Membranoproliferative glomerulonephritis is a histologically and serologically distinct form of primary glomerulonephritis. It derives its name from an increase in mesangial matrix, mesangial cell proliferation and basement membrane splitting that is apparent on light microscopy. In addition, an important diagnostic marker of this disease is a depression of total hemolytic complement activity, especially of the C_3 component [36, 41].

Clincally, membranoproliferative glomerulonephritis is slightly more common in women, and most cases occur under the age of 30 [10–20]. Approximately 30–50% of patients have the nephrotic syndrome at biopsy and an increasing percentage subsequently develop it. An additional group of patients present with asymptomatic proteinuria. Both groups have an active urine sediment including microscopic hematuria and not uncommonly gross hematuria. These nephritic features point to a second important presentation (i.e., an acute nephritic syndrome) that may often follow an upper respiratory infection. An etiological relationship, however, remains unproven. A rapid decline in renal function may sometimes occur and is indicative of an aggressive disease. Physical examination is unremarkable other than a considerable percentage of patients who have mild to moderate hypertension and peripheral edema [12, 36, 41]. A syndrome of partial lipodystrophy is known to be associated with membranoproliferative glomerulonephritis and with abnormalities in complement components.

Laboratory evaluation may reveal azotemia at onset, although this often resolves, and a normocytic, normochronic anemia, disproportionate to the decrease in renal function. Whereas most serological studies are unremarkable (including ESR and ANA), 85% of patients are noted to be hypocomplementemic at some time during the course of their disease [12, 36, 41]. Two patterns of hypocomplementemia emerge and are seen more frequently in distinct pathological entities [63]. Classical complement pathway activation may be seen including depression of early factors (C_1, C_4) and concomitant C_3 depression. In the second pattern that emerges C_1 and C_4 tend to be more normal, in the face of depressed C_3 and suggest some form of alternate pathway activation. C_3 nephritogenic factor, in the presence of certain C_3 breakdown products, promotes alternate pathway activation and is found more frequently when this pattern of activation is evident [9]. Hypocomplementemia occurs in glomerulonephritides associated with streptococcal infections, subacute bacterial endocarditis, infected ventriculo-atrial shunts, mixed cryoglobulinemia, serum sickness and lupus erythematosus. Appropriate diagnostic and clinical evaluation should be carried out to search for these entities. Membranoproliferative glomerulonephritis has been reported after streptococcal infections (not etiological). In this clinical setting, persistent hypocomplementemia lasting beyond 6–8 weeks (by which time typical post-streptococcal hypocomplementemia resolves) should suggest its presence.

Light microscopy reveals glomeruli that enlarge with disease progression. The glomeruli may take on a lobular appearance and mesangial

cells show proliferation with increased matrix [41]. This proliferation may cause capillary loop collapse and mesangial cells may interpose themselves between endothelial cells and basement membranes [36]. These changes give the basement membrane a double contour or tram-track appearance (more common in Type I than Type II) [36]. The basement membrane remains intact, however, although it is often thickened. Crescent formation is sometimes present and this is associated with a more rapidly progressive course.

Electron microscopy confirms these findings and, in addition, is the basis for distinguishing at least two distinct types of membranoproliferative glomerulonephritis. Type I (more commonly associated with classical complement pathway activation) is characterized by subendothelial deposits, with thickened but otherwise normal glomerular basement membrane. Type II (C_3 nephritogenic factor, and alternate complement pathway activation more commonly seen) is characterized by electron dense deposits within the basement membranes of glomeruli, tubules, Bowman's capsule and peritubular capillaries [36]. Other variants, although not as widely accepted, have also been described.

Immunofluorescence reveals a variety of patterns including staining for C_3 alone and various complement and immunoglobulin patterns. Complement is present irregularly along capillary walls and IgG and IgM, if found, are present in a similar but more segmental distribution [36].

Excluding patients who have crescentic disease on biopsy (more common in Type II), the histological pattern is not a key determinant of course and prognosis. Some patients may retain normal renal function for many years, but the overall tendency is to show a gradual decline, so that overall survival approximates 78% at 5 years and 50% at 10 years. Clinical remissions, if they occur, tend to be short and are not necessarily associated with histological remission. Patients who have crescentic disease on biopsy have poorer survival (<3 years). Additional adverse factors include early and persistent azotemia, hypertension and persistent nephrotic syndrome. Although hypocomplementemia is a significant marker of this disease, it bears no relation to either disease activity or progression, and the interaction between C_3 nephritic factor, hypocomplementemia and disease activity is also unclear [4].

Therapy directed at the underlying glomerulopathy in the form of steroids and other immunosuppressants have been generally unsuccessful.

3.4.4. Membranous nephropathy

Membranous nephropathy is the most common primary glomerulonephropathy associated with nephrotic syndrome in adults and is the most common pathological entity seen with secondary nephrotic syndrome. Membranous nephropathy occurs with a peak incidence between the ages of 40 and 60 [22, 25], but may account for approximately 3–10% [37, 77] of primary glomerulonephritis in children. Males seem more commonly affected than females [22, 25, 37, 77].

A significant majority of patients (as high as 85%) present with the nephrotic syndrome. Physical examination may reveal peripheral edema and approximately a third of the patients are hypertensive. If not clinically nephrotic, the remaining patients have at least significant proteinuria. Microscopic hematuria is common (30–90%) and gross hematuria also occurs, but is uncommon. A minority of patients have azotemia when initially seen. Serological evaluation reveals no abnormalities in the idiopathic disease and circulating immune complexes are usually not detected [22, 25, 37, 77].

Light microscopy reveals a diffuse thickening of the glomerular basement membrane [39]. A closer evaluation using techniques to demonstrate immune deposits, including staining with methenamine silver, reveals spike-like subepithelial deposits [39]. These spikes may not be easily demonstrated in very early or late disease and electron microscopic evaluation is necessary to make a diagnosis. Electron microscopy also provides a better evaluation of the evolution of these deposits in relation to the glomerular basement membrane. Little, if any, cellular proliferation accompanies this deposition [39]. Tubular and interstitial changes are not prominent, although when present, correlate better than glomerular changes with functional impairment. Immunofluorescence reveals diffuse deposition of a variety of immunoglobulins including IgG, IgA and IgM, as well as complement in a granular pattern along the glomerular capillary walls.

Membranous nephropathy is a slowly progressive disease, and stable function may be maintained for many years. Actuarial survival at 10 years is approximately 75% [62]. During varying follow-up periods, 25% of patients develop renal insufficiency or failure, 50% remain unchanged and another 25% have a clinical remission [22, 62]. In general, the longer the duration of disease at biopsy, the more likely a more severe lesion will be found. Remission or progression is possible with any stage lesion. Clinical remission is possible without pathological remission, and renal function may deteriorate in the absence of proteinuria. Poorer prognosis has been noted in patients with persistent nephrotic syndrome, hypertension and azotemia at diagnosis.

Whether membranous nephropathy benefits from specific therapy is not entirely clear. Corticosteroids were long held to be of no therapeutic value, but recent studies prospectively examining the benefits of a short course of alternate day steroids suggest better preservation of function in the treated group of patients.

3.4.5. Management of the nephrotic syndrome

In most instances, therapy directed at the pathogenesis of the nephrotic syndrome is inadequate. As a result of this primary failure, measures to control the sequelae of nephrotic induced hypoalbuminemia take on added importance in maintaining patient well-being.

The major manifestations of this hypoalbuminemic-induced decreased oncotic pressure include edema, decreased effective intravascular volume resulting in shock and pulmonary edema and hyperlipoproteinemia resulting in accelerated atherosclerosis. In addition, the abnormal capillary permeability may result in hypoimmunoglobulinemia, specifically hypo-IgG and decreased antithrombin III activity leading to hypercoagulability and possible renal vein thrombosis. The degree of symptomatic therapy will depend on the severity of the sequelae as they arise. Symptoms due to reduced oncotic pressure may be helped by diet, diuretic use and colloid replacement.

Diet therapy in nephrotic patients is important in managing hypoalbuminemia and the concomitant hyperlipoproteinemia. Patients should be encouraged to consume a high protein diet (1.5 g/kg) to minimize the existing negative nitrogen balance by maximizing the available sources of protein synthesis. Salt retention is a result of the edema forming process, and in order to reduce edema, a state of negative sodium balance until equilibrium (edema control) is reached must be produced. A salt restricted diet (frequently 2-3 g sodium chloride) resulting in an intake less than measured excretion and occasionally as low as 500 mg of sodium per day, should be instituted.

All types of hyperlipidemia, except Type I, are seen in patients with nephrotic syndrome [60] and this significantly contributes to their long term morbidity and mortality. An attempt at control using diet therapy should be made to achieve ideal body weight and minimize hyperlipidemia. Adjunctive drug therapy (i.e., cholestyramine, clofibrate, etc.) may be associated with an increased incidence of side effects in hypoalbuminemic patients, but may be tried if cholesterol or triglycerides remain at unacceptable levels.

Diuretic therapy, especially those diuretics acting on the thick segment of the ascending loop of Henle (furosemide ethacrynic acid), are

effective adjuncts in controlling edema. They may be titrated from low doses to doses approaching several hundred milligrams per day to achieve negative salt and fluid balance. Combination with aldactone, whose more distal effect may enhance response, may help in achieving a diuresis. If patients are extremely hypoalbuminemic or show evidence of decreased effective intravascular volume, then diuretics should not be used as a first line therapy for mobilizing fluid, and instead, oncotic pressure should be increased with salt-poor albumin infusions. The effect of salt-poor albumin is limited in that it remains in the circulation for only a short time and repeated infusions may be necessary to maintain an adequate effective intravascular volume. Similar therapy may be necessary in patients who develop pulmonary congestion. Diuretics are only helpful if an adequate effective intravascular volume is present. They may be detrimental when the patient is hypovolemic. In this case, acute renal failure may occur, and dialysis in conjunction with some of the previously mentioned measures to maintain plasma oncotic pressure, may be necessary.

Patients with the nephrotic syndrome may show an increased susceptibility to infections with gram positive organisms. Although hypoglobulinemia may be responsible for this susceptibility, long-term replacement of immunoglobulins is not practical. Patients should receive prophylactic pneumococcal vaccination, as well as other available vaccines during winter months.

There appears to be a significant negative correlation between antithrombin III levels and urinary protein excretion. This may result in hypercoagulability and contribute to a predisposition to venous thrombosis, including renal vein thrombosis [41]. Regardless of how frequently renal vein thrombosis occurs in patients with the nephrotic syndrome, it appears to be of clinical significance in a relatively small percentage. Unless the degree of suspicion is high, screening for renal vein thrombosis using an inferior vena cavagram in all patients with the nephrotic syndrome, is probably unnecessary. This is based on the observation that during the course of the nephrotic syndrome, a single inferior vena cavagram is difficult to interpret, and the role for anticoagulation other than as it effects embolic phenomena, remains unclear. It is more important to be aware that a predisposition to thrombosis exists, and in a nephrotic patient with pulmonary embolism, rapidly declining renal function, or severe edema in the lower extremities, renal vein thrombosis should be considered.

4. ACUTE NEPHRITIC SYNDROME

4.1. Definition

Acute nephritic syndrome refers to an acute disease characterized by microscopic or macroscopic hematuria, proteinuria (not necessarily nephrotic range), edema, and hypertension. A decline in renal function is also common during this acute phase.

The prototype of this syndrome is acute post-streptococcal glomerulonephritis. There is an initiating factor, an infection with a nephritogenic strain of streptococcus, followed by a latent or incubation period, prior to the onset of nephritis. During this time an immunological response occurs, resulting in acute glomerulonephritis. With elimination of the causative factor, the immunological response may subside and its byproduct, glomerulonephritis, may also subside. Variations in immune response may modify this course in individual cases and progressive renal disease may result.

In addition to poststreptococcal glomerulonephritis, a variety of other infections have been associated with an acute glomerulonephritis. These include pneumococcal pneumonia, staphylococcal sepsis, typhoid fever, falciparum malaria, toxoplasmosis, varicella, mumps, infectious mononucleosis, congenital syphilis and enteroviruses. Clinical features of acute glomerulonephritis caused by these infections are similar to those of poststreptococcal glomerulonephritis.

In a variety of glomerulonephropathies, any intercurrent febrile disorder, particularly from infectious origins, may acutely exacerbate the clinical course of the nephropathy and be associated with increased hematuria, proteinuria and azotemia. These changes can be either transient or permanent, and may be seen in membranoproliferative glomerulonephritis, focal glomerulosclerosis, lupus nephritis, Henoch-Schoenlein purpura, mixed essential cryoglobulinemia and Alport's syndrome. This nonspecific phenomenon, secondary to an acute febrile disorder, should be differentiated from an acute primary glomerulonephritis that is pathogenetically related to the preceding or concurrent infectious disease.

4.2. Patient presentation and evaluation

Patients are generally seen first because of the infectious process. Features of the acute nephritic syndrome may become apparent during the course of the disease or after the primary process has subsided and a

latent period has passed. Initial evaluation should include urinalysis, with a careful microscopic examination of the sediment to determine the presence of hematuria, casts and other formed elements, a quantitative assessment of proteinuria (interpreted with caution in the presence of gross hematuria) and a determination of creatinine clearance.

Evaluation of the patient then focuses on identifying an etiological factor. Bacterial culture should be taken from the throat, sputum, blood and any skin lesions. Serological studies should include ASLO titer, febrile agglutinin tests, heterophile antibodies and antibodies against enteroviruses during acute and convalescent periods. Further evaluation may be helped by determining cryoglobulins, ANA and an immunoelectrophoresis. Complement determination is helpful and may be normal or depressed during the acute phase of various infectious diseases, but returns to normal within 6 weeks, if more significant underlying processes such as bacterial endocarditis, shunt nephritis or cryoglobulinemia is not present.

Most post-infectious nephritides generally follow a short benign and self-limited course. Persistence of significant proteinuria or hematuria beyond several months, or a decline in renal function indicate a need for further evaluation, including an intravenous pyelogram and perhaps a kidney biopsy. A kidney biopsy and intravenous pyelogram are not necessary during the acute phase, unless the etiology or sequence of events are unclear.

4.3. Clinicopathological correlation

4.3.1. Acute post-streptococcal glomerulonephritis is a model for the acute nephritic syndrome. Most commonly seen in children after a streptococcal pharyngitis or impetigo, it may also occur in adults. The disease occurs more commonly in males than females (2 : 1) and shows a seasonal variation related to climate [20, 79].

Pharyngitis or impetigo caused by nephritogenic strains of β hemolytic streptococcus, regardless of antibiotic therapy, may be followed after a latency period averaging 8–14 days (may be shorter; or longer in cases of impetigo) by the abrupt onset of hematuria (60%), edema, circulatory overload (i.e., dyspnea, abdominal discomfort) and symptoms related to hypertension (i.e., headache, visual disturbances) [20, 53]. It is at this point that the patient usually sees his physician. Physical examination may reveal circulatory overload possibly including pulmonary edema, hypertension of varying degree accompanied by signs of encephalopathy, if it is sufficiently severe, and peripheral edema. Laboratory evalua-

tion reveals gross or microscopic hematuria, accompanied by red blood cell casts and leukocyturia. Significant proteinuria is common, but the nephrotic syndrome is unusual [53]. A normocytic normochromic anemia is common. A small percentage of patients are frankly oliguric. Throat cultures are positive in about 25% of patients, but ASO titre, anti-hyaluronidase and/or anti-DNAse B titre are elevated in virtually all patients [52]. Anti-DNAse B is particularly important in documenting cases of impetigo since ASO and anti-hyaluronidase titres rise less consistently [19]. Titres are generally at their highest during the initial evaluation and during the first 3 months of follow-up [20]. Hypocomplementemia is also found in up to 95% of patients and circulating cryoglobulins may be detected in some.

If a biopsy is performed at this time, it shows generalized glomerular swelling with increased cellularity due to mesangial and endothelial proliferation, and consequently narrowed and sometimes obliterated capillary loops. Infiltrating polymorphonuclear leukocytes may be seen and the glomerular tuft may fill Bowman's space. Rare cases show numerous and extensive crescent formation [53].

Immunofluorescence study reveals granular deposition of immunoglobulin and complement along the glomerular basement membrane. Electron microscopy reveals subepithelial humps of immune deposits, characteristic of post-streptococcal glomerulonephritis. Deposits are also seen in the mesangium and correspond to the localization of streptococcal antigen when it is found, as opposed to the subepithelial humps, which have not been shown to contain streptococcal antigen [53].

4.3.2. Other acute glomerulonephritides

Acute nephritic syndrome has been attributed to a variety of other infectious agents, as mentioned above. The presentation of acute nephritis in these instances is similar to that following streptococcal infection with a variable, often shorter, latency period and acute onset of hematuria and proteinuria. Hypertension and decreased renal funcion may occur and rarely renal failure. Complement levels are usually normal and renal biopsy generally shows less change than post-streptococcal glomerulonephritis. Most post-infectious acute nephritic syndromes are benign and resolve spontaneously.

Acute nephritic syndrome secondary to underlying primary renal disease should be suspected if an antecedent infection cannot be documented, the latency period seems unusually short, systemic findings fail to resolve or they recur during follow-up. Membranoproliferative glo-

merulonephritis especially should be suspected when hypocomplementemia persists beyond six weeks.

4.4. Management of acute nephritic syndrome

No specific therapy is available for the acute nephritic syndrome, other than that directed at a possible etiological (infectious) agent. Nonetheless, a variety of problems arise that require close medical management.

The need for hospitalization depends on an evaluation of the clinical situation, as well as the ability of the patient to receive adequate care and follow-up at home. Clinical conditions that warrant close observation and hospitalization include: deteriorating renal function including oliguria, azotemia and symptoms of uremia; hypertension and hypertensive encephalopathy; fluid overload with pulmonary congestion.

There are no clear guidelines available for the amount of activity that should be allowed for a patient with acute nephritis. It seems reasonable to maintain general bedrest until the acute signs of nephritis have cleared (gross hematuria, circultory congestion and edema, severe hypertension) and renal function has stabilized or improved. This usually requires between 10 days and two weeks and bedrest beyond this period is unnecessary. It is useful to follow serial renal function measurements as a guide to the rapidity of resumption of normal activities.

Hypertension is a common problem and its management depends on its severity. Mild elevation in blood pressure may respond to bedrest and salt restriction. Diuretic therapy may be required if fluid overload is present. Diastolic blood pressure above 100 mm Hg in the absence of vascular congestion, may be managed with the addition of a beta blocker and vasodilator if necessary. Severe hypertension, over 120 mm Hg diastolic, especially when accompanied by signs of encephalopathy requires immediate control with parenteral antihypertensive drugs.

Evidence of vascular congestion and fluid overload are related to hemodynamic changes rather than to proteinuria. Individualized diuretic therapy with a thiazide diuretic or furosemide and modest salt restriction, are effective measures for fluid overload. Pulmonary edema or congestion may require more aggressive therapy, and when renal function is severely depressed or oliguria is present, dialysis may be indicated.

Adequate attention to nutrition is also important in managing many of the complications of acute nephritis. Salt and fluid restriction have

already been mentioned. In an average 70 kg adult, insensible water loss is approximately 500–600 ml and maintenance fluids should include this amount and ml for ml replacement for measured fluid losses (urine, vomitus, etc.). Overall guidance may be obtained by observing weight and blood pressure changes. Early dialysis is preferable to rigorous protein restriction in a symptomatically uremic patient, and no protein restriction is required when renal function is not reduced. However, dietary protein should be of high biologic value and caloric intake should be adequate.

Antecedent infections require treatment with appropriate antibiotics. In cases of post-streptococcal glomerulonephritis with positive cultures, 10 days of penicillin therapy is recommended. Furthermore, throat cultures from family contacts should also be taken and individuals with positive cultures should be treated similarly. There is no therapy available for the glomerulonephritis itself.

Patients are allowed to ambulate and gradually return to normal activity after acute features have subsided. Although second episodes of post-streptococcal glomerulonephritis are exceedingly uncommon, exacerbations of an underlying disease are more common and patients require continued follow-up. Management is directed at problems that may persist after the acute phase and these will dictate frequency of follow-up. In addition, because of the possibility of slow progression of the disease after initial clinical improvement, longterm follow-up is also necessary. After the acute episode has subsided, clinical evaluation at three-month intervals should be adequate with longer intervals as activity subsides. Follow-up evaluation should include complete physical examination, urinalysis, renal function tests and 24 hour urine protein excretion.

4.5. Prognosis

Complete recovery from acute post-streptococcal glomerulonephritis occurs in a majority of patients, although the exact incidence of such recovery is unclear. Children with either sporadic or epidemic disease in some series show 90–100% recovery [61]. Adults may fare less well, and in a recent series, 30–40% had evidence of renal disease at five-year follow-up. This series may be biased with patients having initially severe disease, and children in this series also had a higher incidence of progressive disease [78].

Initial urine protein and cellular excretion do not predict severity, although persistent nephrotic syndrome may indicate a poor outcome.

Similarly, ASLO titres and complement levels do not reliably predict biopsy results. The extent of glomerular obliteration does correlate with decreased creatinine clearance and evidence of crescent formation suggests a poorer prognosis. Patients with less glomerular alterations tend to have more complete healing, but all degrees of glomerular severity may go on to complete clinical resolution [53].

Renal function usually returns close to normal within 3 weeks, while abnormalities in the urinary sediment may persist longer [79]. Hematuria generally clears before proteinuria, which may persist for many years (5% at 5 years), and may become orthostatic before finally clearing [61, 79]. A biopsy at this point may be quite normal.

5. RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (RPGN)

5.1 Definition

Rapidly progressive glomerulonephritis (RPGN) represents a clinicopathological syndrome characterized by the presence of extracapillary glomerular proliferation (crescent formation) associated with a rapid decline in renal function (often approximating a 50% or greater decline within a 3-month period) proteinuria, hematuria and usually cylindruria in a person without a prior history of renal disease. Rapidly progressive glomerulonephritis is a syndrome and the clinicopathological features of the syndrome may occur as a primary renal disease, or may be part of various systemic disorders.

5.2. Patient presentation and evaluation

Patients with RPGN may present with clinical features related to the abrupt changes in fluid balance that occur, the inflammatory nature of the underlying lesion, and the uremic sequelae that ultimately supervene. The signs and symptoms that result must then be evaluated in a context of disease that appears limited to the kidneys, or in the presence of a systemic disease.

Twenty-five to 40% of patients have a history of a prior upper respiratory or other infectious illness at the time they present. Some patients seek medical care initially because of signs and symptoms of fluid overload and edema, gross hematuria, hypertension (i.e., headache, visual disturbance) and uremia (i.e., malaise, fatigue, nausea, anorexia,

and weight loss). Complaints relating to the infectious illness itself may bring patients to a physician's attention, at which time a urinanalysis or blood tests disclose evidence of renal disease. A final group of patients may be discovered during evaluation and follow-up of individuals presenting with hematuria, edema, hypertension, proteinuria or azotemia and who develop either an unexpected decline in function or some variation in clinical course that then prompts a kidney biopsy.

Evaluation of the patient with RPGN begins with the recognition that this clinicopathological entity may indeed be present. This may be recognized the first time a patient is seen, or alternatively, may require a variable period of observation.

The urinalysis reveals proteinuria, hematuria and usually cylindruria. Renal function may be normal or severely impaired and protein excretion will virtually always be abnormal ranging from several grams to nephrotic range proteinuria. Preliminary laboratory evaluation should include a complete blood count, platelet count, electrolytes and chest X-ray.

While assessing renal function, structural evaluation is helpful, and this requires an intravenous pyelogram or sonogram and renal scan. Mindful of the limitations and hazards of an intravenous pyelogram, if the serum creatinine is stable and <3.0 mg%, we would go ahead with an intravenous pyelogram in a well-prepared, hydrated patient. If function is rapidly declining or serum creatinine is >3.0 mg/100 ml, then similar structural and dynamic information may be obtained using a sonogram and renal scan. Results will often reveal normal sized kidneys with variable function. Small, shrunken kidneys suggest a chronic process, and possible structural abnormalities (i.e., obstruction) will become evident.

If the evaluation supports the clinical impression of RPGN, further studies should be done in an attempt to delineate the etiology of the syndrome. This should include an ASLO titre, anti-GBM antibody, ANA (anti-DNA antibody if indicated), hepatitis B antigen, cryoglobulins, serum complement, blood cultures if indicated and serum and urine immunoelectrophoresis.

A renal biopsy should be considered and several points should be weighed: a kidney biopsy will result in a tissue diagnosis; various studies, including immunofluorescence may establish a pathogenesis suggesting means of specific therapeutic intervention; a biopsy will aid in formulating a prognosis; a biopsy will enable identification of a lesion that may recur in a transplant. A kidney biopsy is then an important procedure as long as the patient retains some degree of renal function. If

a patient has reached dialysis, his renal disease does not warrant aggressive therapy and a biopsy is less significant.

5.3. Clinicopathological correlation

5.3.1. Rapidly progressive glomerulonephritis

Idiopathic rapidly progressive glomerulonephritis is a relatively uncommon entity and may account for $<1\%$ of renal biopsies performed [7]. It seems to occur in a variety of antecedent clinical settings including:

1) infection: such as viral syndromes, streptococcal infection, subacute bacterial endocarditis, ventriculo-atrial shunt infection;
2) hydrocarbon exposure;
3) neoplasm;
4) nonspecific systemic illness.

All age groups appear to be affected and males seem to be affected slightly more often than females.

The patient generally presents with symptoms of brief duration, often traceable for several weeks or months, or of even shorter duration. Commonly, a history of a recent viral-like illness is obtained including complaints of fever, cough, hemoptysis, headache, myalgias, arthralgias, weakness, anorexia, nausea and vomiting. A patient may take note of fluid retention or edema, and a diminished urine output or hematuria. Alternatively, a patient may be relatively asymptomatic and present to his physician for an evaluation of unexplained hematuria or anemia [7, 21, 89].

Initial physical examination is often unremarkable and may only reveal evidence of hypertension. This tends to be a more common physical finding as the disease progresses. Other nonspecific findings relating to uremia and fluid overload, including pallor, pulmonary congestion, pericardial friction rub, arterixis and edema, may be present [7, 81, 89].

Urinalysis invariably reveals evidence of renal disease including gross or microscopic hematuria, proteinuria, pyuria, and granular and red blood cell casts. The majority of patients have variably imparied renal function when first seen and some may be oliguric. Protein excretion generally ranges from several hundred milligrams to more than several grams/24 hours [7, 81, 89].

Anemia is common as is an elevated white blood cell count, and erythrocyte sedimentation rate. Abnormal blood chemistries relate to the degree of renal impairment present. Unless evidence of a systemic disease is found, serological evaluation is generally unremarka-

ble [7, 81, 89]. An elevated ASLO titer, a positive ANA (negative Farr) or, occasionally, antibodies to hepatitis virus may be found in a few patients, but serum complement levels are generally normal. Assays for circulating immune complexes may be positive in a number of patients and circulating cryoglobulins are commonly seen.

Renal biopsies of patients with clinical RPGN show a variety of histological abnormalities. The pathological hallmark of RPGN by light microscopy in all series is the presence of extracapillary proliferation. This varies both in the number of glomeruli affected and in the size of the individual crescents. Different groups of patients are described as having no other proliferation of the glomerular tuft, while others show mesangial and endothelial cell proliferation. Severe disease may reveal varying degrees of tuft necrosis and collapse. Varying degrees of interstitial infiltrate and fibrosis are also common. Electron microscopy confirms these findings and, in addition, the glomerular basement membrane may be wrinkled, and in some areas, ruptured. Electron dense deposits may be seen in subepithelial and subendothelial areas and in the mesangium. Immunofluorescence is especially striking for fibrin deposition in crescents as well as in the urinary space. IgG with or without IgM, IgA and complement, may be present in a diffuse or focal granular pattern throughout the glomerular tufts. In some instances, complement may be present alone. Alternatively, no immunoglobulin or complement may be seen [7, 81, 89].

5.3.2. Prognosis and therapy

Prognosis in patients with RPGN is poor. Estimated survival off dialysis is approximately 5% at 3 years. The patients reported in different series, however, may represent different subgroups of the disease, and thus must be taken into consideration when prognosis, as well as when therapeutic results, are considered. Factors that appear to affect outcome deleteriously include [58, 89]:

1) percent of crescentic involvement (greater than 80% of glomeruli with crescents a poorer prognosis, less than 80% a better prognosis).
2) oliguria at presentation [89];
3) impaired renal function at presentation [89].

Patients who have RPGN associated with bacterial infection, including bacterial endocarditis, whose biopsy often reveal endocapillary proliferation as well as extracapillary proliferation (crescents) tend to have a better prognosis.

Management of patients with RPGN should include consideration of the following:

1) etiology: if a causative agent or systemic disease is identified, appropriate therapy should be initiated and improvement in the associated glomerulonephropathy may result;

2) renal failure: regardless of its etiology, appropriate therapy for the concomitant renal failure as outlined in other sections, must be instituted and is a major factor affecting patient survival;

3) rapidly progressive glomerulonephritis itself: attempts at treating RPGN with anticoagulation, antiplatelet drugs, steroids and other immunosuppressants and plasmaphereses, have achieved variable success. Therapy is often given with combinations of these agents and this may lead to a greater morbidity and mortality than the natural course of RPGN with subsequent dialysis and transplantation. A conservative approach is the following:

a) oliguric patients requiring dialysis are not candidates for aggressive immunosuppressive therapy. Appropriate management of any systemic disease and attention to the problems associated with renal failure constitute appropriate management;

b) early therapy should be instituted in an attempt to prevent further deterioration in patients who retain residual function, and for whom treatment protocols exist, including an evaluation of the benefits of the treatment itself;

c) RPGN should be considered a medical emergency and the patient should be referred to a center capable of initiating and critically evaluating therapy prior to the onset of oliguria and loss of renal function.

5.3.3. Goodpasture's syndrome

Goodpasture's syndrome is a clinicopathological entity in which RPGN occurs, typically associated with pneumonitis and hemoptysis. It's significance lies in the fact that it and related clinical syndromes are associated with circulating antibodies directed against the glomerular basement membrane.

Anti-glomerular basement membrane nephritis accounts for less than 5% of glomerulonephritis with biopsies available [90], although evidence of linear staining may be present in a greater number [56]. There is no clinical feature that distinguishes this entity from other forms of RPGN. Hemoptysis and anemia, features that make Goodpasture's syndrome a primary clinical consideration, can also occur in other forms of glomerulonephritis. Diseases caused by circulating anti-GBM antibodies may present with either pulmonary or renal manifestations alone. Renal involvement in a few cases may even be benign with spontaneous remission [56].

Patients with Goodpasture's syndrome are typically male, in their second or third decade, and may present with a viral-like syndrome. Physical examination often reveals evidence of pulmonary involvement, and there may be some degree of hypertension. Peripheral edema is rarely present and urinalysis reveals proteinuria, varying degrees of hematuria and red blood cell casts. Patients are anemic with varying leukocytosis and may have normal or impaired renal function. Circulating anti-GBM antibodies are detectable by a number of assays, and other serological studies are usually normal (complement, antinuclear antibody, etc.).

Pathological changes on light microscopy are nondiagnostic, but may range from a focal and segmental glomerulonephritis to a necrotizing extracapillary glomerulonephritis. Immunofluorescence reveals a prominent linear deposition of immunoglobulins, especially IgG, and is the distinguishing feature of this entity [80].

Until recently, patients with Goodpasture's syndrome had a uniformly poor prognosis. Spontaneous remissions were uncommon, with about 10% of patients maintaining stable renal function and the remaining 90% either on dialysis or dead at approximately one year. Recently, the therapy combining plasmapheresis with prednisone and cyclophosphamide, has been reported to result in a more rapid decline in circulating anti-GBM antibodies and improved preservation of renal function and patient survival. With this approach, Goodpasture's syndrome may become a more manageable and self-limiting disease [54].

6. CHRONIC NEPHRITIC SYNDROME

6.1. Definition

The chronic nephritic syndrome is not clinically nor pathologically distinct. A wide variety of glomerulonephropathies cause a gradual, chronic, irreversible decline in renal function and patients with these progressive diseases suffer from the chronic nephritic syndrome. Depending on when in their course the diseases are initially discovered, patients may have minor urinary abnormalities or be frankly uremic. As such, overlap with the previously mentioned clinical categories is evident, and biopsy early in the course may permit better classification. Most patients who have a renal disease that belongs to this category have a history of chronic hypertension, abnormal urinary sediments,

proteinuria, some impairment in renal function and shrunken, scarred kidneys, with no apparent etiology.

6.2. Patient presentation and evaluation

Patients generally come to medical attention because of problems associated with renal disease. These may include hypertension, unexplained anemia, or an exacerbation of hematuria during an intercurrent illness. In a child, failure to grow or mature sexually, may promote an evaluation. Patients with this syndrome may also be discovered because of an abnormal urinalysis or, at the other extreme, because of symptoms related to uremia.

Patient evaluation at this point should be directed at evaluating renal function and amount of proteinuria. This may place a patient in one of the other clinical categories already discussed and for which appropriate evaluation has already been outlined. Following this, an intravenous pyelogram (if the creatinine is <3.0 mg/100 ml) or sonogram will delineate any gross structural abnormalities. Kidneys are usually found to be small, in accord with the chronicity of the underlying process.

Further evaluation and management is best directed at attempts to preserve renal function, by correcting underlying chemical abnormalities (i.e., acidosis, hypocalcemia, hyperphosphatemia, hyperuricemia) and preparing the patient for dialysis and possible transplant. We do attempt to identify a pathogenesis if possible, including performing an ANA, complement, hepatitis B antigen, serum immuno- and protein electrophoresis, cryoglobulins and other serological studies if they seem appropriate. A renal biopsy is of no value, since the primary disease is difficult to identify by this time, and may be complicated by pathological changes due to nonspecific scarring, intercurrent hypertension, infection and metabolic abnormalities. Specific therapy is unwarranted, since none has been effective and the risks and consequences of immunosuppression in uremic patients are substantial.

7. GLOMERULONEPHRITIS AND SYSTEMIC DISEASE

The kidney has a finite spectrum of pathological response to systemic disease. At the same time, different diseases may have more than one clinical presentation. The following sections are directed at reviewing the clinical presentation of systemic diseases as they affect the kidney.

Their major purpose is to point out the clinical situations in which each entity should receive consideration.

7.1. Metabolic and inherited diseases

7.1.1. Diabetes mellitus

A clinical triad thought to be the hallmark of diabetic nephropathy is hypertension, edema and proteinuria. This triad occurs in only about half of diabetic patients with nephropathy [75]. It does, however, point to the common signs and symptoms in patients with diabetic renal disease (exclusive of non-glomerular alterations that occur with increased frequency in diabetics, i.e., pyelonephritis, papillary necrosis and atherosclerosis). Thus, in evaluating patients with asymptomatic proteinuria, nephrotic syndrome and proteinuria with microscopic hematuria and pyuria, diabetes mellitus should be considered. Diabetic nephropathy invariably progresses and this may be reflected in progression of clinical manifestations from asymptomatic proteinuria to nephrotic syndrome, that may be associated with an abnormal urine sediment and hypertension. Progressive azotemia also occurs [26, 76].

Screening for diabetes includes a fasting blood sugar, a 2-hour postprandial glucose and, in questionable cases, a glucose tolerance test. The presence of renal failure, however, may make results difficult to interpret. A renal biopsy is not necessary in the vast majority of diabetic patients who develop renal disease, although when the diagnosis is not clear, a biopsy may be helpful.

Pathologically, the diabetic kidney combines features of arteriosclerosis involving large vessels (renal artery and its branches) and small vessels, including hyalinization of afferent and efferent arterioles and glomerulosclerosis. There appears to be excessive accumulation of basement membrane and mesangial matrix in many cases, with the development of diffuse glomerulosclerosis, and in a smaller percentage of patients, a nodular sclerotic lesion, the Kimmelstiel-Wilson lesion. Associated with these changes is a variable degree of tubular degeneration, atrophy and dilatation. Hyaline or exudative lesions, in which eosinophilic material is deposited along Bowman's capsule, in Bowman's space or in capillary lumens may also be seen [2, 26].

Diabetic nephropathy eventually develops in a significant number of patients and accounts for 6% of all diabetic deaths and 20% of deaths in diabetic patients under 40. A poor prognostic sign is the presence of proteinuria, and patients without proteinuria often do not develop renal failure [86]. If proteinuria develops, the time from the diagnosis of

diabetes to its onset is approximately 15 years in juvenile diabetes and 20 years in adult onset diabetes. Once nephropathy is established, it progresses and protein excretion may remain high, in spite of a decreasing glomerular filtration rate. Virtually all patients with persistent nephrotic syndrome will be in renal failure within 5 years. Nodular sclerosis is associated with hypertension, retinopathy, proteinuria and azotemia. It is always accompanied by varying degrees of diffuse sclerosis. The extent of the diffuse sclerosis and not the nodular lesion correlates directly with the extent of clinical renal disease [26].

Therapy for patients with diabetic nephropathy should be directed at its sequelae, i.e., hypertension and nephrotic syndrome, as already outlined. There is no specific treatment for the lesion itself and the role for control of the diabetes, is not clearly established. Other entities including pyelonephritis, papillary necrosis and neurogenic bladder require specific treatment as indicated in other chapters.

7.1.2. Amyloidosis

Amyloidosis may occur in previously healthy adults (primary amyloidosis) or in a setting of chronic inflammatory or neoplastic disease (secondary amyloidosis). In either case, the renal involvement that occurs in the vast majority of cases is often initially clinically overshadowed by involvement of other organ systems [51].

Renal amyloid deposition is usually most maked in glomerular capillary loops and the resulting clinical expression is proteinuria and nephrotic syndrome [40]. These are often accompanied by microscopic hematuria, granular and fatty casts and, if extensive infiltration occurs, azotemia. Uncommonly, tubular syndromes (renal tubular acidosis, nephrogenic diabetes insipidus) are prominent. This may be due to peritubular amyloid deposition. Acquired Fanconi syndrome has been described in amyloidosis, which may be due to proximal precipitation of Bence Jones protein, and which may precede amyloid deposition by years.

Amyloidosis should be a clinical consideration in the following groups:

a) previously healthy adults presenting with proteinuria or nephrotic syndrome. In this setting it is uncommon under the age of 40 but may account for 15% of idiopathic nephrotic syndrome in adults over 50. Systemic infiltration with congestive heart failure, orthostatic hypotension, carpal tunnel syndrome, peripheral neuropathy and malabsorption, may overshadow renal dysfunction [51];

b) patients with chronic inflammatory diseases who develop proteinuria or nephrotic syndrome. The most common clinical situations

include rheumatoid arthritis, osteomyelitis, paraplegics with chronic urinary tract infections or decubiti, syphilis, leprosy, bronchiectasis, ulcerative colitis and regional enteritis [51];

c) patients with multiple myeloma and other neoplastic conditions who develop significant proteinuria [51];

d) familial amyloidosis and patients with familial Mediterranean fever and proteinuria.

Amyloid is a protein that in some cases (primary amyloidosis, multiple myeloma) has the structure of the variable portion of light chains and in other cases is of indeterminate origin. Diagnosis is made by biopsy of an involved organ, and Congo Red staining that reveals a characteristic green birefringence when viewed under polarized light. Although a variety of tissues and urine have been sources for diagnosis, rectal biopsy carefully including lamina propria is positive in 85% of cases [51]. The kidney and liver should be avoided as primary biopsy sites because of an increased bleeding tendency.

Although a variety of agents including steroids, cyclophosphamide, melphalan, and colchicine, have been tried in primary amyloidosis, further trials are necessary to determine their efficacy. Treatment should be directed at controlling clinical sequelae, such as nephrotic syndrome. Secondary amyloidosis, may improve with eradication or control of the underlying disease.

7.2. Hereditary nephritis

A number of inherited disorders are associated with renal dysfunction. The one to which the term is most commonly applied, Alport's syndrome, involves a varying expression of eye, ear and renal involvement.

Alport's syndrome commonly expresses itself in childhood or adolescence. It is usually evident initially as asymptomatic, persistent, microscopic hematuria or as an acute nephritic syndrome with recurrent episodes of macroscopic hematuria, closely following an upper respiratory infection or exercise. Significant proteinuria is also often evident, suggesting significant underlying pathology, but nephrotic syndrome per se is an uncommon event [17, 69].

Alport's syndrome should be a consideration when:

a) other younger members of the family have a history of renal disease;

b) the patient and/or other family members have hearing (neurosensory) or ocular (lenticonus, spherophakia, retinitis pigmentosa) abnormalities.

There are no specific serological alterations in Alport's syndrome, and diagnosis is made in the appropriate clinical setting by characteristic, although not specific, findings in the kidney biopsy. Light microscopic findings are not specific, and in early stages light microscopy may be normal. Progression of disease reveals mesangial proliferation, increased mesangial matrix and thickened capillary walls, which ultimately result in periglomerular fibrosis and hyalinization. Interstitial changes often predominate (chronic interstitial nephritis), and characteristically 'foamy cells' are found especially at the corticomedullary junction. Immunofluorescence is typically negative. Electron microscopy reveals what has become the most characteristic lesion of hereditary nephritis: the glomerular basement membrane has areas of thickening and thinning, and the thickened areas contain a split lamina densa, separated by clear areas containing electron dense particles [32]. This is an important feature, because some families have 'hereditary benign hematuria', a non-progressive condition, with no associated hearing defect and a uniformly thinned basement membrane on electron microscopy.

Most families with Alport's syndrome appear to inherit it in an autosomal dominant pattern with variable penetrance. Males tend to be more severely affected than females and reach end stage renal failure by 25–40 years. Females in affected families may manifest minor urinary abnormalities, but occasionally also develop renal failure.

There is no specific therapy for Alport's syndrome and treatment should be directed at appropriate management of chronic renal failure.

Another inherited disease associated with hematuria, proteinuria and the development of renal failure at a later age, usually in the fifth decade, is Fabry's disease, an inborn error of glycosphingolipid metabolism (deficiency of a tissue alpha galactosidase activity). Patients with Fabry's disease accumulate glycosphingolipid in a number of tissues throughout the body. Although the natural course of the disease often ends in progressive renal failure, and this may be the only presenting sign, other clinical manifestations, including acroparasthesias, coronary or cerebral insufficiency or a characteristic papular skin lesion (in men only) may be more prominent [66].

Therapy in these patients directed at enzyme replacement, including renal transplantation, has met with variable success. Since the course and presentation is most compatible with a chronic nephritic syndrome, conservative management as outlined in other sections is most appropriate.

7.2.1. Sickle cell disease

A number of prominent renal syndromes have been described in sickle cell disease or trait. Although renal infarction, papillary necrosis and tubular dysfunction are all asociated with sickle cell disease, two other syndromes, recurrent hematuria and proteinuria, are relevant to glomerulopathies.

A major cause of gross, painless hematuria in blacks, is the presence of sickle cells. More frequent with trait than with sickle cell disease, the hematuria may be spontaneous or precipitated by exercise. The source of the hematuria appears to be an ischemic renal medulla caused by medullary intravascular sickling (resulting from hypertonicity, acidity, hypoxia) and not a glomerular lesion. Patient evaluation is the same as for all patients with hematuria, but the diagnosis of sickle hemoglobin induced hematuria is still one of exclusion. Associated clinical and laboratory findings include a urine sediment containing sickled red cells, concentrating defects and a high incidence of pyelographic abnormalities, especially calyceal defects. The rest of the evaluation is unremarkable and renal biopsy is unnecessary [21, 87].

Therapy may be directed at the factors predisposing to medullary sickling and include aggressive hydration and diuresis to produce a hypotonic urine, administration of alkalynizing agents [49], and administration of aminocaproic acid in divided doses up to 4 grams per day [24].

The presence of persistent proteinuria and/or the development of nephrotic syndrome in patients with sickle cell anemia should suggest possible underlying glomerulonephropathy. Clinical and laboratory evaluation may reveal evidence of a normocholesterolemic nephrotic syndrome with varying renal function. Other serological parameters (including complement levels) are normal. Renal biopsy most commonly reveals membranoproliferative changes or focal segmential sclerosis. These changes may be related to circulating iron-protein complexes produced during crisis or possibly to circulating immune complexes [21]. The nephrotic syndrome is not associated with sickle trait.

Progressive renal failure may occur in the nephrotic syndrome associated with sickle cell disease and no specific therapy has been of value. Successful dialysis and transplantation is possible.

7.3. Infectious disease

A variety of infectious diseases are occasionally followed by clinical and pathological evidence of glomerulonephritis. Some of the relationships,

including bacterial endocarditis and shunt nephritis, are well established, whereas others remain anecdotal.

7.3.1. Chronic bacteremia and viremia

In the pre-antibiotic era, renal failure was a common cause of death in patients with bacterial endocarditis. Friable valvular vegetations may embolize and produce microscopic or macroscopic hematuria with focal infarctions. Unless infarction is extensive, patients remain asymptomatic and renal function is preserved. An acute nephritis may also occur and patients have hematuria, red blood cell casts, proteinuria and varying degrees of azotemia [34]. This group of patients were often treated for infection late in their course, and the acute nephritis is associated with hypocomplementemia, rheumatoid factor, cryoglobulins and other immune complexes [1, 3]. Nephrotic syndrome is uncommon, but a picture consistent with rapidly progressive glomerulonephritis may evolve. This group of patients may show a striking clinical resemblance to patients with lupus and, from a therapeutic point of view, it is obviously important to distinguish between them [34].

In these clinical situations, especially when a newly detected heart murmur is evident, endocarditis should be considered and blood cultures and an echocardiogram should be done to help arrive at a diagnosis. Circulating immune complexes should also be measured. Antibiotic therapy for the endocarditis results in decreased complex formation and concomitant resolution of the glomerulonephritis [6]. No other specific therapy is available.

Circulating immune complexes and immune complex deposition may also be associated with a membranoproliferative glomerulonephritis in patients with infected ventriculo-atrial shunts for the correction of hydrocephalus. Staphylococcus albus is the most commonly isolated organism. Patients are often nephrotic and may have microscopic or macroscopic hematuria, varying degrees of azotemia and are hypocomplementemic with circulating cryoglobulins, rheumatoid factor and other immune complexes. Antibiotic therapy often results in improvement [48].

A number of other infectious agents that are uncommon in the United States are associated with glomerulonephritis. Congenital syphilis may be accompanied by a mixture of the nephrotic and nephritic syndromes and the nephrotic syndrome may accompany secondary syphilis. In either case, improvement may occur spontaneously or after antibiotic therapy. A small percentage of patients with leprosy may develop an immune complex glomerulonephritis. Chronic parasitic

infection leads to immune complex formation, and secondary glomerulonephritis may be seen in malaria (P. malariae, P. falciparium) and Schistosoma mansoni. These entities are usually unresponsive to therapy directed at the offending agents.

Chronic viremia, specifically hepatitis B virus infection, may be accompanied by hypocomplementemia and a systemic vasculitis that involves the kidneys. Of interest is one report documenting the presence of Hb antigen in deposits eluted from a number of primary glomerulonephritides, although its pathogenetic role has not been established.

Table 4. Acute infection and associated clinical syndromes.

Infectious Agent	Clinical Syndrome
Bacterial infection	
D. pneumoniae	Acute nephritis
Leptospirosis	Acute nephritis
S. typhosa	Acute nephritis
Staphylococcus	Acute nephritis
Tuberculosis	Nephrotic syndrome
Viral infection	
Infectious mononucleosis	Nephrotic syndrome, acute nephritis
CHV	Nephrotic syndrome
Hepatitis B	Nephrotic syndrome, acute nephritis
Varicella	Acute nephritis
Mumps	Acute nephritis
Echo, coxsackie	Acute nephritis
Parasites	
Toxoplasmosis	Acute nephritis, nephrotic syndrome

7.3.2. Acute infection and glomerulonephritis

A number of other infectious agents have been associated with a glomerulopathy. Since few cases have been reported, the true nature of the relationship remains unclear. The agents and the clinical syndromes they have been associated with, are listed in Table 4. Most of these infectious glomerulonephritides are nonprogressive and therapy should be directed at the underlying infection.

7.4. Toxic nephropathy

A variety of substances to which patients become exposed either deliberately as medications or inadvertently may be responsible for the development of nephrotic syndrome. The toxic mechanisms in most

cases are poorly understood and elimination of the toxin does not always lead to resolution of renal involvement. Nonetheless, a careful history is necessary to determine exposure to any of the substances listed in Table 5 and exposure should be discontinued and reexposure avoided.

Table 5. Toxic nephrotic syndrome

Medication
Gold (organic compounds)
Mercury
Penicillamine
Probenecid
Oxazolidine Compounds
Miscellaneous
'Cut' heroin
Snake bites
Bee stings
Vaccinations
Pollen allergen

7.5. Collagen vascular disease

The immune nature of the collagen vascular diseases accounts for an extremely high incidence of associated glomerulonephritis. It is important to remember that these are systemic diseases, diagnosed by clinical and laboratory studies. Renal biopsy is compatible with the systemic disease, but not diagnostic of it.

7.5.1. Systemic lupus erythematosis (SLE)

Lupus nephritis is a diverse clinicopathological entity capable of mimicking all of the clinical syndromes thus far described. Renal manifestations may dominate the clinical picture, suggesting a primary glomerulonephropathy, or extrarenal involvement may make the diagnosis more apparent. In either case, the varying incidence of reported renal involvement probably reflects the diligence with which it is looked for, and clinical and pathological severity may occasionally be quite disparate.

In all of the clinical syndromes mentioned above, SLE should be considered. This includes patients with asymptomatic urine abnormalities, nephrotic and nephritic syndrome, rapidly progressive glomerulonephritis and chronic nephritic syndrome [1, 3]. In each case, a careful history, physical and laboratory evaluation to reveal evidence of systemic disease fulfilling the American Rheumatology Association criteria

for a diagnosis of SLE, is necessary. Similarly, when a diagnosis of SLE is made, evidence of renal involvement should be searched for. In addition to clinical criteria, serological studies (i.e., antinuclear antibodies, anti-DNA antibodies) greatly aid a diagnosis of SLE. The presence of immune complexes, including DNA-anti-DNA antibody complexes, may be found and patients with active renal disease are frequently hypocomplementemic (C_3, C_4 and total CH50 activity). Urinalysis frequently reveals red and white blood cells and a variety of casts, either individually or together in a 'telescoped urine'. Proteinuria, frequently in the nephrotic range, and varying functional impairment, may be evident.

The renal pathology of lupus mimicks many forms of glomerulonephritis and a number of systematic approaches to classification are in use. The lesions seen vary in extent and severity from no obvious light microscopic change, through mesangial proliferation and focal and segmental proliferative glomerulonephritis, to diffuse proliferative lesions including crescent formation. In addition, a membranous lesion may also be seen. Serial evaluation of the pathology and clinical course in some cases, may reveal the transformation of a milder, less severe lesion to a more progressive disease [1, 28]. Immunofluorescence and electron microscopic evaluation confirms the presence of immune complexes and reveals granular deposits of immunoglobulin (especially IgG) and complement in the mesangium and capillary loops. Deposits may be present in the mesangium, subendothelially, subepithelially or intramembranously, and their magnitude and extent corresponds to the severity of light microscopic alteration. Extensive subendothelial deposition gives the appearance of capillary wall thickening, and results in the 'wire loop' lesion [1, 3].

The type of renal lesions may affect the overall prognosis, but as already mentioned, mild lesions may occasionally progress to more severe lesions. The role of therapy in lupus nephritis remains unresolved. Although steroid administration clearly improves extrarenal manifestations, the long term benefit of the wide range of immunosuppressive regimens (azathioprine, cyclophosphamide, high dose steroid 'pulse') used to treat lupus nephritis remains speculative and generally unproven [18, 25]. The following recommendations are reasonable at this time.

(1) Patients with mild lesions including mesangial proliferation do not develop renal insufficiency, unless transformation of the lesion (occurring in perhaps one third of patients) occurs and therapy for the renal lesion itself is not recommended.

(2) Patients with focal proliferative and diffuse proliferative glomerulonephritis may be extremes of a similar type of involvement. Although the courses have been considered to be different (five year renal survival in patients with focal proliferative disease 70%, versus diffuse proliferative disease 25%), a recent study suggests they may be similar. Steroids may benefit these patients. They should be continued for no more than 8–12 weeks in high dosages, then decreasing to the lowest dose that is sufficient to control non-renal lupus. Therapy for episodes of deterioration should be based on protocols allowing objective evaluation of their efficacy. The side effects of prolonged high dose steroids are considerable, and dialysis and transplantation are more suitable alternatives.

(3) Patients wih membranous nephropathy tend to do well (5 year renal survival 85%) and therapy may be the same as for idiopathic membranous nephropathy.

7.5.2. Vasculitides

The vasculitides consist of a wide spectrum of diseases that have in common a pathogenesis characterized by immunologically mediated vascular inflammation and necrosis. Vasculitis may be associated with immune complex deposition in vessel walls, with activation of a variety of mediators of inflammation, or with extensive cellular infiltration [23]. These responses are systemic in nature and the kidney's peculiar vulnerability arises from the high renal blood flow, the large renal vascular surface area and the unique sieving and concentration functions of the kidneys. The clinicopathological results of vasculitis involving the kidneys include a number of recognizable syndromes that have been classified in different ways. Although renal involvement may be significant, systemic manifestations may be more prominent and usually systemic symptoms are the ones that bring patients to physicians' attention.

7.5.2.1. Polyarteritis nodosa. Polyarteritis nodosa is a clinicopathological syndrome in which vascular lesions, at different stages of development, involve small and medium sized arteries throughout the body. Renal involvement, at least initially, is most often characterized by a vasculitis affecting interlobar and arcuate arteries, with disruption of the elastic lamina, fibrinoid necrosis of the vessel wall and subsequent aneurysm formation. The resulting renal lesions are due to ischemia, and glomeruli respond with varying degrees of proliferation and necrosis. Upon healing, these become sclerotic and obliterated. Patients are usually hypertensive and have asymptomatic proteinuria and hematuria. Neph-

rotic syndrome is uncommon, and patients may occasionally present with severe renal insufficiency and few urinary findings. Progressive renal failure is more commonly a late occurrence, when it occurs. Systemic manifestatins of the disease include fever, arthralgia, mononeuritis multiplex and affected organ infarction, and these findings often overshadow renal involvement. Hepatitis B antigenemia may also be present [23, 29].

7.5.2.2. Allergic granulomatosis. Allergic granulomatosis includes many features of polyarteritis nodosa and is distinguished by pulmonary involvement that may be characterized by asthmatic attacks. In addition, eosinophilia, eosinophilic tissue infiltration and granuloma formation occur. In addition to involving the same sized vessels as polyarteritis nodosa, capillaries and venules may be involved resulting in necrotizing glomerular lesions. Systemic manifestations tend to dominate the clinical picture, but uremia may be a sequelae. Although polyarteritis nodosa and allergic granulomatosis appear to be two distinct syndromes, features of both, including renal involvement, may be present in so-called 'overlap' syndromes [23, 29].

7.5.2.3. Hypersensitivity vasculitis (small vessel polyarteritis). The common involvement of medium sized arteries in polyarteritis and allergic granulomatosis contrasts with the characteristic small vessel involvement seen in the syndromes collectively referred to as hypersensitivity angiitis (hypersensitivity vasculitis, allergic vasculitis, leukocytoclastic vasculitis, microscopic polyarteritis). Inflammation in these small vessels is usually associated with immune complex deposition, arising in response to exogenous or endogenous antigens. The most common organ involved is the skin, leading to a variety of lesions, including typical purpura. Other organ involvement may occur and results in nonspecific symptoms similar to typical polyarteritis. With renal involvement, an active urine sediment may also be seen. Renal disease may not progress or may evolve into the syndrome of rapidly progressive glomerulonephritis. Nephrotic syndrome may also be seen. Histologically, renal involvement occurs in small caliber vessels and the glomeruli may be predominantly involved. Focal proliferation or fibrinoid necrosis and crescent formation may be seen. Electron microscopy is nonspecific and immunofluorescence reveals scanty mesangial IgG, IgM and complement deposition. Areas of necrosis and crescent formation may show prominent deposition of fibrin. An episode of hypersensitivity angiitis may occur after an upper respiratory tract infection or may follow drug

exposure. The clinical course may be self-limiting with only one episode or may recur intermittently without new exposure. Clinically distinct recognizable forms of hypersensitivity angiitis include serum sickness. Henoch-Schonlein purpura and the syndromes associated with mixed essential cryoglobulinemia.

7.5.2.4. Henoch-Schonlein purpura. Henoch-Schonlein purpura (anaphylactoid purpura) is a leukocytoclastic vasculitis that includes a characteristic pattern of skin, joint, gastrointestinal and renal involvement [5, 23, 57]. It tends to occur more commonly in children than adults. The characteristic syndrome may be less evident in adults. The severity of systemic signs and symptoms are not related to the severity of the renal lesion, and renal involvement has been reported in 20–100% of cases, depending on the criteria used and the diligence with which it is searched for. The syndrome of Henoch-Schonlein purpura may evolve variably over days or weeks with renal involvement evident at any time, but generally after other symptoms have appeared. The most common urinary abnormalities are microscopic hematuria and proteinuria. Macroscopic hematuria may also be seen, and an acute nephritic syndrome may occur in more severe cases. Nephrotic syndrome, a rapid decline in renal function similar to rapidly progressive glomerulonephritis or gradual progression to uremia may occur. They are seen most commonly as a sequel to a presentation as the acute nephritic syndrome [5, 57].

An upper respiratory tract infection may precede the onset of the syndrome, and ASLO titres may be elevated in some cases. Relapses may occur following exposure to cold or allergens, but their pathogenetic relationship remains unclear. Serological studies are generally normal, except for an elevated IgA on immunoelectrophoresis in about 50% of cases. Immunofluorescent studies on skin biopsies from areas of purpuric and normal skin may reveal IgA deposition in dermal capillaries and connective tissue. Kidney biopsies are usually characterized by a focal and segmental proliferative glomerulonephritis as well as small vessel vasculitis, and are distinguished by the diffuse mesangial IgA deposition seen on immunofluorescence [5, 57].

There is no evidence to suggest that specific therapy affects the course of the renal disease. Less than 50% of patients with the syndrome have renal involvement that exceeds inapparent microscopic hematuria and proteinuria. According to renal presentation, long term follow-up reveals the following:

a) patients with microscopic hematuria alone do very well;

b) 10–20% of patients with significant proteinuria and hematuria may develop renal insufficiency or active renal disease by 10 years;

c) patients who develop nephrotic syndrome have the poorest prognosis and over 50% are hypertensive, nephrotic or azotemic at 10 years.

Children and adults with renal disease may have a recurrence of the clinical syndrome for several years, with no evidence of worsening renal function.

7.5.2.5. Cryoglobulinemia and vasculitis. A number of diseases are associated with circulating cryoglobulins and cryoglobulinemia may also occur spontaneously as part of the syndrome of mixed essential cryoglobulinemia. In both cases, essential and secondary, a typical hypersensitivity vasculitis may occur. Secondary or mixed essential cryoglobulinemia may present clinically with a purpuric rash, occurring especially in areas exposed to the cold, arthralgias, acroparesthesias, fever and hepatosplenomegally [11]. Renal involvement may be indicated by hematuria, proteinuria, the nephrotic syndrome, and rapidly progressive glomerulonephritis may evolve. Patients have an elevated erythrocyte sedimentation rate, positive rheumatoid factor, may be hypocomplementemic, may have circulating hepatitis B antigen, and may or may not have a primary underlying disorder (i.e., rheumatic, neoplastic). The circulating cryoglobulins usually consist of a monoclonal component with antibody activity to a polyclonal IgG, although other variations also occur and may give symptoms [11, 16, 31]. Renal biopsy often reveals a diffuse proliferative glomerulonephritis and some crescent formation may occur. Treatment should be directed at lowering the cryoglobulin level and this may be accomplished by intermittent plasmapheresis. If an underlying disease exists, then treatment directed at its control may be helpful [11].

Circulating cryoglobulins may also be found in a variety of primary glomerulonephritides, without systemic disease. The type of glomerular alteration most commonly seen is a crescentic or an acute exudative glomerulonephritis [11].

7.5.2.6. Wegener's granulomatosis. Wegener's granulomatosis represents another type of vasculitis, in which a clinical picture of upper and lower respiratory tract involvement and a glomerulonephritis develop secondary to a granulomatous vasculitis [23, 91].

The syndrome is more common in males and evidence of systemic involvement may be apparent, including keratoconjunctivitis, uveitis, otitis media, necrotizing skin lesions, arthralgias, mononeuritis multi-

plex and coronary artery insufficiency. Renal biopsy reveals a necrotizing glomerulonephritis that may be segmental or diffuse and includes a granulomatous vasculitis involving both small arteries and veins. Although evidence for the presence of circulating immune complexes during active disease may be present, their pathogenetic role is unclear. Immunofluorescence of renal tissue may reveal patchy deposition of immunoglobulins. Identification of this disease is important since recent reports suggest a combination of prednisone and cyclophosphamide may greatly improve the outcome [23].

7.6. Dysproteinemias

The dysproteinemias include multiple myeloma, benign monoclonal gammopathy and Waldenstrom's macroglobulinemia. Exept for the development of amyloidosis in association with multiple myeloma, significant disease attributable to glomerular pathology is uncommon.

Patients with multiple myeloma rarely develop a glomerular lesion similar to the nodular sclerosis of diabetic nephropathy. 'Myeloma' kidney and its varying clinical manifestations, including renal failure, are attributable to tubular rather than glomerular disease. Some patients with benign monoclonal gammopathy have mild proteinuria and hematuria. Rarely, the nephrotic syndrome and renal failure develop and renal biopsy reveals diffuse proliferative glomerulonephritis. Patients with Waldenstrom's macroglobulinemia behave similarly; they may have mild proteinuria and hematuria, and rarely nephrotic syndrome and progressive renal insufficiency. Acute renal failure may occasionally result from intraglomerular IgM thrombi.

Treatment should be directed at the primary process and includes appropriate chemotherapy and plasmapheresis as indicated.

7.7. Pregnancy

Glomerulonephritis in pregnancy is a complicated issue involving several separate and often overlapping considerations including the following:

a) pregnancy with a history of acute or chronic glomerulonephritis;

b) glomerulonephritis first appearing during pregnancy;

c) toxemia and its postpartum sequelae as it relates to the above two or developing de novo in pregnancy.

In women with a history of acute or chronic glomerulonephritis, consideration is directed at how these conditions affect the fetus, and at

the same time, what effect the pregnancy will have on the underlying renal disease. Women with a history of acute glomerulonephritis may safely become pregnant when no disease activity is evident. After resolution, a one-year interval of observation is suggested before pregnancy is considered and then close attention should be paid to blood pressure, proteinuria and renal function during the pregnancy. Women with a prior history of focal glomerulonephritis and Berger's disease have no added difficulty during pregnancy. In women with chronic glomerulonephritis, the incidence of preeclampsia is approximately 17% and it may occur much earlier in the pregnancy than in normal women. This risk arises especially in women with antecedent hypertension. The presence of azotemia also adversely affects the pregnancy. The same variables also adversely affect pregnancy in women with the nephrotic syndrome and their babies tend to be small and premature. There is no objective evidence suggesting that pregnancy adversely affects the natural course of the underlying renal disease, although this may occasionally appear to occur on an individual basis [24].

Acute glomerulonephritis has been rarely reported to occur during pregnancy. Although fetal loss is high, a successful outcome is possible and termination of the pregnancy is only indicated if blood pressure or fluid balance cannot be controlled and if renal function declines. If preeclampsia develops in the last trimester, it is difficult to differentiate from acute glomerulonephritis. Findings suggestive of acute glomerulonephritis include a history that may suggest an etiology, a urinalysis with red blood cells and red blood cell casts, and appropriate serology including an elevated ASLO titer and hypocomplementemia. There is no evidence to suggest that the course of acute glomerulonephritis is affected by pregnancy, although changes due to superimposed preeclampsia may be expected to improve postpartum [24].

Preeclampsia is a multisystem disease occurring most commonly in the last trimester of pregnancy with an increased incidence in young primiparous and older primiparous women. It is defined by the development of relative or absolute hypertension, proteinuria and edema. The onset of seizures changes the terminology to eclampsia. Physiologically, a relative reduction in glomerular filtration rate occurs, plasma volume is decreased, serum renin and angiotensin levels decline and vascular reactivity to angiotensin infusion increases in the last trimester. Women who develop preeclampsia may complain of generalized edema (dependent edema commonly occurs in pregnancy without preeclampsia), headaches, visual disturbances and irritability. Physical examination reveals a relatively or absolutely increased blood pressure, vasospastic retinal arteries, generalized edema and in more severe cases hyperactive reflexes. Urinalysis is generally benign except for proteinuria and a few

red cells and rare red cell casts. Serum uric acid is increased (>4.5 mg%) and evidence of low grade intravascular coagulation is evident by the presence of circulating fibrin monomer. Renal biopsy at this time reveals a nonimmunological insult characterized by ischemc glomeruli with thickened capillary walls. Endothelial cells appear swollen with foamy cytoplasm, so-called 'endotheliosis', containing fibrin related products [24].

Differentiating preeclampamia from unmasked essential hypertension is often difficult, especially when one is superimposed on the other. Evaluation of protein excretion, serum uric acid and the degree of hypertension may be helpful.

Treatment of women with preeclampsia must be individualized. The goals to be achieved include maternal and fetal well-being with optimal timing of the delivery if possible, control of blood pressure and the prevention of decreasing renal function and eclampsia. Therapy begins with an accurate diagnosis, and symptoms may be controlled with bedrest, sedation and a low salt diet. Antihypertensive therapy is determined by the severity of hypertension. It includes diet and rest, if mild; the addition of apresoline or alpha metyldopa if further therapy is required, but diuretics should be avoided. If hypertension is severe, parenteral medications are required. No absolute drug contraindications exist. Delivery may be necessary if blood pressure cannot be controlled, if renal function declines, if coagulopathy worsens, or if eclampsia occurs. Otherwise, delivery is based on evaluation of fetal viability (lecithin: sphingomyelin ratio) and placental sufficiency.

The long term sequelae of preeclampsia or eclampsia remains unclear. It is not known whether a significant percentage of these women will have sustained hypertension or renal disease, and it appears only a third of them will have subsequent episodes of toxemia.

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5. URINARY TRACT INFECTION AND PYELONEPHRITIS

LUIS TAPIA

The relationship between urinary tract infection (UTI) in the absence of structural abnormalities and chronic renal failure is not well understood [2, 5, 7, 8, 20]. The confusion probably originated from early reports in which nearly 60% of patients dying of uremia had the pathological diagnosis of chronic pyelonephritis, which was based on morphological findings common to all chronic interstitial nephritis. However, new data indicates that only a small percentage of interstitial nephritis is secondary to UTI [24]. Furthermore, long-term follow-up in adults with chronic urinary tract infections revealed that persistent urinary tract infection does not produce renal damage [7, 8, 19], unless it is associated with an obstructive uropathy [13]. Urinary tract infection in young children [32, 54], however, is a more serious problem because it tends to be associated with a high incidence of vesicoureteral reflux and consequent renal parenchymal damage [25].

This chapter will be limited to discussion of incidence, pathogenesis and management of UTI in patients with no obstructive uropathy.

1. PREVALENCE

1.1. Overall incidence

The urinary tract is second only to the upper respiratory tract as the most common site of infection in young women; 12 out of 1,000 consultations in general practice are for symptoms related to urinary tract infection [7]. It accounts for 7% of all infections in the general population and 40% of all nosocomial infections [50].

1.2. Prevalence of urinary tract infection in children

Survey studies in newborns [1, 35] have shown that among children under the age of 1 year, boys are more susceptible to urinary tract infections, with a reported incidence of 1–2.7%. This is probably related to the higher occurrence of congenital malformations of the urinary tract in boys. In pre-school children [15], the incidence ranged from 0.2–2% in boys and 0.8–7% in girls. However, when aseptic conditions were observed and specimens were collected by professional personnel, the incidence was significantly lower. A survey in school entrance [31, 44] revealed that 1.2–1.6% of girls and .03% of boys had significant bacteriuria. Girls are more susceptible to recurrent infections than boys, probably because of the high incidence of urethral abnormalities seen in girls [6, 15]. Seventy percent of girls with recurrent urinary tract infections had distal urethral stenosis and 80% of these girls were cured after dilatation of the stenosis. Follow-up studies in school girls showed that the prevalence of significant bacteriuria rises steadily with age, with an annual acquisition rate of 0.4%. Thus, 5–6% of school girls will have urinary tract infections by the time they leave school.

1.3. Prevalence of urinary tract infection in adults

The prevalence of significant bacteriuria in adults [3, 7, 52] between the ages of 16–65, ranges from 4–6% in females and 0.5% in males. Follow-up studies indicated that spontaneous remissions and new infections occurred at a rate of 1% per year. Consequently, at any given time, the prevalence remains about the same in females. The incidence of significant bacteriuria rises with age to 10–25% in women older than 60 years and 7% in men of the same age. The incidence of bacteriuria in pregnant women [11, 56] is not higher (6–8%) than in non-pregnant women, however, approximately 20–30% of pregnant women with significant bacteriuria develop acute pyelonephritis.

The association of sexual intercourse [12, 30] and urinary tract infection is still controversial. Buckley et al. demonstrated that bacteria may enter the urethra and perhaps the bladder during sexual intercourse. They observed that 30% of intercourse episodes resulted in increases of more than one log in bacterial colony count in urine. The rise in colony count, however, was always transient.

The fact that females, sexually active or not, are more susceptible to bacterial colonization than men has been demonstrated by comparative studies done among sexually active women, nuns and male controls.

However, this study also showed that among the women, celibacy was associated with lower frequency of infection [33]. All these studies suggest that conditions relating to the anatomy and physiology of female genitalia, may play a role in the pathogenesis of urinary tract infection. As suggested by Kunin [33], there is probably a certain population of women whose urethra and vaginal mucosa are particularly susceptible to bacterial colonization.

2. CLINICAL SIGNIFICANCE OF BACTERIURIA

Bacteriuria is an abnormal laboratory finding. Its significance varies in many different circumstances. In a large survey done in the general population, 100,000 subjects were screened; 5,000 of them had significant bacteriuria. Of these, 80% had instrumentation of the urinary tract, previous treatment for urinary tract infection, a history of diabetes or hypertension and past pregnancy. Of these, 1,666 had persistent bacteriuria for over two years and all of them had histories of hypertension, diabetes, abnormalities of the urinary tract, or kidney stones. Thus, pre-existing renal disease seems to be a prerequisite for chronic UTI.

2.1. Pregnancy and urinary tract infection

Urinary tract infection in pregnant women may be deleterious to both mother and child [11, 13, 56]. In the mother, acute pyelonephritis has been reported to occur in 4–63% of the cases. The reason for this wide difference is probably related to the criteria used for the diagnosis of pyelonephritis. Using unified criteria, Brunfitt found that 31% of pregnant women with bacteriuria had acute pyelonephritis [11]. Acute pyelonephritis can induce prematurity and high fetal mortality. Early treatment of pyelonephritis might prevent these complications. Even though bacteriuria in pregnant women more often causes pyelonephritis than in non-pregnant women, it rarely progresses to chronic renal disease.

2.2. Hypertension and urinary tract infection

The causal relationship between hypertension and pyelonephritis [19, 33, 38] is obscure. Miall, Kunin and Freedman, in separate studies, reported that blood pressure is slightly higher in patients with urinary tract infection than in control groups. The cause and effect relationship between urinary tract infection and hypertension is still

controversial. Some observers suggest that hypertension is predisposed to pyelonephritis [45]. They hypothesize that ischemia and/or hypokalemia, that may complicate hypertension, make the kidney more susceptible to infection. Others believe that pyelonephritis induces hypertension, based on the observation that hypertension subsides following the treatment of pyelonephritis and that malignant hypertension is 10 times more frequent in patients with pyelonephritis (15–20%) than in the general population (2%).

2.3. Diabetes and urinary tract infection

Although urinary tract infections are not more frequent in diabetic patients, when they do occur, they are more severe than in non-diabetics. Previous reports indicate that the higher incidence of pyelonephritis in diabetics was probably derived from autopsy findings in which advanced renal changes secondary to diabetes were indistinguishable from those of pyelonephritis. Recent surveys in juvenile diabetics showed that one out of 94 girls and none of 76 boys had significant bacteriuria.

2.4. Bacteriuria in non-pregnant women

Urinary tract infection in non-pregnant women is usually a benign condition [7, 8, 20, 52]. Asscher [7] followed 107 women with significant bacteriuria and 87 matched controls over a period of 3–5 years. He found no evidence of progressive kidney damage in untreated patients with persistent bacteriuria, providing that hypertension and obstructive uropathy were not part of the clinical picture.

2.5. Bacteriuria in children

Significant bacteriuria in young children is a more serious matter [7, 43, 47]. Failure to control it may lead to retardation of kidney growth and pyelonephritis, especially when vesicoureteral reflux or urinary tract obstruction are present. Vesicoureteral reflux is found in approximately 30–60% of children with significant bacteriuria, and approximately 20% of children under the age of five with significant bacteriuria and associated reflux, have evidence of kidney damage by intravenous pyelography.

In older girls (ages 5–11), bacteriuria usually remits spontaneously within six months. Treatment of bacteriuria in this group can be post-

poned for this period of time, allowing spontaneous remissions to occur. Only 'high risk' patients with urinary tract abnormalities may need to be treated. Therefore, in children with persistent bacteriuria, screening for urinary tract abnormalities is mandatory.

The natural history of significant bacteriuria in older boys [22] is different from that in girls. Hallet et al. found that out of 73 boys with significant bacteriuria, 30% had urological abnormalities, and 8% already had pyelonephritic changes. The source of infection was probably the prepuce and urethral flora. Recurrence of infection in the absence of urinary tract abnormalities was rare in this series.

2.6. Bacteriuria in men

In the absence of severe urological disease or concomitant non-infectious renal disease, urinary tract infection in men [21], as in women, is a benign condition. A U.S. Public Health Service cooperative study by Freeman and collaborators followed 249 men with bacteriuria for 10 years. All patients with persistent bacteriuria received specific antibiotic therapy, followed by two years of prophylactic treatment with sulfamethizole, nitrofurantoin, methenaminmandelate or placebo. Continuous therapy with antimicrobial agents delayed reoccurrence of bacteriuria and reduced acute clinical exacerbations. However, after two years of therapy, further antimicrobial therapy did not make any difference in the subsequent clinical course of patients with obstructive uropathy. They demonstrated that the best prognosis was in patients infected with E. coli, without anatomical abnormalities within the kidney or urinary tract, and those who had had no previous antibiotic therapy. The worst prognosis was seen in patients with prostatic disease, stones, pyelonephritis and mixed enterococcal infections.

2.7. Nosocomial urinary tract infections

Urinary tract infection is the most common nosocomial infection in the U.S. [51]. It accounts for 40% of all hospital acquired infections, with over 80% of these following catheterization or other urological manipulations [50]. The risk of infection increases with the duration of hospitalization. Fortunately, the majority of these infections are benign with relatively low morbidity and mortality. However, these infections are a serious problem in patients with impaired immune response, *i.e.*, elderly patients with lengthy hospitalization for surgical and urological procedures and serious underlying disease, immunosuppressed patients with

malignancies such as leukemia and lymphomas, and patients who have undergone kidney transplantation. In fact, 83% of patients with associated bacteremia and 95% of patients that die of sepsis belong to this group.

The transplanted group deserves special attention because approximately 60% of these patients developed urinary tract infections within the first 4 weeks following transplantation [14, 28, 29]. Although these infections were not associated with a particularly poor prognosis for graft survival in general, we observed a significant difference in the bacterialogic spectrum between the successful and unsuccessful transplant groups and demonstrated an association between streptococcus faecalis urinary tract infection and loss of the allograft [14].

3. PATHOGENESIS

Bacteriuria produces symptoms and diseases in some but not all individuals affected. As mentioned previously, there may be a susceptible population of patients in which local and systemic immunological factors may play a role in the pathogenesis of chronic pyelonephritis, some of which are described below.

3.1. Local barriers of invasion

The intact urinary tract has a great ability to resist infections. A normal bladder can eliminate 99% of bacteria instilled into it by the simple mechanical washout effect of urine flow. Furthermore, the bladder wall secretes bactericidal substances including organic acids and other unidentified substances [41]. The pH (<5 or >8) and high osmolality (over 800 in mOsm) of urine also have a bacteriostatic effect [39].

3.2. Cervico-vaginal antibodies

The cervico-vaginal secretions of normal women have antibodies that protect them against bacterial infections. Using an antibody coated bacteria technique, Stamey et al. demonstrated the presence of cervico-vaginal antibodies in 77% of normal women and in only 26% of women with recurrent urinary tract infections [49]. E. Coli were demonstrated to adhere more avidly to mucosal cells isolated from the introitus of susceptible women than the ones obtained from resistant women. This was probably due to the absence of cervico-vaginal antibodies in

the susceptible women. The most common antibody in the cervicovaginal fluid seems to be of the IgA type. IgG is also present and IgM is detected in less than half of them.

3.3. Uroepithelial antibodies

Local antibodies of the IgG type were first documented in patients that had a partial nephrectomy done because of localized pyelonephritis. Subsequently, local antibodies of the IgA type were detected in the urine of patients with urinary tract infections, who at the same time had IgA antibodies to the same organism in serum.

The capacity of E. coli to adhere to uroepithelial cells from patients with symptomatic and asymptomatic bacteriuria was studied by Eden et al. [17] who found that E. coli adhesion to uroepithelial cells was much higher in symptomatic patients than in asymptomatic patients. The capacity for an organism to adhere or not to the renal tissue is probably related to local antibody response: local antibodies coat the bacteria and block their site of attachment to the host's epithelial cells and prevent symptomatic infections. However, bacteria with little or no capacity to adhere may still be able to survive in the urinary tract, especially if residual urine is present.

3.4. Systemic antibody response

In acute renal infections [23, 40], IgM antibodies can be detected in serum. IgG antibodies, on the other hand, are present in patients with recurrent pyelonephritis. Levels of antibody titer correlate well with degrees of radiological abnormalities in the kidney. Antibodies may have a protective effect against hematogenous infections but their role in ascending infections is not clear.

3.5. Other mechanisms

Local immunological factors can protect the host against bacterial invasion of the kidney. However, their importance in the long term prognosis of urinary tract infection is uncertain [37].

Some patients with radiographic changes suggestive of chronic pyelonephritis may give no past history of urinary tract infection. One possible explanation is that these changes may not be due to chronic infection but related to other causes of interstitial nephritis. However, assuming the infection was the cause of these changes, several hypo-

theses, some of them based on animal experimentation, have been postulated. Kalmanson et al. [27] using parabiosed rats, demonstrated that bacteria may initiate the lesion but were not needed for the progression or persistence of the disease. He postulated that a cell-mediated mechanism is stimulated in the host, which would explain the persistence of interstitial mononuclear cell infiltration and fibrosis, despite eradication of the infections, and the occurrence of the disease in the parabiosed rat.

Other studies [37] have shown that antibodies against E. coli cross-react with kidney tissue due to an immunological similarlity between E. coli and kidney antigens. It is conceivable, therefore, that antibodies against E. coli could attack the kidney and the subsequent inflammatory response might produce renal damage even in the absence of active infection. Bacterial endotoxins have been shown to alter the antigenicity of renal tissue. Thus, it would be theoretically possible for auto-antibodies to be produced against this altered tissue and produce renal damage. Bacterial antigenic residues have been demonstrated in the kidneys of experimental animals for months after the induction of pyelonephritis. This residue could stimulate the local production of antibodies by the kidney and perpetuate the renal damage. Although the above immunological mechanisms may be important in the pathogenesis of pyelonephritis in animals, they have not been proved to play a role in human infections.

3.6. Vesicoureteral valve

The competency of the vesicoureteral valve is the most important factor in the prevention of ascending infections in humans. The urinary tract can become infected either by hematogenous or ascending routes. The hematogenous route is uncommon except in those who have either a systemic infection or defective immune system. The initial lesion is usually in the form of cortical microabscesses. However, some organisms, such as group D-streptococci and proteous species, have a predilection for the medullary region. The ascending route of invasion is the most common, but it only occurs when the vesicoureteral valve is incompetent.

3.6.1. Functional vesicoureteral incompetency

Vesicoureteral valve competency can be altered by inflammation of the bladder wall alone, without anatomical changes of the vesicoureteral valve itself. This may explain the 30–60% incidence of vesicoureteral reflux seen in children with bacteriuria. The reason for this vesicoure-

teral valvular dysfunction during inflammation is probably related to the anatomical characteristics of subepithelial tissue of the urinary tract. The subepithelium is a continuous compartment that extends from the bladder to the ureters, renal pelvis and intra-renal interstitium. During an inflammatory process, it could be affected in its entirety, rendering the vesicoureteral orifice incompetent and allowing the urine to reflux into the kidney. All these changes, however, are reversible as the inflammatory process subsides.

3.6.2. Permanent vesicoureteral incompetency

Vesicoureteral incompetency can be permanent by either persistent inflammation and scarring and/or due to congenital anatomical anomalies of the vesicoureteral valve. The latter is common in children under the age of 4 in whom reflux of urine, especially when it is infected [43, 47], will produce permanent renal damage with retarded kidney growth and eventual renal failure.

3.6.3. Vesicoureteral reflux

The mechanism of renal damage by reflux has been studied in humans [43, 47] and pigs [25], by micturation cystograms during which the radio-opaque material flows back from the calyces into the kidney in a 'fan shape' distribution, up to the ducts of Bellini at the papillary tip from where it spreads to the collecting tubules. The leak of urine propelled in this fashion into the renal parenchyma, might produce renal damage either by direct mechanical action or by the release of tubular lysosomal enzymes. Cortical atrophy can be detected in the areas where the reflux of urine is more pronounced. However, cortical scars do not develop unless the urine becomes infected. In these circumstances, the renal medulla, because of its peculiar anatomical and physiological characteristics, is more susceptible to infections than the rest of the kidney. In fact, blood flow and oxygen delivery to this region is markedly decreased, which lowers its resistance to injury. The high ammonia concentration in this region has an anti-complementemic effect that limits its inflammatory and chemotactic response. The hypertonicity of the papilla interferes with the phagocytic function of leukocytes and macrophages, and consequently allows the proliferation of protoplast and L-forms in this part of the kidney.

4. ETIOLOGY

4.1. Bacterial infection

The most common organisms involved in urinary tract infections are the Gram negative bacteria, of which E. coli is the most common [21, 51]. This organism is isolated most often from uncomplicated acute urinary tract infections [21], but it has been involved in chronic infections as well. Approximately 40% of urinary tract infections in the general population are caused by E. coli, followed by Klebsiella, enterobacter, pseudomonas, proteus, group D-streptococcus and staphylococcus. Approximately 20% of these infections are mixed infections. In hospital acquired infections [51], E. coli is also the most common offender with 46% incidence, followed by proteus 19%, klebsiella 14%, pseudomonas 12%, enterobacter 7% and serratia 2%. Infections with klebsiella, serratia and pseudomonas are usually superimposed infections in previously treated patients, with obstructive lesions, and are often associated with bacteremia and high mortality rate.

Urinary tract infections with proteus [47], are commonly associated with the formation of strubite or magnesium ammonium phosphate stones. This bacteria has the ability to produce urease. Urease splits urea and produces an alkaline urine, with higher levels of ammonium ions, which produce super saturated urine and stone formation.

Infections with group D-streptococcus are common in patients with a history of recurrent urinary tract infection [21, 27]. According to Freeman et al. [21], the isolation of this organism was an important signal of a complicated and refractory urinary tract infection and progressive renal failure. Streptococcus faecalis is known to produce protoplasts and L-forms after antibiotic therapy. This may help to explain the persistant infection and progressive renal damage. Also, as demonstrated by Kalmanson in parabiosed rats, it may also trigger immunologic mechanisms of cellular immunity that would explain the progressive renal damage in the absence of active infection.

Streptococcus viridians, staphylococcus aureus and staphylococcus epidermis are occasional urinary pathogens. Anaerobic bacterial infections [29] are rare but have been related to the presence of anatomic abnormalities of the urinary tract, indwelling catheters, advanced age, poor metabolic status and renal transplantation. In our experience, anaerobic infections following renal transplantations occur in patients who received cadaver renal grafts and who had been heavily immunosuppressed.

4.2. Fungal infections

Fungal infections occur more frequently in patients with defective immune systems, as in hematologic or lymphoproliferative malignancy or kidney transplantation. Diabetics are also more prone to develop fungal infections.

The most common fungal infection is candidiasis, which can be acquired by either hematogenous or ascending routes, especially in catheterized, debilitated and elderly patients. Other fungal infections such as nocardia, aspergillosis, blastomycosis, and mucormycosis, may cause urinary tract infection as part of the disseminated state of the disease, usually in immunosuppressed subjects.

4.3. Viral infection

The role of viral infection in chronic renal disease is very speculative [57]. Viruria is known to occur in the course of measles, mumps, Coxsackie B and other systemic viral infections. Though rare, cases of Coxsackie B, lymphocytic choriomeningitis virus and cytomegalic virus pyelonephritis have been reported. Infections with advenovirus type II have been associated with increased susceptibility to E. coli pyelonephritis.

5. CLINICAL MANIFESTATIONS

The presentation of acute pyelonephritis is readily recognized and includes fever, chills, flank pain, headache, myalgia, anorexia and prostration. Concomitant lower urinary tract symptoms, such as dysuria, tenesmus, frequency and suprapubic tenderness, are frequently present. Other symptoms, such as nausea, vomiting, diarrhea and abdominal distention are occasionally seen, and symptoms of central nervous system are rarely seen. By physical examination, costovertebral angle tenderness and a tender kidney on palation are frequently present.

In the evaluation of a patient with urinary tract infection, the past medical history is very important because approximately 28% of the school girls and 40–90% of women with significant bacteriuria, have a past history of urinary tract infection [32]. In these patients, a careful evaluation of the urinary tract to rule out structural abnormalities should be done.

The majority of adult patients with upper urinary tract infection do not have radiologically demonstrable abnormalities [9, 10, 36]. In this

group, acute pyelonephritis may be followed by some loss of renal mass, although no cortical deformity or caliectasis develops. The radiological features that indicate chronic pyelonephritis, have only been seen to develop in infancy with the presence of severe vesicoureteral reflux [43, 47]. However, progressive renal damage does occur in adults if there are associated complicating factors such as hypertension, analgesic abuse, persistent vesicoureteral reflux, diabetes mellitus, obstruction or neurogenic bladder [9, 13, 21]. The extent of investigative studies of patients with urinary tract infection obviously involves many factors. In patients with recurrent infections, urologic evaluation should be performed to rule out urinary tract abnormalities.

6. DIAGNOSIS

The diagnosis of urinary tract infection relies principally upon the demonstration of significant bacteriuria (over 100,000 bacteria per ml. of urine) by quantitative cultures of an aseptically collected specimen of urine [3, 16]. A number of semiquantitative methods are presently available to differentiate between significant and non-significant bacteriuria, of which the dip-slide is the most practical screening method for general practice.

6.1. Urine collection

Urine should be collected during mid-stream voiding. However, when contamination can not be avoided, suprapubic aspiration is the method of choice.

6.2. Microscopic examination

The direct microscopic examination, including Gram stain, of the mid-stream urine specimen, is probably the most valuable initial examination that should be done [34, 42]. In Kunin's series, the presence of bacteriuria by Gram stain had a 80–90% correlation with quantitative cultures. Lewis and Alexander also reported a 99% correlation between them. Robbins had similar results and he concluded that quantitative cultures were not needed when the microscopic stain was negative.

Pyuria does not necessarily correlate with significant bacteriuria but indicates inflammation in the urinary tract [4]. The presence of bacteria and pyuria should be followed by quantitative cultures to establish the diagnosis.

6.3. Localization

The source of bacteriuria can be detected by direct and indirect methods.

6.3.1. Transurethral catheterization

Transurethral catheterization is a direct method to determine the source of bacteriuria [54]. However, this method has a high morbidity rate (2–10%) and is not justified for use in just obtaining a culture specimen.

6.3.2. Fairley test

One of the most popular tests presently used to determine the source of bacteriuria is the bladder washout or Fairley test [18]. It consists of sterilizing the bladder by topical instillation of neomycin sulfate solution, followed by collecting the urine (after administration of a diuretic to increase urine flow) through an indwelling catheter for quantitative cultures. The first samples are urine from the lower urinary tract and the later samples from the upper urinary tract. If the later colony counts increase over the initial count, the site of bacteriuria is assumed to be the upper urinary tract.

6.3.3. Antibody coated bacteriuria

Recently, some emphasis has been placed on the determination of antibody coated bacteriuria in the urine to differentiate between upper and lower urinary tract infection [26, 53]. Bacteria invading the renal tissue presumably induces an antibody response and the antibody coats the organisms, which are shed into the urine where it can be detected by immunofluorescent tests with antihuman immunoglobulin. According to studies by Jones et al. and Thomas et al., this test is a sensitive, reliable and noninvasive technique to differentiate upper and lower urinary tract infections. However, Silverberg [46] reported that 23.6% of girls (ages 2–13 yrs.) with asymptomatic bacteriuria had positive tests of antibody coated bacteriuria, but only one of five children with calyceal scarring and one of three with vesicoureteral reflux, had positive results of antibody coated bacteriuria. Although the test is a sensitive and non-invasive technique to differentiate the location of infection between upper and lower urinary tract, the positive result does not necessarily indicate the presence of renal parenchymal damage.

6.3.4. Renal biopsy

Renal biopsy is contraindicated if a diagnosis of urinary tract infection

or pyelonephritis is suspected. However, biopsies done during an acute attack of pyelonephritis have shown, most of the time, only occasional white cell casts in the tubules and polymorphonuclear leukocyte filtration in interstitial tissue. Histologic changes characteristically associated with chronic pyelonephritis (obtained by nephrectomy or autopsy studies) are marked interstitial round cell infiltration, tubular dilation and atrophy and periglomerular fibrosis. These changes, however, are nonspecific of pyelonephritis and indeed are seen in a variety of conditions that affect the medullary tissue and interstitium of the kidney such as diabetes mellitus, sickle cell anemia, vascular disease, medications like phenacetin and uric acid deposits. Thus, chronic pyelonephritis, if it exists as an isolated entity, could be included in the broader category of diseases called tubulo-interstitial nephritis.

7. MANAGEMENT

7.1. Asymptomatic bacteriuria

Covert or asymptomatic bacteriuria that is discovered during routine screening and is not associated with anatomical defects in the urinary tract, should not be treated immediately. Rather, its presence should be confirmed under strict aseptic conditions. Sometimes, the suprapubic aspiration technique is preferred to obtain a proper urine specimen in young children, when contamination can not be avoided otherwise. If the presence of bacteriuria is confirmed, the location of infection should be determined by either the Fairley test or detection of antibody coated bacteriuria.

Asymptomatic bacteriuria originating from lower urinary tract does not need to be treated. However, high risk patients (diabetes mellitus, pregnancy, immunodeficiency by either disease or drugs and anatomical abnormalities in urinary tract) should be treated.

7.2. Acute pyelonephritis

Acute pyelonephritis should be treated vigorously. Gram stain of the urine should be used as a guide to initiate treatment. Gram positive organisms can be treated with ampicillin and gram negative organisms may require aminoglycosides, and should be given until culture and sensitivities results are available. If the infection is acquired in the hospital, the likelihood is that the organism will be a resistant E. coli,

klebsiella, proteus, pseudomonas or serratia. Then, parenteral aminoglycosides should be used empirically without delay until culture and sensitivity results are available. The oral route should be used as soon as constitutional symptoms subside.

The duration of therapy must be individualized, although 7–10 days is the reasonable period for acute infection. In simple infections, reculture of the urine 48 hours after starting therapy, should confirm the efficacy of treatment by a sterile urine culture. If the organisms are still present, then obstruction or anatomical lesions should be considered. Following treatment, it is essential to obtain urine cultures 2–3 weeks, 3 months and 12 months thereafter.

7.3. Recurrent infections

In recurrent infections, relapses should be differentiated from reinfections by the serotypes of the infective organisms. If the serotype is the same, the recurrence is most likely due to relapse, but if the serotype is different, the present infection is a reinfection. In relapses, antimicrobial therapy should be intensified with the help of a minimal inhibitory concentration (M.I.C.) test to reach the appropriate dose. In reinfections, an anatomical lesion or obstruction should be strongly considered. Sometimes 'intra-renal obstruction' by small radioluscent stones are the cause. Relapses and recurrences characterize the clinical course as long as the obstruction persists.

7.4. Antibiotics

In choosing the appropriate antibiotic, several factors should be considered. If the antibiotic is eliminated by the kidney, the minimal inhibitory concentration is achieved with relatively small doses of antibiotics. Thus, the total dose required is much less and therefore drug toxicity is reduced.

Urine pH is an important factor in the effect of antibiotics on the kidney. Aminoglycosides along with penicillin and erythromycin are much more effective in alkaline urine. Tetracycline, furantoin and mandelamine are more effective in acid urine. Ampicillin has the same effect in alkaline or acid urine.

Although bactericidal drugs are preferable, in practice this may not always be feasible. Besides, there is little evidence that drugs which are bactericidal in vitro, are more effective than those which are bacteriostatic in vitro. When a combination of drugs must used, the synergistic

and antagonistic effect of each agent should be established. Of the antibiotics most commonly used, ampicillin is probably the best one because of its bactericidal effect and high tissue penetration. The cephalosporins are also frequently used. Other antibiotics such as aminoglycosides are nephrotoxic, but they may be used when indicated.

7.5. Prophylaxis

Post-coital bacteriuria or 'honeymoon' cystitis is generally self limited and does not require treatment. In cases of recurrence, prophylactic treatment either with nitrofurantoin, nalidixic acid, slow acting sulfonamides and trimethoprim-sulfamethoxazole at bedtime and the following morning has been recommended. This practice seems to reduce the incidence of symptomatic bacteriuria in sexually active females. For patients who have irreparable urinary tract abnormalities or high risk patients with episodes of recurrent urinary tract infections, it is generally recommended to use long term bacteriostatic drugs.

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6. TUBULO-INTERSTITIAL NEPHRITIS

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INTRODUCTION

Tubulo-interstitial nephritis (interstitial nephritis) includes a group of diseases in which the initial inflammatory process occurs in the interstitium and tubular structures of the kidney. The glomeruli are spared early in the course, but are eventually affected by the sclerosing process.

The response of the interstitium to injury is limited and nonspecific. The interstitium responds to injury with edema and cellular infiltration (lymphocytes, macrophages, plasma cells, polymorphonuclear leukocytes and eosinophiles) in the acute stage, and with increased collagen and mucopolysaccharide deposition, peritubular fibrosis, tubular basement thickening, flattening and atrophy of the tubular cells, accumulation of proteinaceous material within the tubules (so called 'thyroidization' of the kidney), periglomerular fibrosis and patchy infiltration of lymphocytes and plasma cells, in the chronic stage. The clinical manifestations are also nonspecific and include polyuria, isosthenuria, salt wasting, renal tubular acidosis, pyuria and eventually azotemia.

Interstitial nephritis is an important cause of chronic renal disease, representing probably one-quarter of the population of patients on hemodialysis or waiting for transplantation. Conditions that have been incriminated as a cause of interstitial nephritis are listed in Table 1. Among these, obstruction is the most common, followed by analgesic abuse and hyperuricemia. Urinary infection alone is not an important primary cause of chronic renal disease but it frequently complicates other conditions [43]. Although it was at one time thought to be a common cause of chronic interstitial nephritis and chronic renal failure, new information has been accumulated indicating that urinary tract infections in the absence of structural abnormalities in the urinary tract are not an important cause of progressive renal failure.

Table 1. Diseases that have been incriminated as a cause of interstitial nephritis

1. Hereditary Kidney diseases:
   1. medullary cystic disease
   2. sponge kidney
   3. Alport's syndrome
2. Metabolic Kidney diseases:
   1. hypercalcemia and nephrocalcinosis
   2. hypokalemia
   3. oxalate nephropathy
   4. gouty nephropathy
3. Hematologic diseases:
   1. hemolytic uremic syndrome
   2. sickle cell anemia
4. Vascular diseases:
   1. hypertension
   2. arteriosclerosis
   3. diabetes mellitus
   4. aging process
   5. renal artery stenosis
   6. renal thromboembolism
   7. acute tubular necrosis
5. Neoplastic diseases
   1. lymphomas
   2. leukemia
   3. myeloma
   4. amyloidosis
6. Infectious diseases
   1. bacterial
   2. viral
   3. fungal
   4. protozoal
7. Immunologic diseases
   1. anti-tubular basement membrane antibodies
   2. immune complex nephritis
   3. reflux nephropathy and chronic pyelonephritis
   4. drug related nephropathy
   5. renal transplant
   6. Sjögren's syndrome
8. Analgesic nephropathy
9. Heavy metals
10. Balkan nephropathy
11. Radiation nephritis
12. Obstructive uropathy

1. HEREDITARY KIDNEY DISEASES

Among the hereditary kidney diseases, medullary cystic disease, medullary sponge kidney and hereditary familial nephritis (Alport's syndrome) may be associated with interstitial processes in addition to the primary congenital defects.

1.1. Medullary cystic disease

Medullary cystic disease is inherited as an autosomal dominant trait, manifested more frequently in children, and characterized by salt wasting, acidosis, anemia and azotemia. Hypertension is uncommon in this condition. The gross appearance of the kidney is characteristic and consists of small, pale kidneys with atrophic cortex and small, approximately 1 cm in diameter cysts in the corticomedullary junction. Microscopically the cortical tubules are atrophic and the cortical collecting ducts are dilated. Near the papillae, the collecting ducts are very narrow or even obstructed with marked, concentric thickening of the basement membrane. The interstitial space is replaced by fibrous tissue and infiltrated with lymphocytes, macrophages and plasma cells.

There is no effective treatment for this disease other than supportive therapy.

1.2. Medullary sponge kidney

Medullary sponge kidney is a benign disorder, unless it is complicated by stones or infections. Diagnosis is made by the typical pattern on intravenous pyelography that varies from a papillary blush to extensively opacified large cysts. Plain films of the abdomen may show oval calcifications within the kidney.

The lesion consists of ectatic collecting ducts, limited to a few ducts or extended throughout both kidneys. The dilated ducts are lined by stratified, transitional epithelium, and filled with a gelatinous, brown material and precipitates by hydroxyapatite. Some patients, with this condition, have hypercalciuria and distal tubular dysfunction.

Its etiology is unknown but it appears to be familial. It can occur in children but usually becomes apparent between the 2nd and 5th decade of life. It is usually asymptomatic and no treatment is needed. However, in cases of hypercalciuria with stone formation, hydration and thiazide diuretics are indicated. Infections should be treated early, specifically and intensively.

1.3. Hereditary familial nephritis (Alport's syndrome)

Alport's syndrome consists of nephropathy (glomerulopathy and interstitial disease), nerve deafness and eye defects (lenticonus, cataracts and spherophakia). It is inherited in an autosomal dominant pattern.

It was initially described as an interstitial nephritis. However, subsequent reports indicate that glomerular basement thickening is one of the earliest changes. A characteristic of this disease is the presence in the interstitium of foam cells containing neutral lipid. These cells are, however, not specific for this condition.

High frequency hearing impairment is common and its severity is related to the degree of renal involvement. Males are affected more frequently than females and the first symptoms and signs are asymptomatic hematuria, mild proteinuria and pyuria. Renal insufficiency may develop early in life and is rapidly progressive.

There is no effective treatment for this disease.

2. METABOLIC KIDNEY DISEASES

Hypercalcemia, hypokalemia, hyperoxaluria and hyperuricemia are relatively common metabolic causes that can produce interstitial nephritis. Hyperphosphatemia and choline deficiency are rare causes of interstitial nephritis.

2.1. Hypercalcemia

Hypercalcemia and hypercalciuria produce renal disease by two mechanisms. The first is related to the formation of calcium stones and subsequent obstructive uropathy (urolithiasis). The second mechanism is more complicated and probably related to the deposition of calcium in the renal interstitium (nephrocalcinosis).

Acute hypercalcemia in experimental animals [3] produces mitochondrial swelling within one hour of its administration followed by cytoplasmic and basement membrane deposition of calcium. The earliest detectable lesions are seen in the distal convoluted tubules and collecting ducts. The injured tubules plug the lumen with necrotic debris and calcium precipitates producing intrarenal obstruction. The obstructed tubules collapse and the tubular cells atrophy. The cortical areas that correspond to the damaged tubules become atrophic. Atrophic cortical areas alternate with normal cortical tissue. Interstitial fibrosis and lymphocytic infiltration follow this insult, which leads to periglomerular

fibrosis and glomerular hyalinization. Vascular calcifications, superimposed infections and intrarenal stone formation, complete the pathological picture of nephrocalcinosis.

The earliest functional change is a decrease in the maximal concentrating ability. Glomerular filtration rate and renal plasma flow are normal early in the process. However, in acute and severe hypercalcemia, glomerular filtration and renal plasma flow may be significantly diminished. When hypercalcemia subsides, these measurements return to normal. In long-standing hypercalcemia, prolonged inflammatory reaction and interstitial fibrosis make these functional changes permanent, producing renal insufficiency. Other tubular abnormalities seen in nephrocalcinosis are renal tubular acidosis (distal type) as well as sodium and potassium wasting [41].

2.2. Hypokalemia

Profound, prolonged hypokaliemia produces interstitial changes similar to chronic pyelonephritis [41]. The most characteristic lesion, although not pathognomonic, is vacuolization of the proximal and distal tubuloepithelial cells. The vacuoles disappear when hypokalemia is corrected. Irreversible changes are less certain and it is difficult to predict when they will appear [45]. In animal experiments, the most characteristic lesions occur in the inner medulla where intracytoplasmic droplets and whorl-like bodies are detected. The outer medulla and cortico-medullary junction shows hyperplasia and swelling of the epithelial cells of the collecting ducts which produce intrarenal obstruction and increased susceptibility for infection. Chronic hypokalemic changes with tubular dilatation (cyst-like formation) and interstitial fibrosis are difficult to differentiate from chronic pyelonephritis [41].

As in other interstitial disease, the first functional abnormality is a decrease in the maximal concentrating ability. In advanced stages, cortical scarring, tubular atrophy, interstitial fibrosis and glomerulosclerosis are seen. Cellular infiltration is variable. Renal insufficiency is usually present at later stage and may progress to end stage renal disease.

Interstitial nephritis from other causes may lead to urinary potassium wasting and hypokalemia. The role of kaliuria and hypokalemia in these instances is unknown.

2.3. Oxalate nephropathy

Oxalate is a non-metabolizable end product of glycine metabolism [50].

The renal clearance of oxalate exceeds that of creatinine, because oxalate is both actively filtered and secreted by the proximal tubules. Thus, the oxalate-creatinine clearance ratio is greater than 1. Most oxalate is derived from endogenous metabolism. The intestinal absorption rate of oxalate is only 3–5% of that ingested in the diet. A normal diet contains approximately 100 mg of oxalate and therefore only 3–5 mg of oxalate are absorbed by the gastrointestinal tract. The daily excretion of oxalate, on the other hand, ranges from 20–50 mg per 24 hrs.

Hyperoxaluria can be due to increased excretion, absorption or production of oxalate.

2.3.1. Hyperoxalurias can be secondary to two congenital enzyme defects. Type 1: due to a deficiency of soluble 2-oxoglutarate, glyoxalate carboligase. Characterized by an increased excretion of oxalic acid, glyoxilic acid and glycolic acid in the urine. And Type 11 due to a deficiency of a dehydrogenase, associated with an increased excretion of L-glyceric acid.

2.3.2. Abnormal absorption of oxalates may be due to increased ingestion of oxalate precursors such as glycolate, glyoxalate and ethylene glycol. The ingestion (usually accidental) of ethylene glycol [8], in doses as low as 100 ml (equivalent to 3–10 grams of oxalic acid) produces marked hyperoxaluria and extensive crystallization in the renal tubules with interstitial edema and celular infiltration and manifested by flank pain, tenderness and oliguria.

2.3.2.1. Methoxyflurane, a general anesthetic, is known to produce nephrogenic diabetes insipidus in some cases [39]. But also can produce hyperoxaluria up to ten times normal [17]. Massive oxaluria can be complicated by acute tubular necrosis and transient renal failure. A small percentage of patients however may develop permanent renal damage due to interstitial inflammation and fibrosis [21].

2.3.2.2. Hyperoxalurias secondary to intestinal disease [25, 26] (inflammatory bowel disease, intestinal by-pass, etc.) were initially thought to be due to decreased absorption of conjugated bile in the ilium. The bile entering into the large intestine would be in the form of glycine conjugated bile salts. The glycine moiety is split by bacterial action into glyoxalate which is converted into oxalic acid in the liver. This hypothesis was supported by the fact that taurine and cholestyramine, which bind bile salts in the gut, decreased oxalate excretion in the

urine. However, the bile salt theory is not supported by more recent metabolic studies. Present evidence suggests that hyperoxaluria associated with intestinal disease is secondary to increased absorption of oxalate from the diet, probably related to a low free calcium/oxalate ratio in the intestine. Low intestinal calcium may allow free oxalate to be absorbed more rapidly from the intestine.

High urinary concentrations of oxalate for any cause can lead to its precipitation in the distal tubules and produce intrarenal obstruction. Oxalic acid usually precipitates as calcium oxalate in the tubules. Calcium oxalate crystals have a peculiar yellowish-brown color and are anisotropic under polarized light. Following intraluminal deposition, the tubules dilate and the interstitium reacts with cellular infiltration and fibrosis, followed by hypertension and azotemia.

2.4. Gouty nephropathy

The association of gouty arthritis and renal disease was first recognized by Aretaeus the Cappodocian, a contemporary of Galen, approximately 20 centuries ago. Since then, innumerable reports have accumulated implicating nephritis as a common complication of gout [49] with an incidence ranging from 18–41%, depending on the reported series.

The evidence that asymptomatic hyperuricemia produces renal disease is, on the other hand, limited and inconclusive [35]. The only extensive evaluation of the long term effect of hyperuricemia on the kidney is the Framingham study in which 5,000 patients were followed for over 12 years. During this time, 240 of them had uric acid levels of 7 mg per dl or greater, of which 12 patients had 'renal disease'. Seven of the twelve had a new diagnosis of renal disease but their courses were not defined; five of the twelve patients had pre-existing renal disease. Other investigators [16] have shown no statistical difference in mean serum creatinine levels before and after the onset of hyperauricemia. Klinenberg et al. [32], on the other hand, showed that 63% of patients with asymptomatic hyperuricemia had 'some kind' of renal function abnormalities such as a defect in the tubular concentration and acidifying functions.

The pathogenesis of interstitial nephritis associated with hyperuricemia has been recently clarified by the development of animal models in which a chronic hyperuricemic state and uricosuria was produced by feeding rats oxonic acid, a potent hepatic uricase inhibitor, plus a dietary supplement of uric acid [4]. Uric acid crystals precipitated in the distal tubules and disrupted the tubular basement membrane, producing an

exudative response of neutrophilic granulocytes and tophi formation in the interstitium, with giant cell reaction around the crystals, increased collagen deposition and interstitial fibrosis. The glomeruli and blood vessels were normal early in the process.

In humans, three major mechanisms of renal damage have been associated with abnormal uric acid metabolism; 1. 'blockade' uric acid nephropathy, 2. chronic gouty nephropathy and 3. urate stones.

2.4.1. The first mechanism is related to the massive production of uric acid in diseases such as lymphomas and leukemias, in which cell destruction by chemotherapy releases large amounts of nucleoproteins. These are subsequently incorporated into purine metabolic pathways and lead to increased uric acid production. High serum levels of uric acid are associated with uricosuria and precipitation of large amounts of amorphous and crystalline uric acid within the tubules and collecting ducts. These produce a mechanical 'blockade' of the tubules and damage of the tubulo-epithelial cells. This damage is folowed by an interstitial reaction and inflammatory response. The area of the kidney most severely injured by this mechanism is the papilla. Hydration with normal saline, alkalinization of the urine with sodium bicarbonate and carbonic anhydrase inhibitors can prevent this damage. However, when the load of uric acid is too large, acute oliguric renal failure takes place. This process, fortunately, is almost always reversible and the tubular cells regenerate with complete resolution within a few weeks. Nowadays, acute uric acid nephropathy is seen less frequently because of the growing awareness of this possibility in patients with malignancies, and the prophylactic use of allopurinol (xanthine oxidase inhibitor), that prevents the production of uric acid.

2.4.2. The second mechanism is a slow indolent process that occurs in patients with persistent hyperuricemia (familial or idiopathic) that leads to a chronic interstitial process known as 'gouty kidney' and manifests itself clinically by mild proteinuria and slowly progressive renal insufficiency. This condition although commonly associated with gouty arthritis, can occasionally occur in the absence of arthritis.

Necropsy findings of patients with gouty nephropathy reveal bilateral cortical scars and a granular surface with parenchymal deposits of white specks or streaks of uric acid and urates throughout both kidneys. Stones within the collecting system are also frequently seen. Microscopically, uric acid and urate crystals are detected within the collecting

tubules and interstitium respectively, which produce epithelial cell injury, peritubular cell infiltration and interstitial fibrosis.

To make the diagnosis of gouty nephropathy, however, the negative birefringent crystals must be detected by polarized light. In order to do this, the specimen should be fixed in 70% alcohol. Otherwise, because of the solubility of uric acid in water, it can be missed. Two types of crystals can be detected by this technique; a rhomboid crystal with radial striations, which is uric acid, and a crystal of varied size which is sodium-monourate [13]. Both crystals are brilliantly refractile in polarized light with a yellow or yellow green color. The uric acid crystals deposit within the tubules and produce an exudative reaction, similar to that seen in experimental animals [5], with infiltration of neutrophils, interstitial inflammation and atrophy of the epithelial cells. Epithelial cell degeneration is demonstrated by an increase in the lipofuscin granules in the cytoplasm of these cells. The urate crystals, on the other hand, are seen in the interstitium where they form tophi, with aggregation of lymphocytes and monocytes, and the formation of multinucleated giant cells.

The source of urates in the interstitium is still controversial [13, 14]. Some authors believe that they are formed primarily by interstitial crystallization. This is supported by X-ray diffraction studies that identify uric acid within the tubules and sodium monourate in the interstitium. The explanation for this segregation is based on the observation that acid pH decreases the solubility of uric acid causing precipitation within the tubular lumina. The relative alkalinity and high sodium concentration of the interstitium, on the other hand, favors the crystallization of sodium monourates in the pyramids and papillary interstitium [13]. This 'local environment' also explains the absence of crystallization in the cortex, which is hypotonic and highly vascular. Recent animal experiments have shown that intratubular crystals migrate into the interstitium, through the damaged collecting tubules, and produce chronic inflammatory changes in the interstitium [14]. Regardless of their origin, however, urate crystals with tophi formation, are the only characteristic feature of 'gouty nephropathy' and its absence, from a specimen appropriately fixed in alcohol, rules out gout as the cause of the interstitial process.

2.4.3. The third mechanism involves the production of stones, which depends on the solubility of uric acid, or its salts, in the urine [48]. As mentioned above, uric acid precipitates in acid media, urate salt precipitates in alkaline media. Approximately 10–20% of gouty patients even-

tually develop radioluscent stones. Furthermore, uric acid stones are a common complication of otherwise asymptomatic hyperuricemias, and the development of stones is an indication to treat the hyperuricemia. The reason for stone formation is unknown; local factors like acid urine, dehydration, and systemic acidosis are probably the most common contributory factors.

Pure uric acid stones are rare and many of them contain calcium salts. The best prevention for stone formation is hydration. Alkalization of the urine, although important in the prevention of uric acid precipitation in the acute stage, may not be practical in the chronic stage. Thus, short term alkalization is beneficial, but long term alkalinization has not been proved to be effective.

3. HEMATOLOGIC DISEASES

3.1. Hemolytic-uremic syndrome

Hemolytic-uremic syndrome is characterized by disseminated intravascular coagulation, microangiopathic hemolytic anemia and acute renal failure associated with fibrin thrombi in small arteries and afferent arterioles of the kidney. Patients that survive the acute stage of hemolytic uremic syndrome can develop interstitial nephritis consisting of interstitial edema and tubular necrosis in the areas of vascular involvement. These lesions can progress to interstitial fibrosis and tubular atrophy.

3.2. Sickle cell anemia

Sickle cell anemia has long been known to be associated with a specific renal lesion [1]. One of the earliest manifestations of sickle cell disease is a functional inability to concentrate the urine. This defect is not limited to the homozygous (Hemoglobin SS disease), but is also present in the heterozygous (Hemoglobin SA disease); therefore, it is not related to the anemia. The concentration defect is patially reversed after blood transfusion in children [47], but becomes fixed late in life. The reason for the concentration abnormalities are explained by the hypertonic environment of the medulla that promotes sickling and lowering of blood flow in the vasa recta. This concentration defect becomes fixed late in life due to papillary necrosis and interstitial fibrosis. Patients with sickle cell anemia undergo what is called 'spontaneous papillectomy', during the

natural course of their disease. This is due to recurrent episodes of papillary necrosis that lead to the total destruction of the papillae. The cortex is not affected and the glomerular filtration rate remains normal for prolonged periods.

4. VASCULAR DISEASES

Hypertension, arteriosclerosis, diabetes mellitus and aging are systemic conditions that affect the interstitium producing ischemic interstitial fibrosis and tubular atrophy. The glomerular lesions (glomerulosclerosis), however, determine the prognosis, and the interstitial process plays only a small part in the clinical course.

Other conditions such as renal artery stenosis and thromboembolic disease can produce tubular interstitial changes with interstitial fibrosis or acute ischemic infarct, depending on the rapidity of the insult. Renal artery stenosis is usually associated with hypertension and renal insufficiency due to decreased renal blood flow and glomerular filtration rate. Thromboembolic disease may be associated with cortical necrosis and acute renal failure.

5. NEOPLASTIC DISEASES

Leukemia, lymphoma and myeloma can affect the kidney directly by parenchymal infiltration of malignant cells, indirectly by invading the renal vessels or by secondary effects such as hypercalcemia, hyperuricemia, lysozymuria, abnormal proteins (Bence Jones) or amyloidosis.

5.1. The incidence of renal involvement in patients dying of lymphoma ranges from 42–63% [38, 46]. The lesions may be either multiple discrete nodules or diffuse infiltration of the interstitium. The latter is particularly common in lymphosarcoma and reticulum cell sarcoma. Lymphomatous renal involvement is often accompanied by painful flank masses and bilateral enlargement of the kidneys. Renal insufficiency occurs in 14% and uremia in 3.8% of the cases [29]. Acute reversible renal failure due to massive lymphomatous infiltration responsive to radiation or chemotherapy has been reported. This is important because if recognized early, it can be treated successfully.

5.2. Leukemias are rarely complicated by uremia. However, renal par-

enchymal infiltration in a nodular or diffuse pattern has been reported in 52–67% of the cases [44].

5.3. The association of multiple myeloma and kidney disease is well known [37]. However, the renal abnormalities attributed to multiple myeloma have only recently been thoroughly investigated and are probably related to the excretion of Bence Jones protein in the urine [11]. Bence Jones protein appears to exert a direct nephrotoxic effect, at the tubular level, with resultant tubular dysfunction and tubular atrophy. This has been confirmed by the presence of kappa and lambda chains by immunofluorescent studies in the renal tubular cells. It seems that during the process of tubular reabsorption and metabolism of these proteins, the tubular cells are damaged, however, the exact mechanism of tubular injury by these abnormal proteins is not well understood. Intra-tubular precipitation of light chains might also contribute to renal damage (cast nephropathy) by the simple mechanical obstructive effect.

In patients with multiple myeloma, renal tubular defects such as decreased concentrating ability, abnormal acidification of the urine and renal tubular acidosis, are frequently found (Fanconi syndrome).

5.4. Amyloidosis may be associated with multiple myeloma and chronic inflammatory diseases [23]. Amyloid deposition occurs primarily in the glomeruli and in 60% of the cases it results in nephrotic syndrome. However, amyloid deposits in the interstitium, vasa recta, loop of Henle and collecting ducts also occur and may produce renal concentrating abnormalities and renal tubular acidosis (distal type) [9].

Amyloidosis has been reported to regress following the treatment of the original disease [12]. This suggests that an early aggressive treatment of the primary underlying disease could prevent deterioration of renal function.

6. INFECTIONS

This subject will be discussed in detail in Chapter 5.

7. IMMUNOLOGICAL DISEASES

Recently, immunological mechanisms have been recognized as playing a

role in the pathogenesis of tubulo-interstitial diseases [53]. Most of this knowledge was gained through animal experimentation and extrapolated to human pathology. Two major immunological mechanisms are particularly significant in the pathogenesis of tubulo-interstitial nephritis [31, 34]. The first mechanism is related to the production of antibodies directed against the tubular basement membrane. The second mechanism is related to the deposition of immune complexes in the tubular basement membrane. These may either be derived from circulating immune complexes or found *in situ*. Cellular immune mechanism may also play a role.

7.1. Antitubular basement membrane antibodies

Antitubular basement membrane antibodies have been demonstrated in experimental animals following injection of autologous kidney homogenates or partially purified glomerular basement membrane preparations. Sera from such animals react with both glomerular basement membrane (GBM) and tubular basement membrane (TBM) [52]. Following the administration of large doses of these preparations, TBM deposition occurred after GBM sites were saturated. Specifically, guinea pigs immunized with rabbit renal cortical basement membrane developed anti-GBM and anti-TBM antibodies, and produced extensive tubulo-interstitial lesions. Interestingly enough, similar lesions developed even in normal guinea pigs when they received sera containing anti-TBM antibodies from nephritic guinea pigs. Guinea pigs immunized with heterologous (bovine) tubular basement membrane preparation, also produced marked tubular disruption and interstitial injury but only minimal glomerular changes. These lesions appear to be complement dependent since they did not develop in complement-depleted animals.

Anti-TBM antibodies can be demonstrated in approximately 70% of patients with anti-GBM antibody glomerulonephritis [51]. The significance of this finding, however, is unknown. Nevertheless, anti-TBM antibody might contribute to the tubulo-interstitial process that frequently accompanies anti-GBM antibody glomerulonephritis.

Other conditions in which anti-TBM antibodies have been demonstrated, are post-streptococcal glomerulonephritis [40], immune complex glomerulonephritis of unknown etiology [34], membranous nephritis, Fanconi's syndrome [31] and milk allergy complicated with nephrotic syndrome [22]. In the latter, circulating antibodies, that react with renal tubular brush border and the mucosal surface of human jejunum, was reported.

7.2. Immune complex interstitial nephritis

Immune complex can induce tissue injury either by deposition of circulating immune complexes in the target organ or by the combination of circulating antibodies with antigens previously deposited in the renal tissue, similar to the Arthus' reaction.

Experimental serum sickness is a good model to study the nature of immune complex disease in both its acute and chronic forms. In experimental serum sickness, immune complexes can be demonstrated following injection of bovine serum albumin that contains IgG and C_3. These deposit in many susceptible organs, such as the lung, spleen and liver, as well as in the peritubular capillaries and TBM of the kidney. A well studied animal model of natural immune complex disease is the NZB mouse. These mice suffer from an immune complex disease that is similar to systemic lupus erythematosus in humans. In this model, depositions of immune complexes are commonly observed in the GBM as well as in the TBM.

Specific animal models for renal tubular injury have been developed using injection of autologous or homologous antigens. Rats immunized with autologous renal tubular (brush border) antigen develop tubular injury after the immune complexes are deposited in the GBM and in the proximal tubules. Rabbits immunized with homologous kidney or human renal tubular (brush border) antigen develop renal tubular injury associated with deposition of IgG and C_3 in the interstitial tissue.

Seventy percent of patients with systemic lupus erythematosus have evidence of immune complex deposition in the tubular basement membrane and interstitium [7]. The immune complexes contain immune globulins (IgG, IgM and IgA), complement, and nuclear antigens. However, renal injury does not correlate with the amount of immune complex deposited, and extensive deposits can be associated with minimal morphological and functional abnormalities and vice versa.

7.3. Reflux nephropathy

Reflux nephropathy may be associated with an increased excretion of tubular protein, the Tamm-Horsfall (TM) protein. Circulating anti-TM antibodies and deposits of immune complexes containing TM antigen and anti-TM antibody in the tubules have been demonstrated in experimental animals [24]. These findings suggest that interstitial changes seen in obstructive uropathy with reflux, in the absence of infection, could be immunological in nature.

Some cases of chronic pyelonephritis in which eradication of the infection does not stop the chronic, progressive destruction, could also be due to an immunologic process. Kalmanson [28] has demonstrated that rats infected with Streptococcus fecalis develop progressive interstitial nephritis. The nephritis progressed, despite treatment with antibiotics and eradication of the infection. He was able to transfer these lesions to a parabiosed controlled rat, raising the possibility that chronic progressive pyelonephritis, without active infection, may be due to a cell mediated [27] or humoral immunologic process. This might explain many of the so called idiopathic or 'primary' tubulo-interstitial diseases in humans.

7.4. Drug-related interstitial nephritis

Of particular interest is the demonstration of anti-TBM antibodies in patients with methicillin-related interstitial nephritis [6]. IgG and complement are deposited along the TBM, but not the GBM. The pathogenesis of methicillin-related interstitial nephritis has been attributed to the presence of dimethoxyphenylpenicilloyl, a metabolite of methicillin, which combines as a hapten with TBM (protein-hapten conjugate), and induces the production of antibodies reactive with TBM. One of the most characteristic histologic features in the disease is the presence of large number of eosinophils in the interstitium and the excretion of eosinophils in the urine. Other penicillin derivatives (ampicillin, naficillin, oxacillin and penicillin G) as well as cephalosporins, sulfonamides and phenidion have also been incriminated in this type of lesion (see Chapter 10).

7.5. Renal allografts

Anti-TBM antibodies are frequently observed after renal transplantation [2]. The antibodies seen in transplantation are of two types; a broad non-specific, antitubular antibody that reacts with both native and transplanted kidneys, and a more specific antibody, that reacts against the allograft TBM only. Circulating immune complexes are also found in renal transplant recipients. The nature and significance of these complexes have not been clarified.

7.6. Sjögren's syndrome

Sjögren's syndrome is a disease of immune deficiency in which the

renal involvement is limited to the interstitium and consists of lymphocytic infiltration, tubular destruction and interstitial fibrosis [50]. Mild proteinuria (less than 1 gm per 24 hours) is present in less than 10% of the cases. Glomeruli and blood vessels are usually spared. Functional abnormalities, however, are prominent and consist of defects in maximal concentrating ability and urinary acidification. In mild cases, patients can concentrate the urine up to 700 mOsm/l and in severe cases nephrogenic diabetes insipidus may occur. Distal renal tubular acidosis is the most common clinical sign at the time of presentation. Proximal tubular defects (aminoaciduria and decreased reabsorption of uric acid and phosphorus) have also been reported.

8. ANALGESIC NEPHROPATHY

Phenacetin and aspirin, alone or in a combination, are the drugs frequently incriminated as a cause of a chronic interstitial nephritis. The pyrazoles and the newer nonsteroidal anti-inflammatory agents have also been implicated as nephrotoxic agents. Dextropropoxyphene and other analgesics are occasionally reported as a cause of interstitial nephritis [20].

Analgesic abuse is a common cause of interstitial nephritis in the United States; it accounts for approximately 20% of recently diagnosed interstitial nephritis and 7% of all causes of chronic renal disease in this country. The problem of analgesic abuse, and its consequence in the kidney, have only recently been recognized in the United States [42], where this problem may be as prevalent as in other countries. One of the problems in the recognition of analgesic abuse is patient's denial [43]. Because of this, a detailed history about the use of drugs is mandatory in every patient with renal insufficiency of unknown etiology.

Epidemiologic studies on the use of analgesics and development of renal disease are confusing and controversial. However, recent evidence suggests that the adverse effects of these drugs on the kidneys are probably related to the total amount of the drug consumed, duration of analgesic use, and to the levels of the drug within the kidney.

8.1. Aspirin

Short term administration of aspirin produces transient shedding of renal tubular cells in the urine, and increased excretion of tubular

enzymes (LDH and N-acetyl BD glucosamidase) in experimental animals. In humans, the administration of 3–4 grams of aspirin may produce hematuria, pyuria and enzymuria that persists for up to ten days after the dosing. Prolonged consumption of aspirin in patients with rheumatoid arthritis was reported to produce distal tubular dysfunction in some patients. Patients taking aspirin, 1 gm per day, from 10 to 18 months, as prophylaxis for myocardial infarction, have an incidence of microscopic hematuria of 1.2% compared to 0.3% of a control group.

Aspirin can produce almost complete uncoupling of oxidative phosphorylation in the renal mitochondria. It also inhibits the synthesis of prostaglandins, that may interfere with intrarenal blood flow. Salicylate is relatively uniformly distributed throughout the renal cortical and medullary tissue, and there is no significant change in the intrarenal distribution during hydropenia or hydration [30].

8.2. Phenacetin

Phenacetin and acetaminophen, in contrast to aspirin, concentrate 10 times more in the medulla than in the cortex. The renal lesions produced by phenacetin are dose related. Abnormalities in urinary concentration, acidification and sodium conservation are frequently present, independent of the dose. This tubular dysfunction is reversible when phenacetin is discontinued. Chronic administration of large doses of phenacetin or its metabolite, acetaminophen, in the range of 2–7 gm per day in humans, produces tubular changes that are reversible or preventable if the patients are well hydrated. Hydration diminishes the medullary gradient of phenacetin and decreases its toxicity. High concentrations of acetaminophen produce oxidative damage in cells by depleting them of reducing agents, such as glutathion.

8.3. Pathology

Papillary necrosis is the primary lesion caused by analgesic abuse [18]. Early in the course papillary changes occur around the collecting ducts and extend upward through the medulla to the cortex and eventually produce cortical atrophy and fibrosis. The cortical atrophy is proportional to the degree of tubular destruction. Infections usually complicate this process (15–65%) but they are not necessary for the development of the histological changes seen in analgesic nephropathy. One of the most characteristic gross anatomic features associated with analgesic nephropathy is a distinctive deep bluish-black to yellow discoloration of the

cortical medullary junction, representing the accumulation of the drug in the tubules. Chronic interstitial nephritis produced by analgesic abuse is characterized by expansion of the interstitial space with deposition of mucopolysaccharides, infiltration of mononuclear cells, tubular atrophy, epithelial cell pigmentation, intracytoplasmic brown granules containing hemosiderin, tubular membrane thickening and interstitial fibrosis. The peritubular capillaries show varying degrees of obliteration that may be partially the cause of the lesions. The glomeruli overlying the necrotic areas show various changes ranging from periglomerular fibrosis to complete hyalinization of the vascular tuft. The glomeruli in the non-affected areas are normal.

8.4. Pathogenesis

The mechanism of renal damage in analgesic abuse is unclear [19, 42]. Many of the proposed mechanisms that explain these lesions are based on experimental observations in which very high doses of drugs are utilized; higher than those used in clinical medicine. Nevertheless, acetaminophen, a metabolite of phenacetin, may cause more severe oxidative damage in the presence of aspirin, because aspirin depletes the mitochondria of oxidative phosphorylation and acetaminophen interfere with the anaerobic pathway of the cell [19]. Furthermore, any agent that has the ability to interfere with the anaerobic pathway of the tubular cell could produce renal damage in the presence of aspirin. Aspirin (as well as all of the known nonsteroidal antiinflammatory drugs) has also an inhibitory effect on prostaglandin synthesis that could reduce blood flow and shunt blood from the inner to the outer cortex.

Vasoconstriction related to the renin-angiotensin system due to the diminished renal perfusion and reduced blood flow to the inner medulla due to the lack of prostaglandins produce ischemia and necrosis of the endothelial cells of the papilla followed by vascular obliteration, collagen deposition, interstitial inflammation and papillary necrosis. Salicylates also reduce erythrocyte 2–3 DPG [33] which impairs the oxygen carrying capacity of blood and aggravate this anoxic changes.

8.5. Clinical manifestations

The clinical manifestations of analgesic nephropathy are varied. Inability to concentrate urine is almost always present. Azotemia may be sudden and severe when acute papillary necrosis is the initial event, or it may be more insidious when the papillary necrosis is chronic. Renal colic

and hematuria may occur with acute papillary necrosis. Proteinuria is usually less than 1 gm per 24 hours. Renal tubular acidosis is also a frequent early sign. Sterile pyuria is a common finding, present in over 50% of the patients. Discontinuation of the drug usually halts the progress of the disease, but patients that continue to use analgesics often have progressive renal disease with chronic renal failure and uremia.

9. HEAVY METALS

Chronic lead poisoning may produce chronic interstitial nephritis, manifested by a slowly progressive renal insufficiency, mild proteinuria and impaired renal concentrating ability. Of interest, lead nephropathy is associated, in over 50% of the cases, with gout. This is probably related to the decreased tubular excretion of uric acid, in these patients. Histologically, lead nephropathy is characterized by severe bilateral interstitial fibrosis and scarring.

Cadmium intoxication has been associated with Fanconi's syndrome in man and experimental animals, due to proximal tubular changes produced by this metal.

10. BALKAN NEPHROPATHY

This is an endemic renal disease limited to a small area by the Danube [10]. Its etiology is unknown, but may be related to environmental factors rather than to a genetic predisposition. The lesion is seen in approximately 20% of the people of this region. Subjects that leave the area before the age of 10 are not affected; however, after this age people that emigrate from this area can manifest the disease late in life. The minimal exposure to the area to develop functional changes is approximately 10 years and permanent changes occur after 20 years of exposure. Thus, this disease, although reported at different ages, is more common during the third and fourth decade.

The first structural anomalies, before any functional manifestation, are a local tubular atrophy, edema and fibrosis of the interstitium. Glomeruli and blood vessels are not affected. Interstitial inflammatory cell infiltration is minimal and mostly lymphocytic. The interstitium is inexorably replaced by fibrous tissue, with complete destruction of the renal architecture. At the end, the kidneys are small and atrophic and

weigh approximately 40–60 gm each. The hyaline material seen in this condition has been shown to give a positive reaction for amyloid.

The first clinical manifestation of this disease is a decrease in maximal concentrating ability and tubular proteinuria (usually less than 1 gm per 24 hours). The urinary sediment may contain granular casts and few white and red cells. Proteinuria and sediment abnormalities are intermittent, but progressive. Defects in urinary acidification may also be present, with aminoaciduria, glucosuria and ribonuclease excretion. Serum uric acid is low. Hypertension is mild early in the disease, but progressive and severe at the end.

11. RADIATION NEPHRITIS

Radiation nephritis is a form of tubulo-interstitial disease produced by radiation given for the treatment of abdominal or retroperitoneal malignancies [36]. The major clinical manifestations are hypertension, proteinuria, edema and renal insufficiency of varying severity. Renal injury is dose related; large doses (5,000–10,000 rads) produce severe and extensive renal damage that is associated with malignant hypertension and progressive renal insufficiency within 6–12 months following treatment. A smaller dose (1,000–3,000 rads) usually results in a prolonged latent period and later development of either asymptomatic proteinuria or mild hypertension and minimal renal insufficiency. In mild cases the latent period can last an average of 11 years. The renal lesion starts as lipid deposition in the endothelial cells of the glomeruli and tubulo-epithelial cells, followed by mesangial expansion, glomerular basement membrane and tubular basement membrane thickening. The endothelial lesion produces narrowing of the vascular lumen, decreased glomerular blood flow, ischemia and fibrinoid necrosis of the glomerular tuft. Concomitantly, tubular epithelial cells flatten and the renal tubules collapse. After the acute insult, renal parenchyma is replaced by fibrous tissue, with peritubular fibrosis and glomerular hyalinization. The arteries show medial and intimal thickening followed by necrosis and thrombosis. The vessels more frequently involved are the arcuate and interlobular arteries. Inflammatory cell infiltrates are minimal in this form of nephritis.

Unilateral radiation produces the same changes in the irradiated kidney; hypertension is curable by unilateral nephrectomy in this case.

Since renal damage is dose related, large doses of irradiation will produce massive renal damage, rapid deterioration of renal function and

malignant hypertension. Patients that survive the acute insult will progress to chronic renal failure. Although radiation nephritis is a very rare cause of renal failure at the present time, nephrologists should be aware of the problem as long as radiation is used for the treatment of intraabdominal and retroperitoneal malignancies.

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7. CYSTIC DISEASES OF THE KIDNEY

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1. INTRODUCTION

Renal cysts are a heterogeneous group of inherited, developmental and acquired disorders. Despite this non-uniformity, there is value in grouping the types of cystic abnormalities because they share certain characteristics. The major categories of cystic disease are: 1) cystic dysplasia which connotes abnormal renal morphogenesis and differentiation; 2) polycystic disease of both autosomal recessive and autosomal dominant type; 3) medullary cysts of several types including medullary sponge kidney, and the complex of medullary cystic disease; 4) isolated cortical cysts; and 5) inherited syndromes of multiple malformations which are associated with renal cysts.

Table 1. Classification of renal cysts

I. Cystic Dysplasia
A. Segmental Dysplasia
B. Multicystic Kidney
C. Familial
II. Polycystic Disease of the Kidney
A. Infantile
B. Adult
III. Medullary Cysts of the Kidney
A. Medullary Sponge Kidney
B. Medullary Cystic Disease Complex
1. Juvenile Nephronophthisis
2. Medullary Cystic Disease
3. Renal-Retinal Dysplasia
IV. Cortical Cysts of the Kidney
A. Peripheral Microcysts
B. Juxtamedullary Microcysts
C. Simple Cortical Cysts
V. Renal Cysts in Hereditary Syndromes

A major problem besetting workers in the field of renal cystic disease has been one of confusing nomenclature. Despite difficulties in communication, it appears that cystic diseases are probably responsible for approximately 5–10% of all patients reaching end stage renal disease.

2. CYSTIC DYSPLASIA

Cystic dysplasia is a non-inherited, developmental abnormality of the fetal kidney. It is usually unilateral and therefore may be asymptomatic [17, 21]. Infrequently, only a segment of an otherwise normal kidney is dysplastic. The degree to which one or both kidneys are affected comprises a broad spectrum and determines whether symptoms will be present. The end result of this defect is a disorganized renal parenchyma that cannot perform normal renal functions.

2.1. Renal aplasia

Occasionally a kidney is small, fibrous and aplastic and has only a few small cysts in the parenchyma. The kidney or segment of kidney so affected has no functioning or histologically normal nephrons.

2.2. Congenital multicystic kidney

The congenital multicystic kidney, a type of cystic dysplasia, is composed of many cysts of variable size with complete disarray of renal architecture. It is probably the most common cystic renal disease in children [16, 17].

2.3. Pathology

The multicystic kidney consists of many thin-walled cysts of varying size, containing clear fluid and held together by connective tissue. There is no normal pelvis, papillae, or calyces. The ureter is often a fibrous cord. In its fully expressed form, the kidney resembles 'a bunch of grapes'.

The cysts are dilated ducts lined with cuboidal or columnar epithelium. The walls of the cysts contain smooth muscle cells and numerous thin-walled blood vessels. Cartilage is often present while bone is rarely found. Islands of renal parenchyma consisting of clusters of tubules and

small abnormal glomeruli with only a few capillary loops are found in the connective tissue.

2.4. Etiology and pathogenesis

Cystic dysplasia is not hereditary or familial. Sex distribution is equal [17, 21]. The etiology is unknown, although there are several theories [16]: 1) interference with nephrogenesis must be early, probably before 8–10 weeks, when the normal branching collecting tubules and the normally arranged nephrons begin to develop; 2) obstruction to urinary flow in the fetus may be the primary cause. Early back pressure of urine may cause an abnormal environment for nephrogenesis [21]. In support of this theory, is the case of duplication of the ureter where an obstructed ureter is attached to one pole of a kidney which then becomes dysplastic; 3) a basic defect in the ureteric bud or a defect in the metanephric tissue may be present so that the ureteric bud lacks proper stimulation.

2.5. Clinical presentation

Multicystic kidneys most commonly present as a unilateral flank mass found incidently during physical examination of the infant [9, 21]. It is probably the most common cause of a unilateral abdominal mass in infancy. If the contralateral kidney is normal, there may be no symptoms unless there are compressive signs [21]. Urinalysis and laboratory evaluation are normal. Functional impairment may be present if the involvement is bilateral.

2.6. Diagnosis

On abdominal flat plate X-rays, a multicystic kidney may be seen with annular calcifications lining the large cysts [6, 9]. Intravenous pyelography will not reveal the involved kidney but may show the renal mass compressing other abdominal organs [6, 13]. On retrograde pyelography a blindly ending ureter may be seen with diverticula occasionally noted [13]. Complete atresia or hypoplasia of the renal artery may be noted on renal arteriogram. It has been claimed by Kyaw [13] that a triad consisting of a nonfunctioning kidney on intravenous pyelogram, a hypoplastic or absent renal artery and atretic proximal ureter with diverticula distal to the atresia is diagnostic of a multicystic kidney.

There are several findings associated with multicystic kidneys. On the

contralateral side, approximately 30% of affected patients have associated abnormalities such as malrotation, uretero-pelvic obstruction or segmental dysplasia. Cystic dysplasia of the kidney may be associated with trisomies C, D, G, or E, Down's Syndrome or Turner's Syndrome. Associated development abnormalities in other organ systems include: ventricular septal defects, duodenal atresia and meningomyelocele [9].

The differential diagnosis of multicystic kidneys includes unilateral hydronephrosis and Wilm's tumor. With both of these, there is usually found some renal parenchyma on the involved side. X-rays studies show a distorted renal pelvis and renal calyces with Wilm's tumor [9, 13]. Sonography is helpful in differentiating between these entities. Surgical exploration may be necessary for definitive diagnosis. In adults, the differential diagnoses of agenesis of the kidney and renal cell carcinoma must be considered.

2.7. Prognosis and therapy

If the contralateral kidney is normal the prognosis is excellent and no therapy is needed unless infection on the involved side occurs. Compressive symptomatology may warrant surgical removal [21].

3. POLYCYSTIC DISEASE

The term polycystic disease includes two separate clinical entities: adult polycystic disease and infantile polycystic disease. These disorders may be differentiated by their modes of inheritance as well as by their radiologic and pathologic appearances [4, 14]. Confusion in the use of terminology has arisen because adult polycystic disease occasionally appears in infants and during childhood. These entities have also been confused with cystic dysplasia when one kidney is more involved than the other.

3.1. Infantile polycystic disease

Infantile polycystic disease often affects the liver and occasionally other organs. Some have identified congenital hepatic fibrosis as a separate entity from infantile cystic disease, although in 50% of cases there are associated cystic renal lesions [14]. Others feel that this is a variation of the same basic disorder [4]. Infantile polycystic disease is rarer than the adult polycystic disease and is most commonly found in the neonatal period [16].

3.1.1. Pathology

The kidneys are symmetrically enlarged but retain normal renal contour. Tiny cysts are visible everywhere at the surface. The ureters are normal and the pelvis and calyces are of normal shape but enlarged. The cut surface of the kidney shows many tubular cysts.

The parenchyma is made up of large cysts collecting ducts, lined by cuboidal epithelium. There is little increase in connective tissue between the ducts. Glomeruli, proximal and distal convoluted tubules and loopes of Henle appear normal. The cystic and parts of the nephrons communicate freely. The liver is invariably and diffusely abnormal with infolding, proliferation and dilatation of portal bile ducts and ductules. There is a variable degree of periportal fibrosis.

3.1.2. Etiology and pathogenesis

The disease is inherited as an autosomal recessive [2, 4]. Early development of the nephron is normal and all the parts of the nephron are normally arranged. Later in fetal life the collecting ducts become abnormal. Secondary to these changes, those patients who live past the neonatal period develop loss of concentrating ability and produce large amounts of dilute urine [2, 20]. They may also develop a distal type of renal tubular acidosis.

3.1.3. Presentation and diagnosis

These children present at birth usually after prolonged labor, with abdominal distention due to their huge kidneys [2]. Although liver pathology is present, there is no clinical evidence of hepatic dysfunction [4]. Bilateral flank masses may be palpated. If renal function is markedly impaired, oligohydramnios, arthrogryposis, respiratory distress and the typical facial appearance described by Potter; prominant epicanthal folds, flat nose and large, flat low-set ears, are commonly noted.

Urine analysis shows a dilute urine and occasional proteinuria, microscopic hematuria and pyuria. Hypertension, acidosis and progressive uremia may occur within a few months [14].

Intravenous pyelogram is usually pathognomonic, demonstrating bilateral renal enlargement with radiating opaque striation of contrast media extending from the pyramids to the cortex [6, 16].

Blythe, and Ockendon have divided infantile polycystic disease into four categories that they believe to be separate entities that run genetically true in different families [4]:

Perinatal group: Presentation is as described above, histologically 90% of the renal tubules are cystically dilated.

Neonatal group: Children present in the first month of life with abdominal distention and enlarged kidneys. Most progress to end stage renal failure within six months. Histologically, 60% of the renal tubules are cystically dilated.

Infantile group: Present between the ages of 3–6 months. All have both enlarged kidneys and enlarged livers.

Juvenile group: Present between the ages of 1–5 years with hepatomegaly and develop severe portal hypertension. Renal involvement is variable and histologically only 10% of renal tubules are dilated.

3.1.4. Prognosis

Earlier presentation is marked by the prominence of renal involvement. With later presentation, more significant liver disease is noted. The prognosis is invariably poor and the only therapy available is that of dialysis and transplantation [24, 14].

3.2. Adult polycystic disease

Unlike infantile polycystic disease, this entity is a common inherited abnormality occurring during adult life. The disease is the cause of renal failure in about 5% of those patients reaching end stage renal disease [9]. It is inherited as an autosomal dominant trait with high penetrance [14]. The disease may appear symptomatically at any age and several cases have been noted in infancy [2]. Usually, both kidneys are affected identically although this is not invariable. Cysts may also be found in the liver, lungs and pancreas but are rarely of clinical significance. Intracranial aneurysms in the area of the circle of Willis have been found to coexist with adult polycystic disease in up to 15% of patients [9, 14].

3.2.1. Pathology

The kidneys are of normal contour but enlarged and contain cysts of variable size in the cortex and medulla. The cysts grow as the disease progresses. The structure of the renal pelvis, the calyces and papillae are often poorly defined. Ureters and bladder are normal. Normal nephrons and collecting tubules are found intermingled with cysts of variable sizes. The cysts may affect any segment of the nephron but most commonly the Loop of Henle. The walls of the cysts are of variable thickness and may be surrounded by connective tissue [16].

3.2.2. Etiology and pathogenesis

In the early development of the fetal kidney, some of the nephrons develop normally while others are abnormally formed and produce cystic dilatations. The etiology is unclear.

3.2.3. Clinical presentation and functional changes

The mean age of diagnosis is in the fourth or fifth decade with the most common presenting symptom being lumbar or lateral abdominal pain. The kidneys may be palpable [3, 9]. Polyuria and frequency of urination due to loss of concentrating ability may occur. Concentrating ability is decreased early in the disease while the GFR is still normal. This is related to an osmotic diuresis in the remaining functioning nephrons decreasing the ability to maximally concentrate the urine [5]. Hypertension occurs in the majority of these patients. However, it is usually mild and easily controlled with medication. Hematuria, microscopic or macroscopic, is common, occurring in approximately 20% of patients and may be the initial presenting symptom. Proteinuria occurs in many patients but the nephrotic syndrome is rare.

These patients are prone to urinary tract infections and pyelonephritis. Infections play a large part in the morbidity and mortality of the disease. Renal calculi occur in 10% of the patients, probably due to stagnant urine remaining in the cysts [4]. Life expectancy after the appearance of symptoms varies considerably.

3.2.4. Differential diagnosis

The two primary alternative diagnoses are renal carcinoma and cystic dysplasia. The diagnosis may be difficult to make when one kidney is affected more than the other [3]. A positive family history will aid diagnosis. Intravenous pyelography may help to make the diagnosis and will show bilateral enlargement of the kidneys often with calcifications in the collecting system [6]. As the cysts grow, the calyces become distorted and elongated [16]. Arteriography may be useful in ruling out a malignant lesion.

3.2.5. Therapy

Surgical treatment by puncture decompression of the cysts was popular several years ago, but has generally been abandoned. Accepted therapy includes conservative measures to treat hypertension, infection, calculi and renal insufficiency. These patients are usually good candidates for dialysis and transplantation.

4. MEDULLARY CYSTS OF THE KIDNEY

4.1. Medullary sponge kidney

Medullary sponge kidney is primarily a disease of adults, although several reports exist of its diagnosis in children and even infants [9, 12]. Most cases are asymptomatic and discovered radiographically as incidental findings. The diagnosis may be made in relation to secondary complications, such as medullary calcification, stone formation and infection.

The overall incidence of medullary sponge kidney in the general population is unknown. A urographic incidence of 0.5% has been reported but the true incidence may be closer to 1 per 5,000. There does not appear to be any sex or racial preponderance [9].

4.1.1. Pathology

The lesions are limited to the pyramids, while the glomeruli, blood vessels and both distal and proximal tubules are uninvolved. Cysts are concentrated at the tips of one, several or all the renal papillae and are particularly prone to harbor calculi. The lesions are bilateral in approximately 70% of reported cases.

The shape and size of the cysts are variable. Usually a nondescript, simple, cuboidal epithelium lines the spherical cavities. Microscopically demonstable calculi are frequently seen within the cysts. Other microscopic features depend upon the presence and extent of the cortical lesions secondary to obstruction which may cause infection and tubular atrophy [9, 16].

4.1.2. Pathogenesis

Thoughts regarding the pathogenesis of medullary sponge kidney are highly speculative. It is felt that the disorder is a congenital anomaly present at birth in its fully developed form. The occasional association of medullary sponge kidney with other inherited disorders raises the possibility of medullary sponge kidney representing the renal expression of more generalized abnormalities. Most cases of modullary sponge kidney occur sporadically, although genetic transmission has been suggested by the finding of a few families with two or more involved members.

4.1.3. Functional changes

The vast majority of patients have a normal glomerular filtration rate and renal plasma flow. A few patients have proteinuria of a moderate degree ranging from 0.5–1 gm/day.

Although systematic evaluation of proximal tubular function has not been performed, reports indicate that glucosuria, phosphate reabsorption, uric acid excretion and amino acid excretion are normal.

The most consistent changes are related to pathology involving the distal tubule. Renal concentrating ability has uniformly been found to be impaired. Urinary diluting ability is usually normal. A large percentage of patients with medullary sponge kidney have a defect in urinary acidification. It may be secondary to either distal renal tubular acidosis or defective ammonium excretion. No determinations of TmHCO3 have been performed to exclude a defect in proximal bicarbonate reabsorption. Approximately 40% of the patients with medullary sponge kidney have been demonstrated to have hypercalciuria, unrelated to renal tubular acidosis or hypercalcemia. The hypercalciuria may be related to the high fractional excretion of sodium. This would be consistent with a defect in collecting duct function [8, 9, 12].

4.1.4. Diagnosis

The diagnosis of medullary sponge kidney is essentially radiographic. There is diversity of the urographic pattern of medullary sponge kidney reflecting varying degrees of collecting duct dilatation. On plain films, the kidneys are seen to be either normal or slightly increased in size. The diagnostic alterations are limited to the medullary pyramids with clustering of radio-opaque areas within the papillae. There are no cortical abnormalities. On intravenous pyelogram, the dilated tubules fill with contrast on early films producing linear, radial dilatations and a papillary blush. Actual small cysts may be seen. Retrograde pyelography shows that the dilated tubules either fail to fill or are less prominent than on intravenous pyelography. Other studies such as sonography, tomography and angiography are not helpful. Nephrocalcinosis and nephrolithiasis may be acquired. They are usually not seen in younger patients, but do appear in approximately 40–60% of older patients [9, 11, 16].

Clinically, medullary sponge kidney is usually asymptomatic and is often not diagnosed during life. The complicating calculus formation and infection are responsible for a great majority of the presenting symptoms. Symptoms include ureteral colic (50–60%); gross hematuria (10–18%); and urinary tract infection (20–33%). Other patients have the

diagnosis established at the time of evaluation for other conditions such as hypertension, abdominal pain, microscopic hematuria, sterile pyuria, mild proteinuria or enuresis [9].

The radiologic picture of medullary sponge kidney is usually characteristic. However, several entities may coexist with or mimic medullary sponge kidney: 1) pyelotubular backflow is not reproducible with intravenous pyelography if ureteral compression is done; 2) calyceal diverticula arise from the calyx and are visible on retrograde studies; 3) renal papillary necrosis has distinctive radiographic features; 4) other considerations are renal tuberculosis, renal cystic disease with congenital hepatic fibrosis and nephrocalcinosis [11].

4.1.5. Prognosis

As many as 10% of patients with medullary sponge kidney may be regarded as having a poor prognosis reflecting damage incurred from calculus formation and infection.

4.1.6. Therapy

Therapy of patients with medullary sponge kidney should relate to the secondary complications of calculus formation and infection. The usual regimens for treating both renal calculi and infection should be adhered to. Chronic suppressive antibiotic therapy may be indicated in those patients with recurrent urinary tract infection.

4.2. Medullary cystic disease

The renal abnormalities known as medullary cystic disease are a heterogeneous group having in common a number of clinical and morphological features. Many consider medullary cystic disease and familial juvenile nephronophthisis to be synonymous, but it may be helpful to distinguish between them. Medullary cystic disease has an adult onset with either sporadic or dominant inheritance and juvenile nephronophthisis has a predominantly childhood onset and appears to be autosomal recessive in inheritance. A third group, termed renal-retinal dysplasia, is clinically and morphologically similar to the other forms of medullary cystic disease. They are almost always associated with progressive retinal degeneration.

4.2.1. Pathology

Renal abnormalities in all of these entities are remarkable for the severity of damage to the tubules out of proportion to glomerular disturbances. The kidneys are moderately reduced in size with shrinkage

involving both cortex and medulla. The surface of the kidneys is finely granular with small cysts (less than 1 cm in diameter) characteristically found along the cortical medullary junction. Small cortical cysts may be noted as well.

Cortical contraction is the end result of tubular atrophy and interstitial fibrosis. Changes in glomerular function correlate with pathologic change. Early, glomeruli appear normal or show only mild sclerotic change. Later, there is increasing obliteration of the glomeruli often with striking periglomerular fibrosis. Proliferative change, alteration of the basement membrane and changes in the mesangium are not seen. Glomerular changes are secondary to the severe tubulo-interstitial damage [1, 9, 10, 19].

4.2.2. Functional changes and clinical presentation

The most frequent symptoms leading to diagnosis are usually related to impaired glomerular filtration rate with symptoms of uremia. Renal functional deterioration is relatively rapid with progression to end stage renal disease within one to two years of diagnosis. Proteinuria greater than 1–2 gm/day is uncommon [9].

Polyuria and polydipsia appear early and are quite common in medullary cystic disease. Impairment in urine concentrating ability is probably the earliest detectable lesion. Renal salt wasting may become prominent. Impaired response to vasopressin has been found. This may be explained by the extreme thickening of the tubular basement membranes particularly in the collecting ducts, distal tubule and the Loop of Henle. Salt wasting becomes more prominent as the disease progresses. Severe intravascular depletion may occur. Sodium requirements may be extremely large. The combination of salt wasting, decreased concentrating ability, and prerenal azotemia is common. Excessive potassium loss has not been described [18].

Acidosis often accompanies medullary cystic disease and is secondary to the retention of titratable acids occurring with decreasing GFR. A proximal renal tubular acidosis cannot be excluded. Hypercalciuria occurs as the disease progresses. It is probably related to the salt wasting [1, 7, 9, 15, 19].

4.2.3. Diagnosis

Plain films of the abdomen may be normal unless calcifications are present. The kidneys may be of variable size but are bilaterally equal reflecting the diffuse nature of the disease. The intravenous pyelography varies with the concentrating ability of the kidney. Calyces may be

distorted because of pressure from numerous cysts in the cotico-medullary region. No cysts are seen on the renal margin in contradistinction to polycystic disease [11]. Aside from pathologic examination of the kidneys, the diagnosis is primarily clinical, resting in large part on a high index of suspicion and a positive family history.

Hypertension occurs in approximately one-third of the cases. Anemia is common and may be out of proportion to the degree of renal failure. Weakness and pallor are prominent. Decreasing renal mass and concommitantly decreasing erythropoietin production are felt to be responsible for the anemia.

The urinary sediment is usually normal although 50% may have mild abnormalities with small amounts of protein or microscopic hematuria. Signs of azotemia, bleeding and convulsions account for complaints in about 10% of the patients [9].

4.2.4. Pathogenesis

Both dominant, recessive and sex-linked hereditary transmissions have been noted. There appears to be no predeliction for sex or race [19].

4.2.5. Differential Diagnosis

Polyuria and polydipsia may be reminiscent of diabetes insipidus, however, the urinary osmolality is higher. A decreased GFR excludes that condition. The lack of concentrating ability with pyuria may suggest the diagnosis of chronic pyelonephritis. Urine cultures are, however, negative and there are no urologic abnormalities. Polycystic disease of varying types may be differentiated on the basis of clinical and radiologic findings.

4.2.6. Prognosis

The natural history of the disease is unclear. Few studies have delineated the changes in renal function in a temporal fashion. Many patients present during adolescence in renal failure with rapid progression to end stage renal failure. However, there probably is a definite symptom-free interval after birth before glomerular and tubular dysfunction become evident. Onset has not been noted prior to the age of two years.

Dominantly inherited disease appears later and results in later renal failure than does recessive transmission. It is possible that genetic factors control the temporal evolution of renal failure as well as the age of onset of the disease.

4.3. Renal-retinal dysplasia

Progressive retinal degeneration has been associated with three syndromes which include morphologic, functional and radiologic similarities to medullary cystic disease [1, 9].

A. Retinitis pigmentosa with congenital blindness due to retinal atrophy and aplasia has been associated with renal alterations similar to medullary cystic disease.

B. The Lawrence-Moon-Bardet-Biedl syndrome of mental retardation, hypogonadism, obesity and retinitis pigmentosa has also been associated with renal abnormalities similar to those seen in medullary cystic disease.

C. Alstrom's syndrome of deafness, diabetes mellitus and obesity with retinal degeneration may also be considered part of the medullary cystic disease complex.

5. CYSTS OF THE RENAL CORTEX

Cystic disease limited to the renal cortex is uncommon and a unifying clinicopathologic picture is not apparent. These diseases are classified according to the distribution of cysts in the cortical parenchyma. They may be found diffusely throughout the cortex or discreetly in the periphery or along the juxtamedullary border [2, 9, 16].

5.1. Peripheral cortical microcysts are generally encountered in hereditary syndromes. Peripheral microcysts are also found in cases of non-familial, non-genetic malformations, particularly in association with congenital heart disease.

5.2. Intercortical or juxtamedullary microcysts are characteristic of the 'congenital nephrotic syndrome' of the Finnish type which has also been called microcystic disease.

5.3. Simple cysts of the cortex

These cysts may be either solitary or multiple and can become quite large. There is rarely a problem with differential diagnosis as radiologic evaluation delineates these cysts nicely. They appear as an irregularity of the renal outline or cause deviation of the renal axis. Calcification is frequently noted lining the circumference of the cyst.

Table 2. Differential diagnosis of common renal cystic disorders.

Clinical findings	Polycystic disease		Medullary sponge kidney	Medullary cystic disease
	Adult	*Infantile*		
Kidney enlargement	Present	Present	Usually absent	Absent
Flank pain	Common	Common	Usually absent, unless calculi	Absent, unless complicated by stone or urinary tract infection
Infection	Common	Unusual	Common	Unusual
Hypertension	Common	Common	Unusual	About 30%
X-ray findings and Sonography	Large kidneys Cysts Calculi	Large kidneys Cysts Calculi rare	Normal or slightly large kidneys Papillary cavitations Medullary calcifications	Small kidneys No calculi
Renal insufficiency	Frequent	Common	Absent, unless complications	Frequent
Concentrating ability	Frequently impaired	Frequently impaired	Impaired	Impaired
Hematuria	Common	Rare	Common, if complicated	Rare
Liver involvement	Absent	Usually present	Absent	Absent
Age of renal failure	More than 50 years	Usually less than 5 years	—	Usually 2nd decade

These benign cysts must be differentiated from malignant lesions. Most symptomatic renal masses are benign simple cysts. Intravenous pyelography, sonography, tomography and arteriography help in the differentiation of benign and malignant lesions. Percutaneous aspiration of renal cysts confirm the diagnostic impressions gained from other studies and may be helpful in the diagnosis of malignant lesions [6, 9, 11].

6. RENAL CYSTS IN HEREDITARY SYNDROMES

Renal cysts are encountered in many hereditary syndromes, usually in the form of peripheral, cortical microcysts that lack clinical and functional significance. Other syndromes, noted below, may be associated with significant renal cystic disease that may incorporate dysplastic elements.

Table 3. Genetically determined cystic disorders of the kidney

Disorder	Inheritance
Infantile polycystic disease	Autosomal recessive
Adult polycystic disease	Autosomal dominant
Medullary sponge kidney	Sporadic, recessive or dominant
Medullary cystic disease	Sporadic or dominant
Juvenile nephronophthisis	Recessive; ? sex-linked
Retinitis pigmentosa	? Recessive
Lawrence-Moon-Biedl syndrome	Recessive
Alstrom's syndrome	? Recessive
Tuberous sclerosis	Dominant
Von Hippel Lindau syndrome	Dominant
Zellweger's syndrome	Recessive
Jeune's syndrome	Recessive
Meckel's syndrome	Recessive

6.1. Syndromes associated with renal cysts

6.1.1. Tuberous sclerosis may have cysts of the renal tubules which may be large enough to produce renal insufficiency. Hypertension can be a major manifestation. Angiomyolipoma is probably the most common renal lesion.

6.1.2. The Von Hippel-Lindau syndrome includes angiomas of the retina, cerebellum and spinal cord and less often other organs. Renal tumors and cysts of the kidney have been described.

6.1.3. Zellweger's cerebrohepatorenal syndrome and Jeune's asphixiating thoracic dysplasia have elements of cystic dysplasia which are well documented. Zellweger's syndrome presents in infancy with hypotonia, abnormalities of the brain, a characteristic facies, biliary dysgenesis and renal cortical microcysts. Jeune's syndrome presents in infancy with severe constriction of the thorax secondary to bony abnormalities. This condition is frequently fatal in early life because of pulmonary insufficiency. The cystic dysplasias can be progressive and lead to end stage renal failure.

6.1.4. Meckel's syndrome is comprised of an occipital encephalocele, cleft lip and palate, and cystic dysplasia of the renal medulla [9].

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8. UROLITHIASIS

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1. INTRODUCTION

Urolithiasis is an important, treatable and frequently preventable cause of renal disease. In geographic areas, where stones are formed frequently, the economic impact in terms of time lost from work and decreased industrial output has yet to be measured. In the United States, approximately 12–13% of all hospital admissions are urological. Of these, admissions for stone disease rank third behind urinary tract infections and benign prostatic hyperplasia. In general, most epidemiologic studies show the sex incidence of urolithiasis to favor males in a 3–4 to 1 ratio. Stone disease is rare in Blacks, North American Indians, and some South American and Central American Tribes. Heredity plays a role, since there is a definite familial predilection. Renal tubular acidosis and cystinuria are examples of hereditable metabolic defects which can cause stone disease. These diseases are thought to be polygenic, with partial penetrance, and seem to be non-sex linked.

Great geographic variation exists in stone disease. Multiple epidemiologic surveys confirm the presence of geographic areas where the incidence of stone disease is higher than in a neighboring country or section of the world. These areas are called 'stone belts'. No one knows the exact cause of the increased incidence of urolithiasis in these areas, but various studies have incriminated soft water, diet, industrialization, acculturation or other aspects of the environment.

Age seems to play a role in determining the type of stone formed. Children very rarely form upper tract stones. The age of onset of upper tract stone disease is between the age of twenty and fifty.

Bladder stones were common in children before the twentieth century. They are usually a salt of uric acid, either sodium or ammonium urate although other, less frequent, compositions occur. Today, they represent less than 3% of stone disease. When animal proteins and fats are eaten, as in European and North American diets, one sees a predilection towards renal and ureteral calculi. In areas where vegetable

proteins are consumed, bladder stones predominate over upper tract calculi. Vegetable proteins lack phosphates, but when phosphates are added to the diet, upper tract calculi tend to form. Further, excessive dietary intake of a compound may affect its urinary excretion. For example, when one consumes an excess of dietary oxalate, as found in Worcestershire sauce, leafy green vegetables, tea, etc., there may be an excess urinary excretion of oxalate. Milk, as another example, contains high concentrations of lactose, a potent lithogen. Lactose is thought to facilitate stone formation by being slowly hydrolized in the gut, and persisting to the distal ileum, where it increases calcium absorption.

Just as diet changes when society moves from a rural to an urban-industrial setting, so too does the environment. Stone disease has changed with this transition as well. Now, more than 97% of the stones formed throughout the world are formed in the kidney. In fact, in the United States, when one sees a bladder stone in a male age 50 or older, it is considered to be prima facie evidence of bladder outlet obstruction rather than due to dietary, climatic or metabolic causes.

Environmental factors and occupation have been incriminated in stone formation in many epidemiologic studies. People who live in hot climates and who have high sweat loss, tend to form stones. Stones usually form when the weather is hot and pass when the temperature is cooler. Studies have also been made of matched spouses of stone and non-stone forming patients. Of great interest, the spouses of the stone former also had a higher incidence of stone formation, indicting both environment and diet. Further, studies have pointed to occupation as an important variable in stone disease. Patients with sedentary occupations have a higher incidence of stone disease.

Hence, stones occur from a combination of many factors, but the exact cause of the majority of stones remains unknown. Since we are creatures of habit and captives of our environment, 60–80% of patients who pass one stone will form at least 1–2 stones again before death.

2. PATHOGENESIS OF STONE

Urinary calculi are formed by a physical phase change, that is, by the transition of ions in solution to a solid, crystalline phase, salt. Below are listed some of the common theories and chemical principles advanced to explain stone formation:

1. Supersaturation.
2. Crystallization.

3. Free particle and fixed particle growth.
4. Matrix initiation.
5. Nucleation (both homogeneous and heterogeneous).
6. Spinodal decompositon.
7. Inhibitor lack.
8. Aggregation.
9. Epitaxy.
10. Urinary tract infection.
11. Foreign body.

Most workers think that stone formation is caused by combinations of these factors, but the relative importance of any one theory is unknown.

Saturation: with a defined pH, temperature and pressure, a solution is said to be saturated when the maximum amount of solute is dissolved in a given solvent. A system is saturated when the addition of more ions would cause crystallization, or conversely, when a solid can be mixed with the solution phase without changing the solution's concentration. The solubility product is the point where saturation has been reached and crystallization begins to occur. The solubility product is governed by the Mass Action Equation and the second law of thermodynamics involving activation energy. Parenthetically, many of the ions which form urinary calculi normally exist in a saturated or supersaturated condition in the urinary tract. Supersaturation is therefore defined as the ability of a solution to hold more ions in solution than one would predict by the mass action equation. Activity products for many ions have been approximated for urine, and the existence of supersaturated solutions allows us to reason to other physical chemical forces at work which prevent crystallization of supersaturated solute in urine, e.g. inhibitors.

The zone of supersaturation means that urine is able to hold ions in solution well beyond the calculated saturation point before crystallization occurs. When the concentration of a supersaturated solution is such that crystallization occurs, we say that the formation product of the supersaturated solution has been reached. This range, between the calculated solubility product and the formation product, has been termed the 'metastable' region. Many of the ions known to form urinary calculi normally exist in this metastable zone. Several physicochemical phenomena are known to explain the existence of the metastable zone. Polyionic solutions (like urine) have a mixture of electrically active ions which allows for ionic interactions resulting in a change in their individual solubility.

Urinary inhibitors play a large role in raising the formation production and permitting ions to remain in a supersaturated condition in the metastable region. Further, they slow crystal growth and the rate of crystal aggregation. Inhibitors are divided into inorganic and organic substances, present in small concentration in the urine. Other than pyrophosphate, which has been well studied; the other inhibitors are largely unknown. Magnesium has been demonstrated to increase the solubility of calcium, phosphorus and perhaps oxalate. The magnesium/calcium urine ratio is known to be decreased in stone formers on carbonic anhydrase inhibitors, and treatment with thiazides tends to increase this ratio and decrease stone formation. Zinc has also been shown to increase the solubility of calcium in the urine. The organic inhibitors are much less well characterized. There is evidence for a mucopolysaccharide substance, a non-peptide sulfate containing molecule and another very low molecular weight substance with unknown composition. Other organic inhibitors are thought to be citrate, alanine and urea.

Crystal nucleation is the term applied to the change toward spontaneous crystallization in the supersaturated solution. Nucleation occurs when thermal agitation is sufficiently decreased to allow interaction of ions of molecules. Further enlargement of the crystal beyond nucleation occurs by a process called crystal aggregation. Crystals are formed in the urinary tract by all normal individuals, but in non-stone formers, they tend to remain separate and do not grow large enough to obstruct urinary passages. As crystal aggregation occurs, secondary nucleation (creation of new nuclei on the surface of preformed crystals) proceeds, along with the phenomenon of epitaxy. Epitaxy is a form of heterogeneous secondary nucleation. In epitaxy, the surface lattice of one crystal resembles the surface lattice of another crystal closely enough so that the second crystal can grow on the surface lattice of the first. It has been shown, for example, that calcium oxalate can grow rapidly on the surface lattice of uric acid crystals.

It is assumed by many workers that urinary transit time is too rapid to allow significant free particle growth except in an obstructed urinary system. It is commonly believed that fixed particle stone growth, with attachment to a duct wall is a more common occurrence than free particle stone growth. Crystal growth, therefore, is a function of a saturated solution and the time the crystal is exposed to that solution in the urinary tract.

Matrix is an organic glyco- or mucopolysaccharide of unknown sources, which makes up between 2–3% of all stones. It is regarded as a

precipitator of stone formation by serving as a template for the crystalline lattice of stones. Blood clots, epithelial clumps, pus cells, bacteria, necrotic and ischemic tissue, neoplasm and necrotic papillae may play a role as a kind of template or 'matrix' for formation of stones.

Urinary tract infection has also been incriminated in the formation of urinary calculi and is thought to relate to several mechanisms. Urinary tract infection may be the initial insult which causes stone formation by producing epithelial damage, and clumps of pus and epithelial detritus which act as a nidus for stone formation. Bacterial ureases also act on urinary urea to produce ammonia. The increase in urinary pH shifts the solubility product of the ions dissolved in the highly alkaline urine and, via the mass action equation, causes precipitation of crystals.

With this background, we may then arrive at a working hypothesis which allows us to deduce how urinary calculi are formed. There is general agreement on the following principles which act in combination:

1. Renal function must be adequate to excrete excessive crystallizable ions.
2. Urinary pH must be able to change over a wide range.
3. Inhibitor substances must be decreased.
4. Supersaturation of stone forming ions must obtain.
5. Crystal nucleation (nidation) must occur. Matrix may or may not play a role here.
6. Crystal aggregation must proceed and is a sine qua non.
7. Crystal growth by means of epitaxy, decreased zeta potential and secondary nucleation are necessary to form crystals large enough to become clinical stones.
8. The crystal lattice formed must reside in the urinary tract long enough to grow to a size where obstruction of a duct takes place. Megacrystalluria is not clinical stone disease without reaching a size large enough to obstruct.
9. Obstruction and infection may either cause, help and/or favor these conditions and accelerate the process.

3. DIAGNOSIS OF STONE DISEASE

3.1. History

Historical inquiry into stone disease should include family history, country of origin, the area in which the patient usually resides including rural or urban, the socioeconomic situation and occupation (sedentary or

non-sedentary), prior history of stone passage, and the age at which the first stone was formed or passed. A history of recurrent urinary tract infection, or highly alkaline urine suggests a staghorn calculus. Symptoms of chronic renal failure may suggest obstructive renal calculi and/or associated urinary tract infection. These symptoms usually indicate long standing disease. An inquiry into the dietary habits of the patient may elicit excessive dairy product ingestion, and should call to mind the milk-alkali syndrome. Similarly, vitamin D intoxication can be a cause of urinary calculi. Associated diseases should be searched for, and include: sarcoidosis, immobilization, hyperadrenalism, either with exogenous steroids or endogenous production of steroids, intestinal disorders, such as inflammatory disorders, intestinal diversion and intestinal bypass. A history of renal tubular acidosis with familial occurrence should be sought as well as a history of hyperparathyroidism or of hyperthyroidism. One must search for the historical clues of hydronephrosis, urinary tract tumors or the passage of clots.

Frequently, the patient is completely unaware of the presence of the stone, which has formed in the kidney. Usually, as the stone passes into the ureter, the patient experiences severe pain from the hypermotility and stretching of the urinary conduit. This pain is usually described as 'colicky'.

A patient with renal colic can frequently be diagnosed at a distance. The patient will frequently be diaphoretic, pale and in great pain. Characteristically, the patient cannot find a comfortable position and either walks about the room or writhes in bed in a very characteristic fashion. The patient may have periods of relative quiescence only to be plagued by repeated exacerbations of pain. This alternating exacerbation and diminution of pain is typical of renal colic.

Frequently, stones will become lodged in the intramural portion of the most distal ureter as it passes through the bladder wall from the ureteral hiatus to the ureteral meatus in the urinary bladder. The ureterovesical junction is one of the areas of narrowing in the urinary conduit from the kidney to the bladder. Stones lodged at this site often give symptoms of frequency and urgency, and may cause the patient to urinate small amounts of urine very frequently. The symptom complex of frequency, urgency, strangury and tenesmus has been called the 'ureteral tunnel syndrome'. Knowledge of this symptom complex can be used clinically to predict the passage of a stone from the ureteral tunnel into the vesical cavity, since there is usually dramatic relief of the patient's symptoms once the stone has passed into the lumen of the bladder.

3.2. Physical examination

Inspection of the patient with stone disease may be diagnostic in the presence of acute renal (ureteral) colic. However, patients who have chronic renal failure or who are septic from a urinary tract infection may also be suspected of having urinary stone disease and also have a quite typical appearance. Palpation may reveal absence of peripheral pulses, abdominal masses, or peritoneal signs which would lead one to suspect other catastrophic events. Auscultation frequently will reveal increased or decreased bowel sounds. Abdominal distention may be found with intestinal obstruction and/or peritonitis which may, in its own way, mimic colic. However, these patients usually lie quite still in contrast to the thrashing patient with renal colic. Percussion may reveal costovertebral angle tenderness or so-called 'Murphy-Punch' tenderness, indicating renal involvement or distension of the renal capsules by obstruction from the stone.

3.3. Urinalysis

Microhematuria is usually present with stone disease. However, this is not invariable. If a stone completely obstructs the affected ureter, red blood cells may be absent from the urine. Pyuria may indicate a urinary tract infection which affects both the prognosis of the stone disease and the therapy to be employed. Crystals may be noted in the urine, such as cystine, oxalate, urate or phosphate. A gram stain of the urinary sediment may show bacteriuria. The pH of the urine should be tested, and if the pH is over 7.5, one may suspect a proteus infection with a struvite or infection stone, since the human kidney cannot produce a urinary pH over 7.5 in the absence of a urea-splitting organism. Acidic urine suggests uric acid or cystine calculi.

3.4. Radiography

Kidney, ureter and bladder (KUB): The KUB, or plain film of the abdomen, is a valuable aid in diagnosing urinary calculi. Whereas most gallstones are radiolucent, most urinary calculi are radiopaque, and frequently can be seen or suspected on a plain film of the abdomen. A KUB should be performed on every person who is suspected of having urinary calculi. One should outline both renal shadows and search for calcific densities along the expected course of the urinary conduits. A staghorn calculus may be missed unless a KUB precedes an intravenous

pyelogram. Examination of the skeleton may hint at hyperparathyroidism or hyperadrenalism as well as indicating the presence of intestinal disorders.

Intravenous pyelogram (IVP): An IVP, with delayed films, probably ought to be performed on all new patients who have symptoms of acute ureteral colic when seen with their first episode of colic. This determines the presence of a functioning opposite kidney, as well as assessing the functional status of the affected side. Certainly, if the affected side is non-functioning on intravenous pyelography after many hours, one's therapeutic intentions may well shift from a position of watchful waiting to active intervention. In addition, an initial intravenous pyelogram provides a good baseline by which one may judge the progress of the patient.

Plain tomography of the kidneys: This procedure is especially helpful in medullary cystic disease and sponge kidney. Further, postoperative examination of the operated kidney can be facilitated by plain tomography. When one wishes to follow a patient who has had renal surgery for removal of renal calculi, it appears to be good practice to obtain plain tomograms of both kidneys as a baseline for stone recurrence. Plain tomograms can also be useful in delineating tiny calculi and calculi which are only minimally calcified.

Retrograde pyelogram: Occasionally, patients may require cystoscopy and retrograde pyelography. This is usually required in cases of non-opaque calculi or in situations where renal function is not sufficient for dye excretion, or dye does not column to the point of urinary obstruction on delayed films. Retrograde pyelography can be done gently and safely and may be a great help in differentiating a non-opaque calculus from a tumor, clot or renal papilla. In addition, retrograde pyelography is frequently used before and after instrumental extraction of lower third ureteral calculi.

Sonography: Sonography has been used with some success to outline non-opaque urinary calculi in the renal pelvis and in dilated calyces. With a stone size of 1–2 cm or greater, and an expert sonographer, one can often differentiate non-opaque stone disease from a clot or tumor.

Computerized axial tomography: Computerized axial tomography may be used to differentiate non-opaque urinary calculi, tumors and clots.

Radioisotopes: Nuclide scanning may be used in patients who are allergic to the intravenous dye used in excretory urography. Radioisotope techniques allow determination of kidney function and, frequently, one may see columnation of the nuclide in the ureter, thus delineating,

in a reasonable fashion, the site of obstruction. Because of its low radiation, radioisotope scanning has been used to follow patients who have ureteral calculi and who are being treated expectantly and would seem to be a superior method of following stone disease in children and in pregnant females.

4. MANAGEMENT OF STONE DISEASE

4.1. General principles

Analysis of stone: The analysis of the recovered stone is essential to initiate correct metabolic investigation and therapy. Today, most calculi are analyzed by crystalographic and X-ray defraction techniques which give not only the stone lattice composition, but also the relative proportions of the components of the stone. Another more cumbersome, yet acceptable, technique is quantitative chemical analysis. Qualitative chemical analysis and infrared spectroscopy are inadequate.

4.2. Identification of anatomic or metabolic disorders

Anatomic abnormalities and urinary obstruction should be sought and corrected to prevent further stone formation. Corrective surgery should be done very soon after the diagnosis has been made. Similarly, metabolic disorders must be identified to initiate proper medication and/or dietary therapy.

4.3. Fluid intake. To prevent recurrent stone formation, a dilute urine must be maintained at all times. One or two more liters of increased urinary output can reduce the urinary concentration of oxalate by several orders of magnitude. For instance, oxalate stone formers decrease their concentration of urinary oxalate more slowly than normals, but at a urinary output of 3 1/24 hours, their oxalate concentration is as low as 12 mg/l, and, with a urinary output of 4–5 liters per day, falls into the same concentration range as normals. Water drinking should be the foremost therapy in all stone patients; its importance cannot be overestimated. When instructing patients to increase fluid intake, it is necessary to point out that fluid intake must really be measured by urinary output, since an intake of 5 liters per day does little to help their stone disease if most of the intake is lost to perspiration, diarrhea or vomiting. Patients should be instructed to measure their urinary output at regular

intervals, and if at all possible during the work-week. The effect of heat, humidity, sweating, dehydration, etc., should be explained to the patient so that he is prepared to combat these situations and increase his fluid intake accordingly.

4.4. Diet. Dietary excesses and other obvious dietary causes such as the milk alkali syndrome and hypervitaminosis D should be corrected. Patients who drink large volumes of tea, or consume foodstuffs which otherwise contain large amounts of oxalate should be instructed to moderate their diet. Decreased purine intake may be beneficial in certain uric acid stone formers. A low sodium diet also seems beneficial for calcium stone formers who do not have hyperoxaluria, since sodium restriction increases the amount of calcium reabsorbed by the kidney. However, it should be noted that dietary advice is considered controversial by many, since there are theoretical considerations which contradict common wisdom. For instance, why should one limit exogenous oxalate when most oxalatae excreted is produced endogenously?; and why limit purines in all uric acid stone formers, when not all have the same metabolic defect producing these stones?

4.5. Urinary tract infection. Urinary tract infection should be searched for assiduously and continuously in all stone formers, and when found, it must be treated vigorously.

4.6. Classification of stone activity. A classification based on stone activity has been devised as follows: Surgically active; metabolically active; metabolically and surgically inactive; indeterminate. Surgically active stones are those which are presently causing renal colic, urinary tract obstruction or produce intractable pain. This group is frequently treated surgically or, at the minimum, should have a urological consultation. Metabolically active stones are seen in patients who have documented passage of recently formed stone or gravel, growth of a known stone in the past year or formation of a new stone in a year or less. These patients require active preventive measures and, frequently, drug therapy. Management includes fluid therapy, diet, aggressive medical management and diagnostic evaluation.

Metabolically and surgically inactive stones fall into a group where none of the signs or symptoms outlined above has been present for 3 years or more. Treatment centers on observation and general preventive measures.

In the last category, indeterminate, are those stones which have

uncertain activity or have been under observation for less than one year. We advise observation and general preventive measures only, for these patients, until the activity of the stone can be determined.

For the patients with active stones, the following plan of treatment is essential. In patients suffering from acute ureteral colic, first take a history and perform a physical examination. In addition, a microscopic analysis of a voided urine is mandatory to ascertain the presence of red blood cells, white blood cells, or urinary crystals. Urinary pH is also noted. These data may provide clues concerning the nature of the stone. The patient is next taken to X-ray where a plain abdominal film is obtained. If a calculus can be identified on the film, the patient's colic should be relieved by the administration of an appropriate narcotic, such as morphine. Since colic is usually severe, give part of the morphine intravenously and the remaining subcutaneously with the dosage dictated by the patient's overall medical condition.

If a stone cannot be seen on the plain film, an intravenous pyelogram is performed. Using the same needle, the patient has an intravenous drip started and if his cardiovascular system is normal, intravenous fluids are frequently given at 150–200 ml per hour or more, for a short period of time. The intravenous fluid plus the osmotic load from the IVP dye will frequently force the calculus along the ureter, and it is not unusual to see a patient pass his stone with the postvoiding film of his IVP. After the excretory urogram has been performed, the patient should be followed with time-delayed films until the exact site of anatomical obstruction by the calculus is seen. The patient is instructed to strain each voided urine and to look for a calculus in the strainer. If pyuria is present or a gram stain of the urinary sediment shows bacteria, antibiotics should be started while awaiting the results of urine culture. It is recommended to place the patient on a urinary antiseptic for approximately 5–7 days even after the stone has passed.

Five types of stones account for more than 99% of human urolithiasis. These stones may be classified as to location, size, configuration, chemical composition and physical characteristics.

5. CYSTINE STONES

Cystine stones make up about 1% of all calculi. These stones are less opaque than calcium stones, are usually smooth, have a waxy texture and are light yellow or yellow-brown in color. Although radiopaque, they have a low density and can easily be missed on a plain film of the abdomen. They may grow rapidly, be multiple or bilateral, and can form

staghorn calculi. There is usually a family history of cystine calculi or stone disease. This polygenetic defect is divided into completely recessive (homozygote) and incompletely recessive (heterozygote). Cystinuria appears to be an inheritable defect involving renal tubular and intestinal transport of multiple amino acids. Cystine assumes clinical importance because it is excreted in excess amounts and is insoluble in urine. Lysine, arginine and ornithine are also involved in the defect, but are more soluble and only very rarely form stones. Some patients may have the genetic defect, including significant cystinuria, but without stone formation. The urinary concentration of cystine must be 250–500 mg cystine/gram of creatinine (heterozygotes) before cystine stones form, and more commonly greater than 400 mg (homozygotes). The diagnosis is usually made by stone analysis and by screening the urine of stone formers for cystine crystals and by the cyanide-nitroprusside test, a qualitative screening which is positive in the presence of greater than 100 mg of cystine per gram of creatinine.

Cystine is relatively soluble in alkaline urine. About 800 mg of cystine can be dissolved per liter of urine, if the pH is kept at 7.8. Since pH 7.5 is the maximum value attainable by the human kidney without alkalinization, therapy of this disease necessitates urinary alkalinization by drug therapy to keep the pH greater than 7.0 at all times, and especially at night. At a pH of 7.0, urine will hold only 400 mg of cystine in solution. Since homozygotes excrete at least this quantity, alkalinization assumes an important role in therapy. Patients should be encouraged to awaken at intervals during the night to ingest alkalinizing agents and to force fluids. Urinary pH should be monitored by nitrazine pH paper and, if possible, urinary output of 4 liters per day should be maintained.

An important and effective drug has been specifically designed to combat the disease. D-penicillamine has a molecular structure closely resembling cystine. This drug joins with cystine to form a very soluble disulfide dimer of 'cystine-penicillamine'. Aside from the common side effect of skin rash and other less frequent adverse reactions, the only major complication of this therapy has been the nephrotic syndrome, which is usually reversible by discontinuing the drug. Unfortunately, up to 50% of the patients treated with D-penicillamine, may have side effects severe enough to warrant stopping the drug, at least temporarily. D-penicillamine is begun at reduced doses (250 mg daily) on an empty stomach, and gradually increased, as required, up to 2 grams daily. Since pyridoxal 5-phosphate is inhibited by D-penicillamine, pyridoxine, 50 mg twice daily is added to the regimen.

6. URIC ACID STONES

Uric acid stones are characteristically radiolucent. They may be single, or multiple and bilateral, and can form staghorn calculi. They may also be found with an outer rim of calcium, especially calcium phosphate when urinary pH is raised high enough to cause phosphate deposition. They are then frequently radiopaque. Once calcium deposition occurs over a nucleus of a uric acid stone, it is highly unlikely that medical therapy will dissolve the stone.

In most large stone series in this country, uric acid stone accounts for about 5% of all stones. Approximately 20% of patients with symptomatic gout will form stones (85% pure uric acid and 15% mixed uric acid and calcium).

Uric acid crystalluria is common and may be evanescent or cause 'gravel' with concomitant microscopic or even gross hematuria. Uric acid 'sludge' may, from time to time, cause obstruction and even anuria. Chemotherapy and radiation therapy of neoplastic disease and uricosuric drugs may cause uric acid crystalluria and/or sludging with obstruction.

Uric acid exists in two clinical forms: the dissociated monohydrogen urate and free uric acid, the undissociated form. Uric acid has a clinically important pKa of 5.57. Only about 60–120 mg/l of total uric acid is able to be dissolved in acidic urine, whereas at pH 7 about 1500 mg/l are able to be dissolved, mainly as the urate. When urinary pH increases one log (from pH 5 to pH 6) urine uric acid solubility increases six-fold. As the pH decreases, and the amount of free, undissociated uric acid increases, uric acid stones tend to form. The control of urinary pH is dependent upon the quantity of titratable acid and the amount of available phosphate, to buffer it. Titratable acid excretion further depends upon the metabolic proton load and the rate of ammonia production. Patients who form uric acid stones seem to have a persistently acid urine and a blunted response to a post-prandial alkaline tide. The reason for this is not understood. A further factor which appears to be important in uric acid stone formers is their low excretion rate of ammonia which increases titratable acidity and decreases urinary pH. The cause of this defect is unknown. A suspected glutamine deamination defect has yet to be proven.

Thus, the formation of uric acid stones has multiple determinants: hyperuricosuria, urinary volume and urinary pH. The concentration of free uric acid excreted in the urine is related to total uric acid excreted

and urine volume. The total milligram amount of uric acid excreted is not as important as its concentration.

Uric acid production normally depends upon the amount of purine intake, endogenous purine production and the ability to convert purines to uric acid. Since man does not possess the enzyme uricase which converts uric acid to allantoin, uric acid is an end product of purine metabolism. Approximately 1/3 of uric acid is removed through the intestinal tract while 2/3 is excreted in the urine (500–700 mg/24 hours).

In primary gout, up to 30% of patients will consistently excrete excessive uric acid even on a low purine diet. Most patients suffering from gout have a deficient renal excretory mechanism for uric acid and require a higher than normal plasma uric acid concentration to excrete the normal amount of uric acid produced. Why uric acid is overproduced is not clearly known, but several enzymatic abnormalities have been identified.

These are four mainstays to therapy of uric acid stone disease:

Low purine diet: one may achieve a 50% reduction in uric acid stones by diet alone.

Urinary alkalinization: by maintaining urinary pH at 7, especially at night, the solubility of uric acid is icreased 17–20 times.

Urinary dilution: a high urine flow and the production of a large urinary volume decreases uric acid concentration and decreases particle transit time in the urinary tract.

In most cases, rigid adherence to the above three treatment modalities is sufficient to prevent recurrent stone formation. The need of drug therapy should be unusual except with certain enzyme defects and the heritable form of primary gout.

Drug therapy: Allopurinol (200–400 mg/day) has a dual mechanism of action and is effective in both hyperuricemic and hyperuricosuric states. As an isomer of hypoxanthine, it competes with the purine base for xanthine oxidase and thereby blocks the formation of uric acid. Allopurinol decreases phosphoribosylpyrophosphate availability, thus decreasing overall purine biosynthesis. It also works via a negative feedback mechanism to inhibit phosphoribosylpyrophosphate amidotransferase by the formation of a 'false' allopurinol-ribonucleotide which inhibits de novo synthesis. Allopurinol is converted by xanthine oxidase to oxipurinol, the more active form of the drug. Oxipurinol has a half-life of 30 hours compared to a half-life of 30–90 minutes for allopurinol and appears to be the active form of the drug.

Since allopurinol may precipitate an acute attack of gout, when ini-

tiating allopurinol therapy, it is well to begin therapy along with colchicine. Other complications of allopurinol are known, including hemorrhagic skin lesions, exfoliative dermatitis and fatal vasculitis. Fortunately, side reactions are usually confined to pruritus, skin rash and drug fever, and discontinuing the drug will usually abort the more serious complications. The drug may also be used prophylactically before therapy of the myelo- or lymphoproliferative disorders.

There have been reports of reduction in stone size and even dissolution of pure uric acid stones using the above conventional therapies. Furthermore, aggressive medical therapy may occasionally forestall surgical intervention in cases of anuria or high grade obstruction secondary to uric acid sludge or very small stones. Therapy depends on a rapid and correct diagnosis and the early application of vigorous medical therapy which includes: intravenous $NaHCO_3$, allopurinol, acetazolamide, 250 mg every six hours and an intravenous bolus of mannitol and hydration. If the above emergency medical therapy is not successful in 6–18 hours, then the patient must have ureteral catheters passed and the obstruction by-passed. Irrigation with alkali solutions may be helpful, especially in gouty nephropathy and anuria where parenchymal resolution of the uric acid crystals may take several days.

7. XANTHINE STONES

Xanthinuria is a rare disorder and only 60 cases are known worldwide. Theoretically xanthine stones may form in any patient with gout or neoplasm who is receiving allopurinol therapy. In practice, this is a rare occurrence and usually limited to those patients who have an inborn error of metabolism involving hypoxanthine conversion.

8. CALCIUM STONES

The importance of calcium in stone disease is its property of forming salts which are barely soluble. Calcium phosphate, calcium oxalate and apatite are the predominant calcium stones seen. Pure calcium phosphate stones are rare (about 2%), but the compound commonly occurs as a mixture with other stones (8–20%)). Calcium phosphate stones may be seen in association with many of the conditions which cause calcium oxalate stones, but especially are seen in hyperparathyroidism, urinary tract infections, and when urine is highly alkaline. Calcium phosphate is not uncommonly seen as a precipitate around a uric acid nucleus, when urinary pH is altered too vigorously. Physically, calcium phosphate

stones may be soft or hard, yellow or brown, and may form staghorn and laminated calculi.

Calcium oxalate stones are the most common stone formed. They are seen in a variety of conditions and account for 70–80% of the stones seen in clinical practice. Calcium oxalate stones are usually relatively small, but may become large. They have a jackstone or a mulberry configuration. They are more frequently seen in the young adult male and, formed in the kidney, they pass via the ureter with bouts of typical renal colic. The cause of calcium oxalate stone disease can be divided into six categories: 1) absorptive hypercalciuria, 2) resorptive hypercalciuria, 3) renal hypercalciuria, 4) idiopathic hypercalciuria, 5) idiopathic calcium oxalate stone formation (normocalcemia, normocalciuria) and, 6) the conditions associated with calcium oxalate stone formation such as: renal tubular acidosis, primary hyperoxaluria, sarcoidosis, intestinal disorders, medullary sponge kidney and immobilization.

The average daily adult calcium intake in the USA is 800 mg, with a range of 200 mg to 2000 mg. Fecal calcium excretion averages 640 mg per day with concomitant urinary excretion of 160 mg. Normal serum calcium averages 9.6 mg/dl, 60% of which is diffusible and 40% is bound, mainly to albumin; of the 60% ultrafilterable, approximately 90% is free ionic calcium and 10% is unbound, but non-ionic, in close association with loose plasma ligands to PO_4—or citrate.

Approximately 98% of the filtered load of calcium is reabsorbed by the renal tubules and only about 200 mg/24 hours or less appears in the urine. Changes in dietary calcium do cause real but minor changes in urinary calcium excretion up to an average of 6%. The influence of dietary calcium on urinary calcium excretion is also determined by the rate of intestinal calcium absorption by active transport, controlled by the renal cortical hormone, 1,25-dihydroxyvitamin D_3 and by passive diffusion of calcium ions along a concentration gradient. $1,25(OH)_2D_3$ is by far the more important of the two mechanisms and, with normal calcium intake, the plasma concentration of $1,25(OH)_2D_3$ correlates closely with intestinal calcium absorption.

Changes in dietary calcium intake also affect urinary calcium excretion by altering both the filtered load of calcium, and the secretion of parathyroid hormone (PTH). Normally, there exists a direct relationship between dietary calcium intake and serum calcium concentrations. This relationship may account for some of the alterations in the filtered load, but the action of PTH on the renal tubules, mediated via cAMP, to alter calcium reabsorption, is more important.

Parathyroid hormone increases renal tubular reabsorption of calcium.

When dietary calcium is raised, serum calcium levels are also increased and the resultant decrease in PTH decreases the tubular reabsorption of calcium and increases urinary calcium excretion, favoring calcium stone formation. Alternatively, when dietary calcium is decreased, serum calcium decreases and the resultant increase in PTH and urinary cAMP cause increased tubular reabsorption of calcium and, concomitantly, a fall in urinary calcium excretion, thus mitigating calcium stone formation.

Both PTH and $1,25(OH)_2D_3$ then, move inversely with dietary and serum calcium, in an integrated system, which determines intestinal absorption of calcium via the intestinal calcium transport system. Other dietary factors, such as acid-base, sodium, phosphate and glucose, also appear to alter urinary calcium excretion.

It is not commonly appreciated that urinary calcium excretion rises as dietary protein increases. As dietary protein intake increases, fixed acid production is increased by the formation and excretion of organic acids and the production of inorganic sulfate from the oxidation of amino acid sulfur; and as urinary acid excretion increases, urinary calcium excretion rises exponentially. The increased urinary calcium excreted in states of fixed acid excretion seems to come from bone reabsorption and not increased intestinal absorption.

Clinically, dietary sodium intake is associated with increased urinary calcium excretion, but experimentally the increments in calcium excretion seem to be small. Chronic mineralocorticoid therapy causes a progressive increase in urinary calcium excretion because of reduction in both calcium and sodium reabsorption at the proximal tubules.

Urinary calcium rises acutely and transiently after alcohol ingestion and after glucose. This increase is insulin dependent and is the result of reduced net tubular reabsorption of calcium. Patients with calcium nephrolithiasis have an exaggerated calciuric response to large amounts of glucose.

It has been noted that many patients who form calcium stones have a lower serum and urinary phosphate concentration than do non-stone formers. It has been postulated that an undefined defect exists in phosphate metabolism causing an increased serum $1,25(OH)_2D_3$ and hypercalciuria.

8.1. Hypercalciuria

Hypercalciuria is usually defined as urinary excretion of calcium in excess of 300 mg per 24 hours. However, some patients may have

hypercalciuria intermittently, only for a short time after meals, or relative to other respective ions with which calcium may precipitate. Therefore, an analysis of a 24-hour urinary calcium excretion alone may not be clinically useful. The ratio of urinary calcium creatinine concentration (mg/dl) has been also used to identify hypercalciuric patients. A ratio greater than 0.11 in a fasting patient indicates hypercalciuria, and a ratio greater than 0.2 in a patient after calcium load indicates either absorptive hypercalciuria and hyperparathyroidism. There are four types of hypercalciuria associated with calcium stone formation that have been identified: primary absorptive hypercalciuria, resorptive hypercalciuria, renal 'leak' hypercalciuria and 'idiopathic' hypercalciuria (Table 1).

Table 1. Differentiation of the hypercalciurias.

	Idiopathic	Renal calcium leak	Resorptive	Renal* phosphorus leak	Absorptive
Serum Ca	N	N or ↓	↑ or N	N	N
Serum P	N	N	N or ↓	↓	N
1,25 $(OH)_2D_3$	N	↑	↑	↑	N or ↑
PTH	N	↑	↑	↓	↓
Ca absorption	N	↑	↑	↑	↑
Calcium excretion					
Filtered	N	↓	↑	↑	↑
Reabsorbed	N	↓	↑	↓	↓
Urinary Ca^{++}/ creatinine					
Fasting	N	↑	↑	N	N
Ca^{++} load	N	↑	↑	↑	↑
Urinary cyclic AMP/creatinine					
Fasting	N	↑	↑	N	N
Ca^{++} load	N	N	↑	N	N

Adapted from Maggio, A.J., et al, J Urol 122: 147–151, 1979 and Broadus, A.E. and Thier, S.O., NEJM, 300: 839-845, 1979.

N = Normal ↑ = Increased ↓ = Decreased * A subset of absorptive

8.1.1. Primary absorptive hypercalciuria

The cause of this form of hypercalciuria in an excessive absorption of calcium from the intestine. The increased calcium absorption causes hypercalcemia which turns off PTH secretion and provides an increased filtered load of calcium to the renal tubules, where, due to the decreased availability of PTH, tubular reabsorption of calcium is depressed and hypercalciuria results. The exact reason for intestinal hyperabsorption is

not known, but the serum $1,25(OH)_2D_3$ level is known to be elevated in this situation. Further, it also has been postulated that the intestinal transport mechanisms may be hypersensitive to $1,25(OH)_2D_3$.

A primary renal tubular defect for phosphorus reabsorption (renal phosphorus leak) can also produce an absorptive form of hypercalciuria. These patients have low to non-measurable PTH and no abnormality of renal tubular calcium reabsorption. The low serum phosphorous stimulates renal synthesis of $1,25(OH)_2D_3$ and increases intestinal calcium absorption. But, it should be kept in mind, that not all patients with absorptive hypercalciuria have low serum phosphate levels.

Both primary absorptive hypercalciuria, and its renal phosphorus leak subgroup, can be treated with the usual regimens of low calcium diet, orthophosphates or thiazides. Primary absorptive hypercalciuria can also be treated by binding calcium in the intestine with cellulose phosphate. Although not widely available, this therapy has the theoretical advantage of specificity. However, it has the disadvantages of bulkiness, compliance problems, expensiveness and close monitoring of electrolyte parameters to avoid overtreatment.

8.1.2. Resorptive hypercalciuria (primary hyperparathyroidism)

Primary hyperparathyroidism causes resorption of bone as well as increased intestinal absorption of calcium. This increases serum calcium and presents an increased calcium load to the renal tubules. PTH causes reduced proximal and distal tubular phosphate reabsorption, resulting in phosphaturia, hypophosphatemia and phosphate depletion. It is the phosphate depletion which decreases renal tubular calcium reabsorption and the tubular response to PTH, and produces an elevated serum ionized calcium which tends to reduce PTH secretion. The resulting hypercalciuria thus favors stone formation. About 55% of patients with hyperparathyroidism form stones, and approximately 5 to 10% of all calcium oxalate stone formers have hyperparathyroidism.

Hypercalcemia remains the sine qua non of diagnosis, but urinary cAMP excretion, PTH, serum phosphate, chloride and Mg^+ levels all aid in diagnosis, after the other causes of hypercalcemia have been ruled out.

There is no place for medical therapy in the treatment of the patient who has HPT with stone disease. Surgical exploration and removal of an adenoma or hyperplasia is mandatory. In rare instances, the patient's condition will not allow surgery or, if the diagnosis is not secure, medical therapy may be employed using orthophosphates in a dose of 1500 mg per day in 3–4 divided doses. Orthophosphates may cause

dyspepsia, diarrhea, ectopic calcification and increased stone formation if urinary pH is alkaline and especially, in the face of urinary infection. Orthophosphates are contraindicated in infected cases, or in patients at high risk for infection such as with residual stones or staghorn calculi. If azotemia or hyperphosphatemia develops during therapy, treatment should be discontinued. Other forms of medical therapy, such as saline loading and furosemide, should be avoided since these will increase the hypercalciuria and tend to promote stone formation.

8.1.3. Renal 'leak' hypercalciuria

A primary renal tubular leak of calcium can produce hypercalciuria. The cause for this defective renal tubular reabsorption of calcium is unknown, however. The inability of the kidney to conserve calcium causes a mild hypocalcemia which stimulates PTH secretion (secondary hyperparathyroidism) and $1,25(OH)_2D_3$ synthesis, causing increased intestinal absorption of calcium. High calcium absorption from the intestine ultimately increases the filtered load of calcium and worsens the hypercalciuria. The renal tubule appears to be insensitive to the increased PTH levels and so hypercalciuria persists despite elevated PTH levels.

The majority of patients with hypercalciuria may fall into this category. In some patients, thiazide therapy decreases calcium excretion and normalizes PTH levels as well as serum calcium. However, there are other patients who have persistently elevated PTH levels on thiazide therapy. Many of these patients have parathyroid adenomas (not hyperplasia). When the adenoma is removed, their renal calcium leak persists despite serum PTH levels which have returned to normal. Whether this group represents tertiary hyperparathyroidism or a syndrome of 'normocalcemic primary hyperparathyroidism' remains to be elucidated.

8.1.4. Idiopathic hypercalciuria

Approximately 10 to 20% of patients with hypercalciuria have no apparent metabolic or renal defects that can explain persistent hypercalciuria.

8.2. Other causes of calcium stone formation

8.2.1. Renal tubular acidosis (RTA)

Two main types of RTA are described, Type I or the distal tubular defect and Type II or proximal tubular acidosis (see Chapter 3). Distal RTA is the more common of the two. Distal RTA (Type I) is charac-

terized by an inability of the distal tubule to generate or maintain luminal and peritubular hydrogen ion gradients. However, bicarbonate and ammonia production are usually normal. This is the defect associated with urinary acidification and stone formation. The patient is unable to produce urine of pH less than 5.3–5.5. It is associated with hypokalemia and excess urinary loss of sodium, potassium, calcium and phosphorus. Muscle weakness, osteomalacia and nephrocalcinosis may develop in addition to stones. Systemic acidosis is usually present with a decrease in arterial pH and serum bicarbonate. Serum chloride is frequently elevated. There is also a marked decrease in urinary citrate excretion and thus a decrease in urinary inhibitor activity. The skeleton acts as a buffer in the presence of acidosis with resultant mobilization of calcium, hypercalciuria and decreased solubility of calcium in the urine. Urinary pH, in the classic picture, seldom is found below pH 6.0 and if the pH does not fall below pH 5.3 at any time during a 24-hour period, the diagnosis is secure.

The incomplete form has many of the aforementioned features, but is usually less severe. The pH may range from 5.0–5.4, but is never below 5.0. An ammonium chloride loading test is of great help in this situation.

Therapy is directed toward oral alkalinizing agents and correction of electrolyte abnormalities. Polycitra®, a combination of citric acid, sodium citrate and potassium citrate, given 15–20 ml, 4 times per day is effective. Alkalinization may prevent progression of nephrocalcinosis and decrease the frequency of stone passage.

The drug induced variety of RTA is of interest and is relatively common. Carbonic anhydrase inhibitors such as acetazolamide used in the treatment of glaucoma may cause RTA, underscoring the importance of a drug history. Cessation of drug therapy will reverse the RTA.

The proximal RTA (Type II) is associated with a proximal tubular defect in bicarbonate reabsorption, and is not usually associated with the development of stones or nephrocalcinosis. Some patients may have both the proximal and distal defect which may complicate the diagnosis. Many diseases co-exist with RTA and incomplete or subclinical forms of the disease abound. These varieties usually are not associated with renal stones, however.

8.2.2. Primary hyperoxaluria

This is a rare hereditary disease. It is usually seen in childhood and since there is no truly effective therapy, many children do not survive

to adulthood. Urinary oxalate excretion is greater than 100 mg per 24 hours (normally 10–50 mg/day). Usual therapy includes urinary dilution, orthophosphates, magnesium oxide and pyridoxine. Pyridoxine is given in doses of 50 mg 3 times daily. Hyperoxaluria is also seen in ethylene glycol ingestion and with methoxyflurane anesthesia.

8.2.3. Intestinal disorders

Patients with intestinal disorders have a high incidence of uric acid as well as calcium oxalate stones. Patients with colitis or ileostomy may form uric acid stones. This is due to a chronic loss of fixed base causing acidosis as well as volume loss which causes a concentrated urine. Therapy with oral calcium has been of some help in these patients.

Calcium oxalate stones are often seen in patients with regional enteritis, short bowel syndrome or ileal bypass surgery. These patients have marked hyperoxaluria and low urinary calcium excretion because of intestinal calcium binding to non-absorbable fats, allowing more unbound oxalate in the intestine to be absorbed. The incidence of hyperoxaluria is approximately 15% in these patients.

Therapy is directed toward diet, increasing fluid intake and oral calcium supplements which bind intestinal oxalate and decrease the absorption of oxalate from the intestine, and thereby the urinary excretion of oxalate. Cholestyramine is also used in the therapy of urinary stone disease in these patients.

8.2.4. Medullary sponge kidney

Medullary sponge kidney is a congenital disease associated with dilated tubules (ducts of Bellini) causing stasis of urine with resultant stone formation, infection and hematuria (see Chapter 17).

The treatment of this disease depends on the metabolic defects found and associated complications. If RTA and hyperparathyroidism can be ruled out, then effective therapy usually can be given with thiazides, fluids and control of infection.

8.2.5. Immobilization

Immobilization causes calcium resorption from bone and resultant bony demineralization and hypercalciuria. However, today, the true incidence of non-infectious stones in a population of immobilized patients is probably small. Knowledge of the condition, and therapy including diet, fluids, more rapid mobilization and antibiotics have reduced the incidence dramatically. Orthophosphates have been used with some success, provided urinary infection is not present.

Many other metabolic disorders can be associated with calcium oxalate stone formation such as sarcoidosis, Cushing's syndrome, steroid therapy, thyroid disease, malignancies of all types, primary bone diseases (e.g., Paget's disease of bone) and furosemide administration.

8.2.6. Struvite stones

The last group of calcium stones is the struvite stone which is always associated with infection. Struvite stones consist of triple phosphate (calcium, magnesium and ammonium phosphate) and carbonate apatite. These stones are formed in highly alkaline urine when urea splitting organisms cleave urea to form ammonia, thus raising urinary pH to levels greater than 7.5.

These stones tend to grow rapidly and form casts of the renal collecting system (staghorn, branched or coral calculi). They may be yellow or grey in color, and are somewhat soft and tend to break or crumble at surgery. They are usually laminated stones and are radiopaque, except where they are formed primarily by matrix. They may be unable to be seen by X-ray, but more commonly, a thin shell of calcium makes them radiopaque, especially where plain tomography is utilized.

The following general principles apply to the treatment of struvite calculi: 1) complete removal of all calculi, 2) antibiotic therapy for urinary sterilization, 3) repair of anatomic obstruction, 4) treatment of predisposing metabolic defects, 5) low phosphate diet, and 6) urease inhibitor therapy.

Complete removal of all calculi is mandatory because even small amounts of debris remaining after surgery can harbor bacteria and act as a nidus for new stone formation. Obviously, the urine must remain sterile, or at least be free from infection with urea splitting organisms, since this is thought to be the major cause of struvite stones. Anatomic obstruction must be repaired if possible, since obstruction causes stasis of urine which promotes precipitation as well as infection. Diseases which cause other types of stones are not infrequently the initiating event in struvite stone disease. For example, hyperparathyroidism may cause the formation of many stones before it is diagnosed with resultant renal injury and chronic infection. The aftermath of the initial disease may set the stage for repeated struvite stone formation.

In 1948, Shorr advanced the concept that if one of the urinary elements of the crystalline phase of stone disease was reduced, then, via the mass action equation, this might prevent calculus formation and perhaps even dissolve pre-existent calculi. He presented a regimen consisting of aluminium hydroxide gels and a diet of 700 mg of calcium

and no more than 250 mg of dietary phosphate. Serum and urinary calcium and phosphorous are monitored and urinary phosphorous should be less than 200–250 mg per 24 hours. When used in conjunction with a high fluid intake, this regimen has been demonstrated to be effective therapy in preventing the growth of retained calculi, and a very few have even dissolved.

Recently, inhibitors of the bacterial enzyme urease have been used to prevent struvite stone formation. Urease inhibitors include hydroxyurea, thiourea and acetohydroxamic acid (AHA). AHA specifically inhibits the bacterial enzyme urease from producing ammonia. AHA therapy is now being used where infection cannot be erradicated by antibiotic therapy and/or where retained stones are present, in a dose of 0.5–1.0 grams per day in divided doses. This therapy significantly decreases urinary pH and ammonia levels and when used with antibiotic therapy, has produced a sterile urine where it had been previously impossible. Side effects include hemolytic anemia, which is reversible and dose related, and headache.

9. THE EVALUATION OF THE RECURRENT STONE FORMER

Most patients will be easily identified as falling into the large groups of stone disease: cystine, uric acid, calcium phosphate, calcium oxalate or struvite. But about 70 to 80% of the patients form stones of calcium oxalate, calcium phosphate or a mixture of these two compounds. Approximately 10 to 15% of the patients may have struvite stones and another 5 to 10% uric acid stones. The rest are composed of cystine, xanthine or silicon dioxide. Since the management and prevention of recurrent stone formation is primarily based on the chemical composition of stones and the mechanism of stone formation, analysis of retrieved stones is an essential part in diagnosis. Further, each stone should be analyzed when retrieved since this will alert the physician to changing stone compositions or to changes in the stone nidus.

The evaluation of the initial event in a patient in a stone belt area should include serum creatinine, Ca, P and uric acid, and urinary Ca, P and uric acid, and these are probably more than sufficient. Advice concerning diet and hydration are also very important. However, the initial event in a non-stone belt area demands the same type of evaluation as a recurrent calcium oxalate stone former. The conditions responsible for producing a stone, having once existed, may continue to exist or, may exist again. Therefore, these patients should be evaluated no

differently from recurrent calcium oxalate stone formers, in stone or in non-stone belt areas.

The metabolic evaluation centers on the calcium oxalate stone former. It can be extremely difficult to identify a metabolic defect in these patients. Indeed, there is a group of patients who form calcium oxalate stones, who have neither hypercalciuria nor any other detectable metabolic defect. However, more and more patients can be placed into one of the categories of the hypercalciurias as described earlier.

On the patient's normal diet, the following blood and urine tests should be obtained on at least two separate occasions when hypercalciuria is discovered. Blood: calcium, phosphorous, uric acid, albumin, globulin, alkaline phosphatase, T3, T4, sodium, potassium, chloride, carbon dioxide, fasting blood sugar, BUN, creatinine, osmolality, magnesium, oxalate, parathormone and $1,25(OH)_2D_3$. Urine: 24-hour urine collection for calcium, phosphorous, uric acid, protein, creatinine, sodium, chloride, osmolality, magnesium and oxalate.

Depending upon the findings, determination of absorptive versus renal leak hypercalciuria may be performed by placing the patient on a restricted calcium diet, 500 mg or less/24 hours, for one week with the appropriate urine and blood parameters, followed by a week of a high calcium diet, 2–3 grams/24 hours and again repeating the appropriate urine and blood tests.

10. TIMING OF SURGICAL INTERVENTION

While it is true that a stone of large size can pass spontaneously over a protracted time period, it is equally true that this may result in significant renal damage.

Clinical prognostication of spontaneous stone passage must take into account the following factors: size, configuration and orientation. Several studies in the literature indicate that stones 4 mm or less in greatest diameter have an 80% chance of spontaneous passage if they are first symptomatic in the kidney or renal pelvis; and a 90% chance if they are first symptomatic in the lower ureter. Stones 4–6 mm in greatest diameter have a 20% chance of passage if found in the kidney and about a 50% chance in the lower ureter. Calculi 6 mm or greater have but a small statistical chance of spontaneous passage. Two-thirds of patients who present with a stone 5 mm or less in diameter in the lower ureter, pass their calculus spontaneously within a three-month period. Spontaneous passage of small stones is greatest in the first two to three weeks after clinical presentation. If the stone does not pass after 3–4

weeks, one may be suspicious that the entire stone is not calcified, thereby spuriously decreasing actual stone size, as measured from the radiograph. It is also well to remember that there is a magnification effect of the radiograph which usually requires subtracting 1 mm for each 4–5 mm of measured size on X-ray. For example, a stone of 5 mm measured from an X-ray, is likely to be slightly smaller than 5 mm in actual size.

Configuration and orientation of a stone may preclude passage. It is not unusual to find a small stone virtually embedded in the epithelial lining of a ureter at surgery, or to find a linear stone with a transverse lie at the ureteropelvic junction which prevents passage. However, re-orientation of a calculus is possible, provided it is not embedded in mucosa, and one is often surprised to see a stone progress down a ureter after proper orientation has occurred.

How long then should the clinician wait before intervening in stone disease? If urinary tract infection is present, stones so associated have a decreased chance of passage and a greatly increased risk of producing severe renal damage and sepsis. These stones should be removed forthwith. If operative removal is precluded by the clinical setting, then urinary drainage should be instituted either by passage of ureteral catheters beyond the stone, or if this is not possible, by percutaneous nephrostomy. Rarely, basket extraction may be safely performed in this setting.

If infection is not present, one is usually faced with some form of ureteral obstruction, either complete, or more frequently, partial. Measurable loss of renal function, at least in experimental animals, can be seen after 5 days of complete obstruction, with longer periods producing proportionately more loss of function. Experimentally, at least, 5 days to 2 weeks of total obstruction will be associated with some permanent loss of renal function. After 6 weeks, only slight recovery is to be expected. Operative intervention with partial obstruction depends upon the degree and duration of the obstruction. It is the more frequent clinical presentation, and functional loss in this setting is most difficult to quantify. Each case must be individualized and the decision when to operated evolves on prudent clinical judgment and the clinical setting. It is a truism that even with partial obstruction, at least some nephrons are being lost as long as a relatively high grade partial obstruction exists. Unquestionably, if an anatomic obstruction is discovered, surgical intervention should be prompt and at the first earliest convenience of the patient.

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9. DRUG-RELATED NEPHROPATHY

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1. INTRODUCTION

Drug-related nephropathy is defined as any adverse functional or structural change in the kidney resulting from administration of drugs or diagnostic agents. The recommended dose as well as excessive amounts of drugs may cause renal damage. The term drug-related nephropathy has been applied to any form of unexplained kidney disease seen in persons habituated or addicted to drugs, although the etiological relationship is not always apparent.

In this chapter, the discussion of drug-related nephropathy will be limited to those renal disorders that are caused by chemical compounds used in the diagnosis, treatment and prevention of disease. Thus, any renal disease caused by toxic chemicals and poisons (industrial or agricultural) and biologically active compounds (venom, hormones, blood products and vaccines) will not be considered.

Drug-related nephropathy is not a rare clinical entity. Seven to 30% of acute renal failure and 3 to 10% of chronic renal failure are attributed to drugs given to patients for diagnostic procedures or treatment. Furthermore, analgesic drugs account for end stage renal disease in approximately 2% of patients in this country, and as many as 25% of patients in other countries. Nephropathy caused by drugs is neither pathologically specific nor clinically unique. Thus, evidence for diagnosis of drug-related nephropathy is rather circumstantial, and unequivocal documentation of the cause-effect relationship between the drugs and the observed nephropathy cannot often be made.

The importance of recognizing drug-related nephropathy is two-fold. Early recognition can prevent development of iatrogenic renal disease. In addition, the functional and histologic changes associated with drugs are reversible upon discontinuation of the drugs.

The kidney is one of the most vulnerable organs to drugs toxicity because of its unique functional and anatomical properties. First, the two kidneys comprise only about 0.4% of body weight, but they receive

about 25% of the resting cardiac output. Thus, the kidneys can be exposed to large amounts of a drug, even if toxic levels are only transiently maintained. Second, the renal countercurrent mechanism results in hypertonicity of the medullary and papillary interstitium. This serves to concentrate drugs and their more polar metabolites in these regions. Renal tubular cells may therefore become exposed to drug concentrations that far exceed those encountered in any other organs. Third, renal mechanisms for the release of drugs from protein, and their subsequent transcellular transport, lead to high levels of free drugs in the renal interstitial space and tubular cells. Fourth, the unique vascular supply of the kidney provides it with the largest vascular endothelial surface area relative to its weight of any other organ. This large endothelial surface renders the kidney particularly susceptible to deposition of antigen-antibody complexes and to hypersensitivity-related vasculitis. Fifth, since the kidney is a major excretory route for many drugs and their metabolites, pre-existing renal disease, with impaired excretory function, leads to accumulation of drugs and prolonged exposure of functioning nephrons to increased levels of nephrotoxic compounds.

Two major pharmacologic mechanisms have been identified in the genesis of drug-related nephropathy. First, drugs may have therapeutically desirable actions on the kidney, but excessive inappropriate use of the drugs may result in metabolic changes that adversely affect renal function or structure. For example, excessive use of thiazide diuretics may produce fluid-electrolyte imbalance and azotemia, and inappropriate use of uricosuric agents may induce urate nephropathy. Second, drugs may have direct nephrotoxic properties that may result in reversible or permanent renal damage. For example, lithium can induce dose-dependent, reversible, nephrogenic diabetes insipidus, and prolonged use of lithium can also produce renal tubulo-interstitial abnormalities with tubular dysfunction and renal failure.

The pathogenesis of drug-related nephropathy is, however, poorly understood. Possible mechanisms include: dose-dependent nephrotoxic effects of the drugs or their metabolites (*e.g.*, gentamicin or amphotericin B-related acute tubular necrosis); immunologic mechanism including either drug-induced auto-immunogenecity of the kidney, glomerular deposits of drugs as part of immune complexes and involvement of the kidney in hypersensitivity vasculitis (*e.g.*, penicillamine-related membranous nephropathy and methicillin-related interstitial nephritis); and finally crystallization and precipitation of drugs or their metabolites in the kidney and urinary tract (*e.g.*, sulfonamides, methotrexate).

Drug-related nephropathy is associated with a wide range of renal

functional and structural changes, from a slight, reversible impairment of renal function, without recognizable histologic alteration, to severe, progressive renal failure leading to end stage renal disease. Drug-related nephropathy can be classified into the following clinicopathological syndromes based on histological, pathophysiological and clinical characteristics of the nephropathies produced by different drugs [5, 10].

Acute tubular necrosis
Tubulo-interstitial disease
Glomerulonephritis, nephrotic syndrome and vasculitis
Hemolytic-uremic syndrome
Obstructive uropathy
Fluid-electrolyte and acid-base imbalance

2. ACUTE TUBULAR NECROSIS

The syndrome of acute tubular necrosis results from an acute and severe reduction in renal function by either ischemic or toxic injury that cannot be reversed by manipulation of extrarenal factors. Renal hemodynamic changes in acute tubular necrosis associated with nephrotoxic damage are characterized by a sustained homogenous reduction in renal cortical perfusion, preglomerular vasoconstriction and efferent arteriolar relaxation. These changes are sufficient to induce the cessation of glomerular filtration [13]. The hemodynamic changes are essentially similar to those occurring in acute renal failure of widely different etiologies, including shock and hemolysis. It is unlikely, however, that cortical hypoperfusion is the only factor responsible for oliguria. Tubular obstruction due to casts, crystals and necrotic cells, and tubular compression due to interstitial edema increase proximal intratubular pressure and oppose glomerular filtration. Finally, diffusion may take place through necrotic tubules, and prevent the scanty glomerular filtrate from ultimately reaching the collecting system.

2.1. Predisposing factors

Predisposing or contributory factors for the development of drug-related acute tubular necrosis include pre-existing renal or hepatic disease, diabetes mellitus, dehydration, electrolyte imbalance (especially sodium deficit), hypotension, septicemia, recent major surgical procedures, and older ages (Table 1). The more predisposing factors present in association with exposure to a nephrotoxic drug or repeated exposures to

Table 1. Predisposing factors for drug-related acute tubular necrosis

Pre-existing disease:
Renal
Others: hepatic, diabetes mellitus, multiple myeloma, advanced arteriosclerotic cardiovascular disease
Fluid-electrolyte imbalance:
Dehydration, hypovolemia, sodium depletion, hypotension
Associated problems:
Recent surgical procedure(s)
Concurrent septicemia
Other drug(s):
Use of multiple nephrotoxic drugs
Concomitant use of furosemide or indomethacin
Old age:

multiple nephrotoxic drugs, increase the incidence, morbidity and mortality of acute tubular necrosis. The use of nephrotoxic drugs, such as aminoglycoside antibiotics and iodinated radiographic contrast agents, in patients with pre-existing kidney disease, requires special consideration. It has been repeatedly observed that diseased kidneys with impaired function are more susceptible to nephrotoxic agents. This increased susceptibility is probably due to retention of drugs, with higher peak and trough levels, and increased free drug levels resulting from decreased protein binding. Furthermore, the consequences of even minor nephrotoxic effects could be disastrous in patients whose kidney function is already compromised. Nephrotoxic drugs should thus be avoided in patients with renal disease, if possible, or only the minimum therapeutic or diagnostic dose should be given, with frequent measurements of fluid and electrolyte status, renal function and drug levels. Drugs that may cause acute tubular necrosis are listed in
Table 2 [2, 5, 8, 10–12, 21, 22].

2.2. Incidence

Drug-related acute tubular necrosis is relatively common and consists of 7 to 30% of all causes of acute renal failure [2]. The true incidence would perhaps be substantial if mild cases, that are frequently overlooked, were included.

In general, the highest incidence of acute tubular necrosis in association with nephrotoxic drugs, is seen in older patients (over 65 years) with disseminated systemic diseases, or with other complications such

Table 2. Drugs that may cause acute tubular necrosis

Antimicrobial drugs:
Aminoglycosides
Amikacin
Gentamicin
Kanamycin
Neomycin
Streptomycin
Tobramycin
Amphotericin B
Bacitracin
Cephalosporins
Cephaloridine
Cephalexin
Cephalothin
Colistimethate
Para-aminosalicylic acid
Penicillin
Pentamidin
Polymixin B
Rifampicin
Sulfonamides
Tetracycline
Vancomycin
Viomycin
Analgesics, anesthetics and anti-inflammatory drugs:
Acetaminophen overdose
Acetylsalicylic acid
Indomethacin
Methoxyflurane
Phenazopyridine (Pyridium®)
Phenylbutazone
Diuretics:
Furosemide
Spironolactone
Thiazides
Iodinated radiographic contrast agents:
Anti-neoplastic drugs:
Cis-Dichlorodiamine-Platinum
Mithramycin
Methotrexate
Miscellaneous
Cimetidine
1,25-dihydroxycholecalciferol

as septicemia, shock, dehydration and the concurrent use of other nephrotoxic agents. Chemical compounds that are most commonly associated with acute tubular necrosis in recent years are aminoglycosides and iodinated radiographic contrast agents [21]. The incidence of

nephrotoxicity in patients who receive therapeutic doses of gentamicin ranges from 2 to 30%, amikacin from 8 to 14%, kanamycin from 10 to 75% and tobramycin from 1 to 2%. The incidence of acute tubular necrosis after intravenous or arterial infusion of radiographic contrast agents ranges between 0.5 and 3% in non-diabetic patients with normal kidney function and is over 50% in diabetic patients with renal insufficiency.

2.3. Clinical features

Acute tubular necrosis caused by nephrotoxic drugs is a form of acute renal failure; neither its clinical features nor its laboratory findings are specific. Thus, the evaluation, diagnostic approach and management of patients with drug-related acute tubular necrosis are the same as for patients with acute renal failure of various other etiologies (see Chapter 10).

The severity of renal failure and the natural course of acute tubular necrosis related to nephrotoxic drugs are extremely variable. Urinary output may range from anuria to polyuria, azotemia may be mild to severe, duration of renal failure may be a few days to a few months, and renal function may recover completely or progress to end-stage. In general, drug-related acute tubular necrosis tends to lead to a milder renal failure, a shorter oliguric period (2 days to 2 weeks), or even polyuria, and a more complete return of renal function than acute tubular necrosis precipitated by other causes. Uncomplicated drug-related acute tubular necrosis has a good prognosis with minimal morbidity and mortality. The overall prognosis, however, depends on the patient's underlying disease.

Treatment of drug-related acute tubular necrosis is essentially identical to that of acute renal failure produced by other causes as discussed in Chapter 10. As soon as deterioration of renal function is observed, all potentially nephrotoxic drugs should be discontinued and non-nephrotoxic alternative drugs should be carefully maintained.

Use of diuretic regimens, such as mannitol and furosemide, have been advocated to prevent impending acute tubular necrosis or to reverse established acute tubular necrosis, despite the lack of clinical evidence for beneficial effects. In animal experiments, however, furosemide given before, during or after injection of nephrotoxic drugs, tends to increase the incidence and severity of acute tubular necrosis [18]. Nevertheless, a trial of such diuretic regimens, in moderate doses, in patients with acute onset of oliguria and/or azotemia, is not

unreasonable and may help to differentiate pre-renal azotemia from acute renal failure. However, repeated use of large doses of diuretics to increase urinary output may not only increase the severity, but also complicate the clinical course of acute tubular necrosis.

3. TUBULO-INTERSTITIAL DISEASE

Many drugs can produce acute or chronic tubulo-interstitial disease. This form of renal disease is the second most commonly occurring drug-related nephropathy.

Tubulo-interstitial disease is characterized histologically by the presence in the interstitium of variable numbers of inflammatory cells (usually mononuclear cells, lymphocytes, plasma cells, eosinophils and polymorphonuclear cells), accompanied by a variable degree of interstitial edema, fibrosis and tubular necrosis or atrophy. Interstitial edema and polymorphonuclear cellular infiltration are more prominent in acute forms while interstitial fibrosis is greater in chronic forms. The histologic findings are, however, non-specific for drug-related tubulo-interstitial disease.

3.1. Acute tubulo-interstitial disease

An acute tubulo-interstitial disease is usually due to immune mediated processes, probably involving both humoral and cellular mechanisms. Drugs that may cause acute or chronic tubulo-interstitial disease are listed in Table 3.

Clinical evidence of renal failure usually develops one to two weeks (ranging from 5 days to 5 weeks) after exposure to the drug. Some patients may have been exposed to the same drug or a similar drug previously without an adverse reaction. Clinical manifestations include oliguria, azotemia, mild proteinuria, pyuria, hematuria (gross or microscopic), and cellular casts, in association with systemic signs (fever, pruritus and morbilliform skin rash) and eosinophilia. Oliguria and renal failure may be severe enough to require dialysis.

It is sometimes difficult to differentiate acute tubulo-interstitial disease from acute tubular necrosis, especially when systemic signs are minimal or absent. Demonstration of large numbers of eosinophils in the urinary sediment by Wright's stain may help in making the diagnosis of acute tubulo-interstitial disease. In some instances, varying degrees of acute tubular necrosis and tubulo-interstitial disease may

Table 3. Drugs that may cause tubulo-interstitial nephritis.

Acute:
Allopurinol
Azathioprine
Cephalosporin
Furosemide
Methotrexate
Penicillin derivatives (ampicillin, methicillin, nafcillin, oxacillin, penicillin G)
Phenindion
Phenylbutazone
Phenytoin (diphenylhydantoin)
Sulfonamides
Thiazides
Rifampicin
Chronic:
Acetaminophen (?)
Aspirin
Lithium
Phenacetin
Analgesic mixtures
Methyl cyclohexynitrosourea (methyl CCNU)

occur simultaneously, and the clinical presentation, as well as the pathological findings, may be a combination of both.

In general, recovery is the rule and clinical manifestations usually resolve following withdrawal of the drug. Short courses of steroid therapy may hasten recovery of renal function and improve systemic manifestations. Some patients, however, may have permanent impairment of renal function. Patchy areas of interstitial fibrosis and loss of renal tubules have been observed in renal biopsies of these patients.

Hypersensitivity reactions appear to be the most likely pathogenetic mechanisms for drug-related acute interstitial nephritis. The adverse reactions are not usually dose-related. They are often accompanied by fever, skin rash, and eosinophilia, and may be attended by circulating anti-drug antibodies. This mechanism has been studied best in patients with methicillin-related interstitial nephritis [4, 6]. The penicilloyl haptenic group and the tubular basement membrane, acting as antigens, seem to incite a humoral immune response resulting in deposition of immune complexes in the tubular basement membrane. These can be identified by linear immunofluorescent staining of the tubular basement membrane with IgG, C3 and dimethoxyphenyl penicylloyl. Sensitized lymphocytes also mediate this immune response with subsequent tubular and interstitial damage. In addition, elevated levels of IgE in the serum of patients with drug-related interstitial nephritis and presence of IgE in plasma cells of the interstitial infiltrate, raise the possibility of

allergen-reaginic antibody complexes in the pathogenesis of this lesions. Whatever the inciting immunologic mechanism is, it appears that there is a primary damage to the tubule and a secondary reaction in the interstitium.

3.2. Chronic tubulo-interstitial disease

Acute tubulo-interstitial disease produced by drugs rarely progresses to chronic disease. Chronic tubulo-interstitial disease can be associated with prolonged and excessive intake of analgesic compounds [16, 25–27]. Analgesic nephropathy is a unique form of interstitial disease in that it is often associated with chronic papillary necrosis (50%) and occasionally with transitional cell carcinoma in the urinary tract (2 to 7%) [14].

The association between the use of analgesic drugs and tubulo-interstitial disease has been recognized for over a decade, and the existence of a cause-and-effect relationship appears to be established. However, primary causative agent(s) among various analgesic compounds and their pathogenetic mechanisms have not yet been clearly delineated.

The incidence of analgesic nephropathy varies greatly not only among countries but also among geographical regions within a country. In the United States, approximately 20% of chronic tubulo-interstitial disease, 5% of chronic renal failure and 2% of end stage renal disease requiring dialysis, are estimated to be caused by analgesic drugs. In general, however, the prevalence of analgesic nephropathy is much higher in other countries (5% in Canada, 11% in the United Kingdom, 22% in South Africa, and 25% in Australia).

Analgesic nephropathy usually occurs in women (85%), above the age of 35, who have a long history of psychiatric disturbances and social inadequacy, and who have been taking analgesics for recurrent episodes of pain (headache, backache or arthralgia) for a prolonged period of time. Most patients have consumed large quantities of phenacetin (1 to 3 kg total dose or about 1 gm per day for one to three years) along with aspirin and other drugs, but the lowest total dosage at which these drugs are nephrotoxic are unknown. At present, phenacetin has been removed from the market in many countries.

The clinical course of the disease is usually insidious and progressive, but it can be stormy at times, with acute complications of papillary necrosis, urinary obstruction, hematuria and secondary infection. Renal functional abnormalities are manifested by azotemia, hyperchloremic metabolic acidosis, mild proteinuria, microscopic or gross hematuria, sterile pyuria, hyposthenuria or isothenuria, refractory to vasopressin,

and impaired renal conservation of sodium. In the majority of patients who stop analgesic ingestion, azotemia either stabilizes or improves. Improvement is more likely to occur if the level of renal impairement is mild. Patients who continue to use analgesics almost invariably suffer progression of the disease.

Although phenacetin or its major metabolite, acetaminophen, have been shown to be non-toxic in experimental animals, either aspirin alone or combinations of aspirin and phenacetin can produce papillary necrosis and cortical lesions resembling those seen in analgesic nephropathy. At the present time, it is unclear whether these drugs and/or their metabolites are directly toxic to the kidney or whether they impair physiologic protective mechanisms in the renal medulla (*e.g.*, medullary protaglandin depletion and, consequently, reduction in medullary blood flow). Whatever the pathogenetic mechanisms are, it appears that renal papillary necrosis is the primary lesion and that the cortical changes of chronic interstitial nephritis are secondary.

4. GLOMERULONEPHRITIS, NEPHROTIC SYNDROME AND VASCULITIS

Drug administration can be associated with the development of circulating immune complexes. These may lead to glomerulonephritis, or to a generalized vasculitis. Occasionally, deposition of immune complexes is confined to the kidney with minimal extrarenal involvement. In such cases, it appears as a primary acute or chronic glomerulonephritis.

Drug-related nephritis may be associated with various histological patterns and clinical syndromes. Drug-related nephritis may nevertheless be classified into three major categories based on clinicopathological characteristics: acute glomerulonephritis, chronic glomerulopathy and vasculitis.

The drugs that may cause glomerulopathy and vasculitis are listed in Table 4 [3, 9, 29, 30, 32, 33].

4.1. Acute glomerulonephritis

A focal or diffuse proliferative glomerulonephritis with crescents, has been described in a few patients following therapy with penicillin G, sulfonamides and penicillamine.

The syndrome is characterized by acute onset of azotemia, proteinuria, hematuria, hypertension and abnormal urinary sediment. Some

patients may have other signs of hypersensitivity reaction to the drug, such as fever, arthralgia, rashes, purpura and eosinophilia. The nephritic process usually recedes gradually when the drug is withdrawn. However, a short course of adrenocorticosteroid therapy is indicated if systemic manifestations of the hypersensitivity reaction are severe.

Table 4. Drugs that may cause glomerulonephritis, nephrotic syndrome or vasculitis

Proliferative glomerulonephritis and/or vasculitis:
Heroin
Methamphetamine
Penicillamine
Penicillin
Sulfonamides
Membranous nephropathy:
Colchicine
Gold
Mercury
Penicillamine
Focal segmental sclerosis:
Corticosteroids
Heroin
Puromycin
Minimal change:
Paramethadione
Puromycin
Trimethadione
Methimazole

4.2. Chronic glomerulopathy

Chronic glomerulopathy with varying degree of proteinuria and azotemia has been observed in patients receiving the following drugs; heavy metal organic compounds (gold, bismuth, mercury), anticonvulsants (trimethadione, paramethadione), puromycin, penicillamine, tolbutamide, probenecide and heroin.

Although each drug often produces a specific histologic pattern of glomerulopathy, as shown in Table 4, the particular glomerulopathy is non-specific and cannot be differentiated from similar lesions of other etiologies.

Pathologic and immunologic studies indicate that drug-related glomerulopathy is caused by immune mediated mechanisms. However, the

precise role of the drug in the abnormal immune mechanisms and the subsequent processes that lead to glomerulopathy are not yet well delineated. It has been suggested that, since some drugs (gold, penicillamine) can directly induce tubular damage, such damaged tubules might release an autologous antigen that, in turn, might activate an immune response with the formation of immune complexes. This hypothesis is consistent with the observation that discrete, subepithelial deposits of immunoglobulins (epimembranous nephropathy) are present in the kidneys of patients with nephrotic syndrome associated with these drugs. However, no autologous antigen has yet been demonstrated in gold or penicillamine-related nephritis.

The nephrotic syndrome occurs after days or years of drug treatment, and it may be either mild and transient or severe and progressive. Usually, the nephrotic syndrome recedes with discontinuation of the drug. Some patients with persisting proteinuria have been treated with corticosteroids and immunosuppressive drugs with apparent beneficial results. An important exception to this relatively benign course of drug-related nephritis is the glomerulonephritis and nephrotic syndrome occurring in heroin addicts. (Heroin-associated nephropathy.)

Controversy exists as to whether or not the incidence of glomerulonephritis in heroin addicts is higher than in the general population. However, many believe that glomerular disease is substantially higher (8 to 10%) in such individuals and that focal segmental sclerosis is the most common pathological finding (90%), although other lesions (proliferative and membranoproliferative glomerulonephritis) have also been noted [29, 32]. The focal segmental sclerosis in heroin addicts is often accompanied by tubular atrophy, interstitial fibrosis and chronic inflammatory cellular infiltration. It usually progresses to uremia within 6 to 48 months, as long as heroin injections continue, despite steroid or cytotoxic drug therapy.

4.3. Vasculitis

Drug-related vasculitis often affects the kidney as part of a serum sickness-like syndrome by the deposition of circulating immune complexes in the renal vasculature. The amount of immune complexes deposited in an individual organ is determined by the levels of circulating immune complexes and by the vascular surface area of the organ. Thus, the kidney is the visceral organ that is most often involved in systemic vasculitis.

Renal manifestations of vasculitis are similar to those of acute or

chronic glomerulonephritis (proteinuria, azotemia, hematuria and hypertension). However, the clinical features of drug-related vasculitis may vary greatly; either the acute form of classical hypersensitivity angiitis with systemic manifestations may be present (fever, rashes, purpura, arthralgia, arthritis, lymphadenopathy, and eosinophilia) or there may be an insidious onset of a systemic necrotizing angiitis that is pathologically indistinguishable from periarteritis nodosa. The former type occurs in patients receiving penicillin or sulfonamides. Clinically, it is self-limited and usually resolved within one week. However, if long-acting penicillins or sulfonamides are used, the syndrome may persist for a month or longer. In contrast, the latter type of vasculitis occurs in heroin or methamphetamine addicts and it may be progressive leading to death after arterial rupture, uremia or visceral infarction, despite steroid and immunosuppressive therapy.

Systemic disorders with serological abnormalities similar to idiopathic systemic lupus erythematosus have been observed in patients receiving various drugs for a prolonged period of time. Drug-related lupus, however, rarely involves the kidney and central nervous system and usually recedes when the offending drug is discontinued. However, hydralazine and procainamide induced lupus may be associated with glomerulonephritis. Drugs that have been implicated in the development of lupus-like syndromes are listed in Table 5 [1, 19],

Table 5. Drugs that may incite lupus-like syndrome.

Antimicrobials: penicillins, tetracycline, streptomycin, para-aminosalicylate, sulfonamides, INH
Antithyroid drugs; methyl and propyl thriouracil
Anticonvulsants: phenytoin, mesantoin, primidone, trixidone
Antihypertensive drugs: reserpine, methyl dopa, guanoxan, hydralazine
Miscellaneous: phenylbutazone, griseofulvin, oral contraceptives, penicillamine, procainamide

5. HEMOLYTIC-UREMIC SYNDROME

The hazards of hypertension, venous thromboembolic disease, arterial occlusive disease, hemolytic-uremic syndrome and nephrosclerosis in women taking oral contraceptives have been recently reported. Although the results of epidemiological studies and circumstantial evi-

dence are not conclusive, they suggest a possible cause-and-effect relationship between the drugs and the clinical disorders. However, too few systematic studies have been conducted to adequately evaluate the incidence, clinical significance and pathogenesis of renal disorders.

There is increasing evidence that estrogenic compounds, natural or synthetic, have stimulatory effect on the renin-angiotensin-aldosterone system. Renin substrate from the liver is also consistently increased during the administration of estrogenic compounds in normal subjects.

The incidence of hypertension among young women taking oral contraceptives ranges from 11% to 18%. The development of hypertension may occur as early as a few weeks and as late as a few years after initiation of contraceptive drug therapy. Hypertension associated with the drugs often recedes when they are withdrawn. Occasionally, patients may develop accelerated hypertension, severe renal failure and microangiopathic hemolytic anemia. The clinical features and pathological findings in these patients are consistent with hemolytic-uremic syndrome observed in children as well as in young women in the postpartum period (postpartum nephrosclerosis). The induction of a pseudopregnancy state by oral contraceptives containing estrogen-progestin combinations associated with a hypercoagulable state may be an important predisposing factor.

Clinical features include acute or progressive development of accelerated hypertension, retinopathy, seizures, fever, severe renal failure, usually with oliguria, thrombocytopenia, microangiopathic hemolytic anemia and fibrin split products in the systemic circulation [7]. The clinical course is usually progressive and often leads to a fatal outcome, although some patients have survived with partial reversal of kidney failure.

Pathological findings are usually, but not always, confined to the kidneys and include fibrinoid necrosis, proliferative endarteritis, fibrin thrombi and hemorrhagic infarcts. Similar findings can be observed in the pancreas, adrenal glands and lungs.

6. OBSTRUCTIVE UROPATHY

Both acute and chronic obstructive uropathy, secondary to either intrarenal or extrarenal obstruction, may be produced by drugs.

Intrarenal obstruction, usually presents as acute renal failure and may be produced by precipitation of uric acid, oxalate, protein, drugs or their

Table 6. Drugs that may cause obstructive uropathy.

Drugs	Pathology
Intrarenal obstruction:	
Uricosuric drugs;	Urate nephropathy
Probenecid	Uric acid stone or sludge formation
Sulfinpyrazone	Uric acid stone or sludge formation
Antineoplastic drugs;	Urate nephropathy
Methotrexate;	Crystallization of the drug and its metabollite (7-hydroxy methotrexate)
Radioiodinated contrast agents;	Crystallization of contrast agent, precipitation of Tamm-Horsfall protein, or urate nephropathy
Methoxyflurane	Oxalate deposits
Extrarenal obstruction:	
Ascorbic acid	Oxalate stone
Uricosuric agents	Uric acid stone or sludge formation
Sulfonamides	Crystallization and urolithiasis
Analgesic compounds	Ureteral and/or periureteral fibrosis
Methysergide	Retroperitoneal fibrosis
Hydralazine	Retroperitoneal fibrosis
Ergotamine	Retroperitoneal fibrosis
Dihydroergotamine	Retroperitoneal fibrosis
Acetazolamide	Nephrocalcinosis and urolithiasis

metabolites within tubular lumina. Drugs that may cause intrarenal obstruction and their pathogenetic mechanisms are summarized in Table 6.

Acute urate nephropathy occurs most frequently in patients with massive cellular destruction, a few days after chemotherapy for hematologic neoplasia. To prevent this complication, these patients should receive allopurinol to inhibit uric acid production, at least 48 hours before chemotherapy, in addition to other adjunctive measures (increased fluid intake and alkalinization of the urine with sodium bicarbonate).

Prolonged use of uricosuric agents (probenecid, sulfinpyrazone) may cause extrarenal obstructive uropathy secondary to uric acid stone or sludge formation. For this reason, allopurinol is an ideal drug for lowering serum uric acid in patients with primary or secondary hyperuricemia, particularly when associated with impaired renal function.

Retroperitoneal fibrosis with gradual obstruction of the ureters as well as the reno-vascular system, occasionally occurs in patients taking methysergide or other drugs (ergotamine, dihydroergotamine and hydralazine) for a prolonged period of time [17]. The usual histologic appearance is that of a chronic inflammatory process in the adipose tissue of the retroperitoneal space, progressing to diffuse fibrosis. Although the etiology of the disease is obscure, it is postulated that retroperitoneal fibrosis is an autoimmune disorder provoked by drugs acting as haptenes.

7. FLUID, ELECTROLYTE AND ACID-BASE DISORDERS

Drugs may produce various degrees of fluid, electrolyte and acid-base imbalance by numerous mechanisms. Although most of the disorders are reversible upon discontinuation of the drug(s), some may be serious enough to require immediate treatment. It is important to recognize the possible cause and effect relationship between drugs that patients are taking and observed metabolic abnormalities. However, it is more important to anticipate the possibility of adverse drug effects and to monitor fluid, electrolyte, and acid-base status.

7.1. Antidiuresis and dilutional hyponatremia

Drugs may possess water retaining properties (antidiuresis) by either augmentation of the ADH effect on the renal tubules or by increase of ADH release from the neurohypophysis, leading to hyponatremia. Excessive use of diuretics can produce sodium abnormalities, either hyponatremia or hypernatremia, depending upon the relative amount of salt and fluid intake. The drugs that may cause antidiuresis are listed in Table 7 [23, 24].

7.2. Diabetes insipidus

Mild diuresis, or a syndrome of polyuria refractory to exogenous and endogenous ADH, has occurred in patients receiving drugs. A transient central diabetes insipidus can be produced by drugs such as ethanol, phenytoin or naloxone hydrochloride. Most clinically significant, drug-related polyuria, is a reversible state of nephrogenic diabetes insipidus, caused by lithium, methoxyflurane, and demeclocycline. The drugs that may cause diuresis or diabetes insipidus are listed in Table 7 [31].

Table 7. Drugs that may cause fluid imbalance.

Drugs that may cause antidiuresis
Hypoglycemic agents
Chlorpropamide, tolbutamide, biguanides
Cytotoxic drugs
Vincristine, cyclophosphamide
Miscellaneous
Carbamazepine, clofibrate, acetaminophen, vasopressin, oxytocin, morphine, nicotine, barbiturates, diazoxide, salicylate, minoxidil
Drugs that may cause diuresis
Lithium
Phenytoin (Diphenylhydantoin)
Demeclocycline
Acetohexamide
Tolazamide
Naloxone hydrochloride
Prophoxyphene
Colchicine
Vinblastine
Methoxyflurane
Glyburide

7.3. Potassium imbalance

Drugs may produce either hyperkalemia or hypokalemia by abnormal external (actual changes in total body potassium) or internal (maldistri-

Table 8. Drugs that may cause potassium imbalance.

Hyperkalemia:
Salt substitute (KCl); 12 mEq (480 mg) of K per gram
Potassium penicillin; 1.7 mEq per million units
Amino-acid infusion (arginine, lysine, ornithine)
Spironolactone
Triamterene
Digitalis intoxication
Propranolol
Hypokalemia:
Diuretics (thiazides, furosemide, ethacrynic acid, acetazolamide, chlorthalidone)
Carbenicillin
Penicillin
Polysterene sulfonate
Insulin
Sodium bicarbonate
Amphotericin B
Salicylate intoxication
Corticosteroids

bution of potassium between intracellular and extracellular fluid compartments) potassium balance. The drugs that may cause hyperkalemia or hypokalemia are listed in Table 8.

7.4. Acid-base imbalance

Many drugs may produce acid-base imbalance directly by addition of protons, as part of the drug, or indirectly by alteration in proton distribution, energy metabolism or renal tubular function. In most cases, withdrawal of the causative drugs will be sufficient to normalize the abnormality. Acute and severe forms of metabolic acidosis, however, require prompt and aggressive treatment to restore plasma pH (*e.g.*, salicylate intoxication, phenformine-induced lactic acidosis). The drugs that may produce acid-base imbalance are listed in Table 9.

Table 9. Drugs that may cause acid-base imbalance

Acidosis
Renal mechanisms:
Acetazolamide
Amphotericin B
Degradated tetracycline
Paraldehyde
Non-renal mechanisms:
Amino-acid infusion (arginine, lysine)
Ascorbic acid
Ammonium chloride
Hydrochloric acid
Cholestyramine
Salicylic acid, methyl salicylate
Phenformine
Nalidixic acid
Paraldehyde
Sodium nitroprusside
Alkalosis
Diuretics (thiazides, furosemide, ethacrynic acid)
Mineralocorticoids
Licorice
Carbenicillin
Penicillin
Sodium bicarbonate

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Appendix. Nephrotoxic Drugs

Drugs	Nature of Toxicity
Antimicrobial Drugs	
Aminoglycosides	Acute tubular necrosis
Amikacin	Gentamicin; Renal tubular dysfunction
Gentamicin	Streptomycin; Lupus-like syndrome
Kanamycin	
Neomycin	
Streptomycin	
Tobramycin	
Amphotericin B	Acute tubular necrosis
	Renal tubular dysfunction
Bacitracin	Acute tubular necrosis
	Renal tubular dysfunction
Cephalosporins	Acute tubular necrosis
Cephalothin	? Acute interstitial nephritis
Cephalexin	
Cephaloridine	
Cefazolin	
Colistimethate	Acute tubular necrosis
	Hematuria
Demeclocycline	Nephrogenic diabetes insipidus
Para-aminosalicylic acid	Acute tubular necrosis
	Lupus-like syndrome
Penicillins	Acute interstitial nephritis
Ampicillin	Vasculitis and glomerulitis
Methicillin	Penicillin; Lupus-like syndrome
Nafcillin	Nafcillin; pseudoproteinuria
Oxacillin	
Penicillin G	
Pentamidin	Acute tubular necrosis
Polymixin B	Acute tubular necrosis
Rifampicin	Acute interstitial nephritis
	Acute tubular necrosis
Sulfonamides	Acute interstitial nephritis
	Necrotizing vasculitis and glomerulitis
	Lupus-like syndrome
	Urolithiasis
	Acute tubular necrosis
Tetracycline	Acute tubular necrosis
	Renal tubular acidosis and dysfunction (Fanconi's syndrome)
	Lupus-like syndrome
Vancomycin	Acute tubular necrosis
Viomycin	Acute tubular necrosis

Drugs	Nature of Toxicity
Analgesic and Anti-Arthritic Drugs	
Acetaaminophen	Acute tubular necrosis Chronic interstitial nephritis Antidiuresis
Allopurinol	Vasculitis Acute interstitial nephritis
Colchicine	Membranous nephropathy Acute tubular necrosis Diuresis
Indomethacin	Acute tubular necrosis
Phenacetin	Chronic interstitial nephritis Ureteral stricture and uroepithelial neoplasm
Phenazopyridin	Acute tubular necrosis
Phenylbutazone	Acute tubular necrosis Acute interstitial nephritis Lupus-like syndrome
Probenecid	Urate nephropathy and urolithiasis
Propoxyphen	Diuresis
Salicylates	Acute tubular necrosis Chronic interstitial nephritis Metabolic acidosis Hypokalemia Antidiuresis
Sulfinpyrazone	Urate nephropathy and urolithiasis
Drugs Acting on Central Nervous System (Narcotics, Anesthetics, Anticonvulsants, etc.)	
Amphetamine and methamphetamine	Vasculitis (periarteritis nodosa)
Heroin	Glomerulitis, vasculitis Myoglobulinuria-acute tubular necrosis
Lithium	Nephrogenic diabetes insipidus Chronic interstitial nephritis
Mesantoin	Lupus-like syndrome
Methoxyflurane	Acute renal failure Nephrogenic diabetes insipidus
Morphine	Antidiuresis
Naloxone HCl	Diuresis
Paraldehyde	Acidosis
Paramethadione	Nephrotic syndrome (minimal change)
Phenformin	Lactic acidosis
Phenindion	Acute interstitial nephritis
Phenytoin	Acute interstitial nephritis Lupus-like syndrome Diuresis

Drugs	Nature of Toxicity
Primidone	Lupus-like syndrome
Trimethadione	Nephrotic syndrome (minimal change)
Trixidone	Lupus-like syndrome
Diuretics	
Acetazolamide	Acidosis Nephrocalcinosis and urolithiasis
Furosemide	Fluid, electrolytes and acid-base imbalance Acute interstitial nephritis ? Acute tubular necrosis
Spironolactone	Acute tubular necrosis Hyperkalemia
Thiazides	Fluid, electrolytes and acid-base imbalance Acute interstitial nephritis ? Acute tubular necrosis
Triamterene	Fluid, electrolytes and acid-base imbalance
Antihypertensive and Anti-Arrhythmic Drugs	
Diazoxide	Antidiuresis
Hydralazine	Lupus-like syndrome Retroperitoneal fibrosis
Methyldopa	Lupus-like syndrome
Minoxidil	Antidiuresis
Procainamide	Lupus-like syndrome
Propranolol	Hyperkalemia Decreases renal blood flow and GFR
Reserpine	Lupus-like syndrome
Cytotoxic and Immunosuppressive Drugs	
Azathioprine	Interstitial nephritis
Cis-platinum diamminedichloride	Acute tubular necrosis
Cyclophosphamide	Antidiuresis Hemorrhagic cystitis Sterility Bladder cancer
Methotrexate	Intrarenal crystallization. Acute tubular necrosis Interstitial nephritis
Mithramycin	Acute tubular necrosis
Puromycin	Nephrotic syndrome (minimal change, focal segmental sclerosis)
6-Mercaptopurine	Hematuria
Vincristine	Antidiuresis
Vinblastine	Diuresis

Drugs	Nature of Toxicity
Hormonal Drugs and Vitamins	
Ascorbic acid	Acidosis Oxalate stone
Corticosteroids	Hypokalemia ? Focal segmental sclerosis
Methimazole	Nephrotic syndrome (minimal change)
1,25-dihydroxycholecalciferol	? Acute tubular necrosis
Oral contraceptives	Accelerated hypertension Nephrosclerosis Lupus-like syndrome Hemolytic-uremic syndrome
Oxytocin	Antidiuresis
Thiouracil	Lupus-like syndrome
Vasopressin	Antidiuresis
Miscellaneous Drugs	
Amino acids (intravenous infusion)	Hyperkalemia Acidosis
Cholestyramine	Acidosis
Cimetidin	Acute tubular necrosis. ? transplant rejection
Ergotamine and dihydroergotamine	Retroperitoneal fibrosis
Gold	Nephrotic syndrome (membranous nephropathy)
Iodinated radiographic agents	Acute tubular necrosis. ? Transplant rejection
Mercury	Acute tubular necrosis. Nephrotic syndrome (membranous nephropathy)
Methysergide	Retroperitoneal fibrosis
Penicillamine	Glomerulonephritis (Focal proliferative) Nephrotic syndrome (membranous nephropathy) Lupus-like syndrome.

10. ACUTE RENAL FAILURE

BRUCE R. LESLIE

Normal renal excretory function requires an adequate supply of blood at pressures sufficient to promote glomerular filtration, functional and structural integrity of the glomerular filtration barrier and tubular epithelia and a patent route of egress for urine. Events that disrupt these conditions for normal renal function may result in an abrupt fall in glomerular filtration rate (GFR), a situation termed 'acute renal failure' (ARF).

1. CLINICAL RECOGNITION OF ACUTE RENAL FAILURE

In the following discussion, the various etiologies of ARF are categorized according to the primary site of physiologic disturbance. 'Prerenal' forms of ARF are associated with diminished effective renal perfusion. 'Classical' or 'parenchymal' ARF is defined as that resulting from ischemic or toxic damage to the filtering and reabsorptive mechanisms of the nephron. 'Post-renal' ARF results from obstruction to urine drainage. Some etiologies of ARF in each physiologic category are listed in Table 1.

1.1. Urine volume

The patients with ARF are frequently oliguric (defined as a urine output of less than 400 ml per 24-hours). The oliguric phase of parenchymal ARF may be as short as a few hours or as long as 72 days [9]. Non-oliguric forms of ARF are being recognized with increasing frequency, particularly following antibiotic nephrotoxicity, and may be associated with a more favorable clinical course [1]. Total anuria is often associated with total urinary obstruction or vascular catastrophies such as renal cortical necrosis or bilateral renal artery occlusion. Nevertheless, we have observed patients with classical parenchymal ARF who have been transiently anuric. Oligo-anuria alternating with polyuria may also be

seen wih fixed partial urinary tract obstruction. Thus, the absence of oliguria should not dissuade the clinician from considering the diagnosis of post-renal ARF.

Table 1. Pathophysiologic Classification of Acute Renal Failure (ARF).

I. *Pre-renal ARF*
   A. Decreased intravascular volume
      1. Hemorrhage
      2. Extracellular fluid loss
         a. Gastrointestinal: vomitus, diarrhea, gastrointestinal fistula, enterostomy
         b. Renal: diuretics, salt-losing nephropathy, Addison's disease
         c. 'Third space': peritonitis, ileus
         d. Cutaneous: burn, profuse sweating, cystic fibrosis
   B. Decreased cardiac output
      1. Acute left-ventricular failure
         a. myocardial infarction
         b. acute mitral or aortic insufficiency
         c. pulmonary embolism
      2. Acute pericardial tamponade
   C. Decreased perfusion pressure
      1. Septic shock
      2. Adrenal insufficiency

II. *Parenchymal ARF:*
   A. Ischemic
      1. Hypotension
      2. Renal artery occlusion
         a. thrombotic: trauma, hypercoagulable states, disseminated intravascular coagulation
         b. embolic: thrombo-embolic, atheroembolic
         c. stenotic: dissecting aneurysm
         d. vasculitis
      3. Renal vein thrombosis
   B. Nephrotoxic: antibiotics, radiographic contrast media, myoglobin, organic solvents, anesthetics, endotoxin, etc.
   C. Glomerulonephritis and tubulo-interstitial nephritis:
      1. Rapidly progressive glomerulonephritis
      2. Acute (allergic) interstitial nephritis
   D. Renal involvement in systemic disease: myeloma kidney, accelerated hypertension, hypercalcemia, acute uric acid nephropathy

III. *Post-Renal (Obstructive) ARF*
   A. Mechanical obstruction
      1. ureters: stones, papillae, clots, ureteral edema following retrograde pyelogram, accidental intra-operative ligation
      2. bladder neck
      3. urethra
   b. Functional obstruction: impaired bladder motility: anticholinergics, spinal cord trauma, transverse myelitis

1.2. Azotemia

Rising values for blood urea nitrogen (BUN) and serum creatinine concentrations are often the first evidence of a fall in GFR. Urea and creatinine excretion temporarily decline and BUN and creatinine concentrations rise until a new steady-state is attained, provided some excretory function remains, at which time urea and creatinine excretion rates will again equal their rates of production. Normally, the ratio of BUN (in mg/dl) to creatinine (mg/dl) equals approximately 10:1. In ARF, the relative rates of increase of BUN and creatinine are influenced by their production rates as well as differences in their mechanisms of excretion [3].

The urea production rate reflects both the rate of protein catabolism as well as the ability of the liver to synthesize urea. Patients who are infected, burned, severely traumatized, or receiving glucocorticoids, are in a 'catabolic state' and have high urea production rates. Their BUN's may rise rapidly by 30 mg/dl or more per day, apparently out of proportion to the rate of rise of serum creatinine, and the BUN/creatinine ratio will exceed 10/1. Patients with severe liver dysfunction may be unable to synthesize urea at normal rates. They may have only modest elevations of BUN despite severe impairment of GFR, and the BUN/creatinine ratio will be less than 10/1.

Creatinine is the produce of spontaneous dehydration of muscle creatine. The daily rate of creatinine production is a function of the skeletal muscle mass. Clinical states associated with rhabdomyolysis may lead to the release of large amounts of pre-formed creatinine into the circulation resulting in rapid rises in serum creatinine. The BUN/creatinine ratio is less than 10/1 in these conditions.

In the kidney, both urea and creatinine are filtered at the glomerulus. Urea may undergo passive tubular reabsorption, a process promoted by slow tubular fluid flow rates. Additional creatinine enters the urine by tubular secretion. Creatinine secretion is not a function of tubular fluid flow rate. When the fall in GFR is associated with slow rates of tubular flow, the passive reabsorption of urea is increased. The rise in BUN reflects the decline in GFR plus the potentiated passive reabsorption. The BUN/creatinine ratio will be greater than 10/1. This occurs in pre-renal and acute post-renal ARF, provided that there is no prior chronic renal disease.

1.3. Urine sediment

Examination of the urine sediment is often helpful in the differential diagnosis of ARF. Parenchymal ARF is typically associated with the excretion of broad, coarsely granular casts ('renal failure casts'), renal tubular epithelial cells, and abundant granular debris, giving the sediment a 'muddy' appearance. Hematuria accompanying ARF may indicate acute glomerulonephritis or acute interstitial nephritis. Red cell casts are most often associated with glomerulonephritis, but have been reported in some cases of acute interstitial nephritis. The presence of hematuria may also signify infection, stone, neoplasm, or renal infarction.

Urine sediments devoid of formed elements or with only small numbers of hyaline or finely granular casts are associated with pre-renal or, occasionally, post-renal ARF.

1.4. Urine chemistries

A variety of chemical determinations performed on simultaneous urine and serum or plasma samples have been proposed to aid in the differential diagnosis of ARF [8]. They are summarized in Table 2.

Table 2. Urine Chemical Guidelines in ARF.

	Pre-Renal	Parenchymal	Post-Renal
U_{Na}	< 20	> 40	> 40
Uosm/Posm	> 1.5	1–1.5	1–1.5
U_{cr}/P_{cr}	>30/1	< 20/1	< 20/1
$U_{Na}/U/P_{cr}$ = (RFI)	< 1	> 1	> 1
FE_{Na}	< 1	> 1	> 1

U_{Na} = urinary sodium concentration meq/l
Uosm = urinary osmolality mosm/kg H_2O
Posm = plasma osmolality mosm/kg H_2O
U_{cr} = urine creatinine concentration mg/dl
P_{cr} = plasma creatinine concentration mg/dl
RFI = 'renal failure index'
FE_{Na} = percent excretion of filtered sodium (see text)
< = less than
> = greater than

The stimulus for pre-renal azotemia—renal hypoperfusion—elicits renal sodium and water conservation. This is reflected by a low urinary sodium concentration (typically less than 20 mEq/l) and a high urine osmolality (at least 50 mOsm/l greater than serum). The ratios of the

concentrations of creatinine or urea in simultaneous urine and plasma samples are also indices of relative urinary concentration (u/p creatinine >20; u/p urea >10). Of note is that some patients with acute glomerulonephritis have urine chemistries similar to those described for pre-renal ARF. The finding of erythocytes and red cell casts on urinalysis should permit identification of these patients.

Post-ischemic and nephrotoxic forms of ARF are frequently referred to as 'acute tubular necrosis' or 'ATN'. This appelation may not reflect the prevailing events in either the generation or maintenance of the renal insufficiency. Tubular necrosis is frequently not observed on examination of renal tissue in patients with ARF. A variety of experimental models may explain parenchymal ARF without invoking tubular cell death [11]. Nevertheless, all forms of parenchymal ARF are accompanied by disturbances in tubular salt and water reabsorption that may be reflected in urine chemistries. Urine sodium concentrations are typically greater than 30 mEq/l. The urine osmolality is less than 10% greater than a simultaneously determined serum osmolality. The ratio of urine-plasma creatinine is less than 20 and urine/plasma urea, less than 10.

Urine chemistries in obstructive uropathy (post-renal ARF) may resemble those of pre-renal ARF when the obstruction is of less than 12 hours duration. Obstruction of longer duration frequently produces tubular and glomerular dysfunction. Urine chemistries are then indistinguishable from those of parenchymal ARF.

Because of the frequent overlap in urine chemical indices among pre-renal, post-renal, and parenchymal ARF, several determinations have been combined according to prescribed arithmetic calculations in an attempt to provide better discrimination. One such calculation is the 'renal failure index' (RFI). The RFI is defined as the urine sodium concentration divided by the ratio of urine-to-plasma creatinine concentrations. Patients with pre-renal ARF and acute glomerulonephritis frequently have RFI's less than one, whereas in patients with ARF of other etiologies, RFI is greater than one. Another such derived function is the fractional excretion of filtered sodium (FE_{Na}), defined as the ratio of urine/plasma sodium concentrations divided by the ratio of urine/plasma creatinine concentrations, multiplied by 100. In pre-renal ARF, FE_{Na} is less than 1% whereas FE_{Na} greater than 1% indicates a non-pre-renal etiology.

It must be emphasized that urine chemistries are only one component of the evaluation of the patient with ARF. The use of urine chemical indices should supplement and not supplant a careful history, clinical

examination, and urinalysis in the differential diagnosis of ARF. While chemical indices may be helpful in many cases, their validity may be impaired in a variety of circumstances, including: antecedent chronic renal disease, concomitant diuretic administration, coexistant adrenal insufficiency or chronic liver disease.

1.5. Radiologic investigation

By providing information on renal size, radiologic data may permit a distinction between chronic renal failure (small kidneys) and ARF (normal-sized or occasionally swollen) in the patient with severe renal insufficiency of indeterminate duration.

Renal sonography represents a significant advance in the diagnostic investigation of ARF because it can provide information about renal size, contour, and the presence of urinary obstruction, without administration of radiographic contrast material. These iodinated compounds have long been incriminated in the causation of ARF in patients with multiple myeloma. Recent observations suggest that contrast medium may also be nephrotoxic in patients with diabetes mellitus, congestive heart failure, essential hypertension, and chronic renal insufficiency of a variety of etiologies [13, 14].

The hallmark of urinary obstruction is diffuse pyelo-calyceal dilatation. Gray scale ultrasonography is currently employed to provide this evidence of acute obstruction, although the precise location of the obstructing lesion may not be delineated. Where sonography is unavailable, 'high-dose' or 'drip-infusion' intravenous urography with nephrotomograms may permit indirect visualization of the renal collecting system. If neither sonography nor intravenous urography-nephrotomography are available, a *unilateral* retrograde pyelogram may be performed. ARF as a consequence of obstruction requires the presence of bilateral obstruction or obstruction of a solitary kidney. Assuming otherwise normal renal parenchymal function, obstructive uropathy is not likely to be responsible for ARF if there is no evidence of obstruction on one side. In addition, a unilateral diagnostic retrograde pyelogram is preferable because ureteral edema as a result of the procedure can impede urine flow. When the diagnosis of obstructive uropathy has been confirmed by other methods, urethral catheterization or cystoscopy may be both diagnostic and therapeutic of lower urinary tract pathology. If bilateral ureteral obstruction is suspected, bilateral retrograde pyelography may be used to define the sites of obstruction prior to providing relief through unirary diversion.

Radiologic procedures are not usually required to confirm a clinical diagnosis of parenchymal ARF. When performed for other reasons, the intravenous urogram may show a dense nephrogram phase that persists for 24–48 hours in the patients with parenchymal ARF [4]. Arteriography will demonstrate reduction in renal cortical blood flow with attenuation of cortical arterioles [5].

In patients with suspected renal artery occlusion, a radioisotope flow study, *e.g.*, using Tc^{99}-pertechnetate, may provide corroborative evidence. Definitive diagnosis requires contrast angiography. While bilateral renal artery occlusion would be presumed necessary to produce ARF, recent observations suggest that falls in GFR may be associated with unilateral arterial occlusion [6]. The mechanism of his phenomenon may involve diffuse reflex vasospasm in response to a thrombo-embolic event. Thrombo-embolic disease should be suspected in patients with potential sources for emboli, including: mitral stenosis, atrial fibrillation, left ventricular mural thrombi, fungal endocarditis and cardiac myxomas.

Acute renal vein thrombosis is an uncommon cause of ARF. It should be considered in patients wih nephrotic syndrome, hypercoagulable states including sickle cell disease, and severely salt-and-water-depleted infants who have unexplained decrements in GFR. Selective renal venography is required to confirm this diagnosis.

2. MANAGEMENT OF ARF

2.1. Prevention

2.1.1. Maintenance of normal systemic hemodynamics

Normal GFR depends in part on adequate hydrostatic pressure for filtration at the glomerular capillary. Glomerular capillary pressure is critically affected by systemic blood pressure. Renal 'autoregulation' may maintain normal glomerular hydrostatic pressures despite a fall in systemic blood pressure. However, when mean arterial blood pressure falls below the autoregulatory limit, renal hypoperfusion and a drop in GFR supervene. Hormonal factors, as may come into play during hypovolemia or with general anesthesia, may upset the renal autoregulatory mechanism and make the kidney especially vulnerable to ischemic damage induced by small decreases in renal blood flow [11]. Maintenance of a normal cardiac output is thus important for preserving normal

renal function. Normal cardiac output requires sufficient ventricular filling pressure and normal ventricular function. The former is a direct function of intravascular volume. Adequacy of intravascular volume may be indirectly assessed by orthostatic blood pressure changes (a fall of 20 mm Hg in systolic or 10 mm Hg in diastolic pressure is considered abnormal) and bedside estimation of the jugular venous pressure. Direct measurement of central venous pressure (CVP) provides information on right ventricular filling pressures. In critically ill patients, measurement of pulmonary capillary wedge pressure, using the Swan-Ganz catheter provides a direct index of left ventricular filling pressure. It is often necessary to maintain 'high-normal' values for CVP and pulmonary capillary wege pressure in order to insure adequate intravascular volume in patients with ARF. In the oliguric patient in whom a diagnosis of neither pre-renal nor parenchymal ARF can be made with certainty, a 'therapeutic trial' of 500 ml of normal saline administered over 30–60 minutes may be both diagnostic and therapeutic: an increase in urine output implying pre-renal azotemia and the need to further support intravascular volume.

2.1.2. Pharmacologic prophylaxis

Mannitol. The use of intravenous mannitol has been proposed as a preventive measure in patients at risk for the development of ARF, especially those undergoing cardiovascular surgery or sudden massive hemorrhage. Pre-treatment with mannitol may reduce the incidence and severity of ARF in laboratory animals. However, adequate hydration with saline prior to the renal insult may provide the same benefit, indicating the efficacy of any measure that sustains intravascular volume. In adition, mannitol is an osmotic diuretic. Intratubular obstruction by debris derived from damaged tubular epithelial cells may maintain ARF under some circumstances. Wash-out of this debris by osmotic diuresis may be the basis for an additional protective effect of mannitol. The clinical use of mannitol, however, is not without risk. Hypertonic mannitol injection may expand intravascular volume. This may precipitate pulmonary edema in patients with left ventricular dysfunction. In addition, the osmotic diuresis may cause severe intravascular volume depletion unless urinary water and electrolyte losses are quantitatively replaced. Provided these precautions are noted, the addition of 25–50 grams of mannitol per day to intravenous fluids beginning, during and for 24 hours after cardiac or major vascular surgery may possibly be effective in preventing or mitigating parenchymal ARF. Mannitol should not be administered in cases of established ARF.

Furosemide. The use of intravenous furosemide in oliguric patients has been advocated as a means of preventing parenchymal ARF or of converting established parenchymal ARF from the oliguric to the non-oliguric state. There is experimental evidence that furosemide may increase urine output in some patients with ARF and thereby facilitate fluid management. However, the duration of ARF and the number of dialyses required are probably not altered [2]. While decreased mortality of non-oliguric compared to oliguric patients with parenchymal ARF has been suggested [1], there is as yet no evidence that conversion from an oliguric to a non-oliguric state with furosemide will confer the same benefit. In view of the potential ototoxicity of loop diuretics such as furosemide administered in high doses to patients with ARF, and the uncertainty regarding its prophylactic effect, we do not advocate its use in oliguric patients with established parenchymal ARF.

2.2. Established parenchymal ARF

2.2.1. Sodium and water balance

During the maintenance phase of parenchymal ARF, modification of patients' fluid and electrolyte intake is required to compensate for compromised renal excretory function. Daily intake of water from all sources should equal approximately the volume of measured fluid losses (urine, stool, gastrointestinal fluid) plus an estimate of perspiration and insensible fluid losses (400 cc per day, or more in the presence of fever or hyperventilation). Electrolyte losses can be measured by analysis of urine and other fluids. Daily water and sodium chloride allowances can be ordered to replace losses from the previous day plus prior deficits. Ideal fluid balance results in a loss of 0.5 kg per day as a result of tissue catabolism. Excessive administration of sodium and water is a common cause of pulmonary edema and hypertension.

2.2.2. Potassium

To avoid fatal hyperkalemia, intravenous solutions should not contain potassium and other exogenous sources of potassium should be avoided (*e.g.*, sodium penicillin should be specifically ordered when this antibiotic is required lest the routinely provided potassium salt be administered). Exceptions to this rule include patients with severe acidosis or hyperglycemia who present with low or normal serum potassium concentrations prior to alkali or insulin therapy. These treatments in such patients may produce a rapid decrease in serum potassium concentration as a result of extra to intra-cellular shifts. The sudden fall in serum

potassium may cause skeletal muscle paralysis. Potassium therapy may also be necessary in patients with hypokalemia and cardiac arrhythmias secondary to digitalis toxicity. Situations calling for exogenous potassium therapy are unusual and the clinician is more often confronted with hyperkalemia. It should also be noted that the adverse effects of hyperkalemia appear to be more pronounced when accompanied by hyponatremia.

Emergency treatment of hyperkalemia is necessary when: the serum potassium concentration is greater than 6.9 mEq/l; abnormal electrocardiographic findings are associated with any degree of hyperkalemia (tall, narrow-based, peaked T waves; loss of R wave amplitude; loss of P wave; QRS prolongation; AV block; sine wave); skeletal muscle weakness is due to hyperkalemia. In addition, crises should be anticipated in patients with rising serum potassium concentrations and measures should be instituted to remove excess potassium from the body before signs of potassium intoxication appear.

The adverse electrophysiologic effects of hyperkalemia on the heart can be antagonized by intravenous calcium. One gram of calcium gluconate (10 ml of a 10% solution) may be administered over 2 minutes under electrocardiographic monitoring. The infusion should be stopped when the electrocardiographic abnormalities disappear. The dose may be repeated. The calcium effect begins within 5 minutes and may continue for 1–2 hours. Calcium should not be given to patients receiving digitalis in whom malignant ventricular arrhythmias may be provoked.

A rapid fall in serum potassium concentration can be achieved by shifts of potassium from extracellular to intracellular fluid. This can be effected by intravenous sodium bicarbonate or glucose and insulin. The decrease in serum potassium may begin within 30 minutes and persist for 2–4 hours. Sodium bicarbonate may be administered in 50 ml ampoules each containing 45 mEq of bicarbonate. One or two ampoules may be given directly intravenously or added to solutions of dextrose in water to create a therapeutic 'cocktail'. Additional bicarbonate may be necessary to correct severe metabolic acidosis, which may exacerbate hyperkalemia. Regular insulin and dextrose should be administered in a ratio not to exceed 1 unit insulin to 5–10 grams dextrose so as to avoid hypoglycemia. If fluid intake must be limited, 50 ml of 50% dextrose in water can be given intravenously accompanied by 5 units regular insulin. Hypertonic dextrose should be followed by 250–500 ml 5% dextrose in water over 4–5 hours in order to avoid rebound hypoglycemia. If the patient can tolerate the fluid load, one or two ampoules (45–90 mEq) of sodium bicarbonate can be added to one liter of 10% dextrose in water.

One-third of this mixture can be infused over 30 minutes, and the remainder over 2–3 hours. Ten to 20 units of regular insulin can be given subcutaneously at the start of the infusion.

The above therapies provide only temporary benefit as they do not eliminate excess potassium from the body. Potassium is most efficiently removed by dialysis, and spontaneous hyperkalemia is usually an absolute indication for this form of therapy in patients with ARF. Potassium can also be removed by therapy with the ion exchange resin, sodium polystyrene sulfonate (Kayexalate®). Kayexalate may be employed until dialysis can be instituted. It can be used without subsequent dialysis if there has been an identifiable, self-limited cause of the acute rise in serum potassium (*e.g.*, gastrointestinal bleeding, inadvertant potassium administration), and no other indications for dialysis exist. Kayexalate can be given by mouth or by enema. Reduction in serum potassium is more rapidly evident with rectal (onset 30–60 minutes) than with oral (onset 2 hours) administration. However, the total amount of potassium removed per gram Kayexalate® is greater when the oral route is employed. This is because the entire absorptive surfaces of the small and large intestines are available for drug action. In order to avoid resin impaction in the colon, Kayexalate® is accompanied by the osmotic cathartic, sorbitol. Typical doses are: *oral*: 15–30 grams Kayexalate® with 50–100 ml sorbitol solution (20% – 70%) every 4 hours; *rectal*: 50 grams Kayexalate® in 200 ml sorbitol solution or 200 ml 10% dextrose in water, retained for 30 minutes with a rectal tube, every 2–4 hours. To avoid hypokalemia due to retained drug, Kayexalate therapy should be discontinued when the serum potassium concentration falls to 5.5 mEq/l or below. Because the mechanism of action of the resin involves ion exchange of sodium for potassium, increments in total-body sodium may attend its use.

2.2.3. Acid-base balance

Metabolic acidosis is a common finding in ARF. Depression of net acid excretion due to the fall in GFR is accompanied by retention of acid byproducts of metabolism. Severe acidosis (arterial pH 7.10 or less) may produce a depression of central ventilatory drive as well as a diminished cardiovascular responsiveness to catecholamines. Decreases in serum bicarbonate concentration below 10 mEq/l can be associated with large decreases in arterial pH. Therapy for metabolic acidosis is therefore advisable to prevent severe acidosis and should be instituted when the serum bicarbonate level falls below 15 mEq/l or the arterial pH falls below 7.2. While sodium bicarbonate may correct acidosis, the atten-

dant sodium and water load may cause pulmonary edema. Therefore, dialysis is the therapy of choice when treatment of metabolic acidosis is necessary. It should be emphasized that restoration of a normal serum bicarbonate concentration is neither necessary nor advisable. Acidosis may contribute to the maintenance of normal ionized serum calcium concentration despite the subnormal total serum calcium frequently present in ARF. An increase in arterial pH may be associated with an increase in the binding affinity of serum albumin for calcium and hence a reduction in ionized calcium concentration. This may result in tetany or convulsions. Maintenance of serum bicarbonate betwen 15 and 20 mEq/l is sufficient to provide an adequate bicarbonate 'reserve' while avoiding the risk of symptomatic hypocalcemia.

Both peritoneal and hemodialysis bath solutions contain organic anions (lactate or acetate) whose metabolism by the liver results in generation of new bicarbonate. A difficult clinical situation occurs when ARF is accompanied by metabolic alkalosis, as may occur in a post-operative patient receiving continuous nasogastric suction. Severe metabolic alkalosis may produce compensatory alveolar hypoventilation and shifts in the oxygen-hemoglobin dissociation curve which may interfere with tissue oxygenation. Prophylactic therapy with cimetidine to reduce gastric acid secretion may diminish on-going gastric acid losses. The maintenance dose of cimetidine should be reduced by approximately 50% in the presence of ARF. When hemodialysis is required for ARF accompanied by metabolic alkalosis, special dialysis baths with comparatively low acetate concentrations may be prepared. Alternatively, severe metabolic alkalosis may be treated with intravenous hydrochloric acid [15].

2.2.4. Calcium, phosphorus, and magnesium

Hypocalcemia is a frequent occurrence in ARF [7]. Among its causes are impaired gastrointestinal calcium absorption and resistance to the skeletal calcemic effect of parathyroid hormone. The acidosis that accompanies ARF may result in a normal ionized serum calcium despite a low total calcium concentration. This may be due to a decrease in the affinity of serum albumin for ionized calcium in the presence of acidosis *(vide supra)*. Patients with rhabdomyolysis (with myoglobinuric ARF) may have substantial increases in serum phosphate concentration accompanied by falls in serum calcium. This is associated with precipitation of calcium in skeletal muscle. In addition, patients with rhabdomyolysis may deveop hypercalcemia during the recovery phase of ARF, presumably due to mobilization of ectopic calcium deposits.

Calcium supplements in ARF should be withheld in the absence of paresthesias, Chvostek or Trousseau signs, tetany, or other manifestation of neuromuscular irritability. Hyperphosphatemia may contribute to the depression of serum calcium. Mechanisms for this effect may include the promotion of ectopic calcium-phosphate precipitation, or inhibition of renal vitamin D 1-hydroxylase. Hyperphosphatemia can be corrected by alimentary phosphate binding agents such as aluminium hydroxide or aluminium carbonate. It is important to administer phosphate binders with meals. Extreme hyperphosphatemia secondary to phosphate release from endogenous sources (rhabdomyolysis, intravascular hemolysis, chemotherapy of leukemia) requires hemodialysis to effect phosphate removal. Hyperphosphatemia must be corrected before calcium supplements are administered in order to avoid ectopic calcium precipitation in cardiac conduction system, lung, blood vessels, renal parenchyma, joints, and other tissues. A detailed discussion of calcium metabolism in renal failure is presented in Chapter 13.

Hypermagnesemia can cause neuromuscular paralysis, coma, respiratory depression, and hypotension. Magnesium-containing antacids or laxatives (*e.g.*, milk of magnesia) should not be prescribed.

2.2.5. Nutrition

The post-operative, infected, or traumatized patient with acute renal failure is frequently described as being in a 'catabolic state'. This implies a hormonally mediated breakdown of his own tissues. The consequences of this state include accelerated acidosis, hyperkalemia, and rapid development of signs and symptoms of uremia (encephalopathy, pericarditis, nausea and vomiting). Provision of adequate calories and essential nutrients from exogenous sources may help reduce catabolism. A figure of at least 100 grams carbohydrate per day has been proposed, but this may be insufficient for many seriously ill patinets. The early institution of dialysis may facilitate provision of an adequate volume and composition of nutritional supplement.

2.2.6. Anemia; platelet dysfunction

The hemoglobin concentration declines during ARF, due to both myelosuppression and a hemolytic process resulting from acquired, extracorpuscular factors. A hematocrit in the range of 25–30% may be tolerated. Transfusion therapy should be considered in the presence of heart failure, angina pectoris, hypotension, continuing bleeding or when general anesthesia is planned.

Prolongation of the bleeding time due to platelet dysfunction can

occur during ARF. This qualitative platelet deficiency is believed to be due to retained toxins such as guanidinosuccinic acid. When bleeding is thought to be exacerbated by this platelet defect, confirmation may be obtained by demonstrating a prolonged bleeding time. Platelet function may be improved by dialysis. Dialysis to correct platelet dysfunction should be considered in patients with persistent bleeding and a prolonged bleeding time. If an accurate bleeding time is unobtainable, patients with serum creatinine concentrations greater than 6 mg/dl may be considered candidates for dialysis therapy.

2.2.7. Infections

Sepsis is a leading cause of death in patients with ARF. Nosocomial infections associated with urethral catheters and intravenous lines are particularly frequent. We discourage the use of chronic indwelling urethral catheters. If a Foley catheter is deemed essential, a closed drainage system is preferred. Important recommendations for catheter care have been presented by Stamm [10].

In intravenous therapy, steel 'butterfly' needles are less often associated with septic phlebitis than plastic equipment and are therefore preferable. Central venous catheters should be changed every 48 hours and removed as soon as possible.

2.2.8. Dialysis

The appearance of hyperkalemia, congestive heart failure, severe metabolic acidosis, and signs or symptoms of uremia (nausea, vomiting, hiccoughs, encephalopathy, asterixis, pericarditis) constitute absolute indications for the institution of dialysis. A regimen of chronic intermittent dialysis, begun prophylactically before absolute indications appear, helps reduce morbidity and mortality. We have initiated such prophylactic dialysis as a rising serum creatinine exceeds 8 mg/dl or blood urea nitrogen exceeds 100 mg/dl.

Peritoneal dialysis may be preferable in patients with severe cardiac disease because it produces gradual fluid and electrolyte shifts. The freedom from systemic heparinization with peritoneal dialysis may be desirable in patients with intracranial, retroperitoneal or other life-threatening bleeding. The risks of peritoneal dialysis include peritonitis and pulmonary compromise from diaphragmatic elevation. Fresh abdominal incisions and drains are relative contraindications.

Hemodialysis may be preferable in catabolic patients or when peritoneal dialysis is contraindicated. The widespread availability of hemodialysis facilities and the ease of initiation of dialysis using a Scribner shunt

or a percutaneously placed femoral venous catheter have contributed to the frequent choice of hemodialysis in management of ARF. New techniques of peritoneal dialysis, employing chronic indwelling abdominal catheters and automatic dialysate cycling machines, are making peritoneal dialysis increasingly popular.

3. THE RECOVERY PHASE

Increases in urine output above 400 ml per 24 hours signal the onset of the recovery phase ('diuretic phase') of oliguric parenchymal ARF. While the BUN and creatinine concentrations may continue to increase for a day or two after the onset of diuresis, once they begin to fall, the downward trend should persist. An increase in BUN or creatinine during the recovery phase should prompt a search for intravascular volume depletion, gastrointestinal bleeding, or administration of a nephrotoxin. The GFR may ultimately not achieve the same level as before the onset of ARF. This seems to occur more often in older patients. The recovery may be prolonged, and improvement in GFR may be expected even as long as a year after the original injury.

Despite the reversibility of much of the renal dysfunction in ARF, mortality in patients with ARF has been as high as 60% in some recent series [12]. About one-fifth of the mortality in ARF occurs during the recovery phase as a consequence of fluid and electrolyte depletion, infection, gastrointestinal bleeding, or respiratory failure.

Massive diureses are currently uncommon during the recovery phase because antecedent conservative fluid management and early institution of dialysis prevent accumulation of excess salt and water. During the diuretic phase, daily replacement of three-quarters of the measurement of the previous day's urinary sodium, potassium, chloride, and water losses plus fluid and electrolyte deficits from other sources should permit a physiologic diuresis without compromising plasma volume or electrolyte balance. Daily determinations of body weight, intake and output, orthostatic blood pressure and pulse changes should help gauge the adequacy of fluid therapy. This information should be supplemented by daily determinations of BUN and serum creatinine and electrolyte concentrations until a stable state is attained.

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11. CHRONIC RENAL FAILURE

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1. INTRODUCTION

Chronic renal failure implies a progressive reduction in glomerular filtration rate (GFR) due to irreversible nephron loss. The term renal insufficiency is often used to describe a mild reduction in GFR, usually before the point that presents uremic symptoms. On the other hand, end stage renal disease is used to describe a severe reduction in GFR, that is not only irreversible but also incompatible with life, unless dialysis or kidney transplantation is instituted. Pathologists often use this term to describe advanced renal disease that is beyond recognition as to specific etiology. Thus, the term chronic renal failure has been used clinically in a comprehensive sense that includes all degrees of chronic and irreversible reduction of GFR, with varying degrees of azotemia and uremic symptoms, irrespective of the etiological and anatomical nature of the disease. In contrast, acute renal failure is characterized not only by its sudden reduction of GFR but also by improvement of GFR as renal injury reverses.

To make a diagnosis of chronic renal failure, the presence of reduced GFR or azotemia and chronicity of the disease should be documented. Clinical findings such as small kidneys, renal osteodystrophy and uremic peripheral neuropathy are supportive evidence for chronic renal failure. Although anemia is seen in both acute and chronic renal failure, the absence of anemia is strong evidence against chronic renal failure.

Since there is no specific treatment for most kidney diseases, these often progress steadily toward end stage renal disease. Common renal diseases that progress to end stage requiring either dialysis or kidney transplantation are listed in Table 1. However, the incidence of each disease as a cause of end stage renal disease varies depending on age and geographical distribution of the patient population studied. For instance, congenital and hereditary kidney diseases are the more common causes of end stage renal disease in children, while kidney diseases secondary to diabetes mellitus, hypertension and neoplasms are the

Table 1. Distribution of primary kidney diseases in patients with end stage renal disease.

Diseases	Pediatric patients* (%)	Overall patients** (%)
Glomerulonephritis	33.5	56.0
Pyelonephritis	22.1	13.1
Cystic disease	7.8	5.4
Hereditary nephropathy	7.9	1.2
Renal hypoplasia-dysplasia	12.1	1.4
Nephrosclerosis	—	4.9
Others	16.6	18

* Donckerwolcke, R.A. et al. Combined report on regular dialysis and transplantation of children in Europe, 1978.

** American college of Surgeons/National Institutes of Health Renal Transplant Registry, The 12th Report of the Human Renal Transplant Registry. JAMA 233: 787, 1975.

more important causes in adults. Similarly, analgesic nephropathy is an important cause of end stage renal disease in some developed countries, while infectious diseases, such as schistosomiasis, are more important causes in other countries. Irrespective of age and geography, however, chronic glomerulonephritis, inclusive of all etiological and morphological types, is the most common disease causing end stage renal disease.

Some kidney diseases, even if they have been chronic, can be completely cured or partially reversible, functionally as well as anatomically, by appropriate medical and/or surgical management. Thus, the initial evaluation of a patient and diagnostic work-up should be designed to look for those potentially reversible diseases or co-existing second renal diseases. The renal diseases belonging to this category are listed in Table 2.

Table 2. Chronic renal diseases that are potentially reversible.

1. Obstructive nephropathy.
2. Analgesic nephropathy.
3. Toxic nephropathy.
4. Nephrotic syndrome with nil or minimal change and membranous nephropathy.
5. Hypertensive nephropathy.
6. Post infectious nephritis.
7. Lupus nephritis.
8. Nephropathy secondary to hypercalcemia, hyperuricemia or hypokalemia.
9. Hypersensitivity angiitis and vasculitis.
10. Renal disease secondary to thrombosis in renal veins and/or inferior vena cava.

Table 3. Acute disorders that can exacerbate existing chronic renal failure.

1. Fluid and electrolyte imbalance; dehydration, sodium deficit and hypokalemia.
2. Hemodynamic decompensation; congestive heart failure, hypotension and shock
3. Infection; systemic or renal; bacterial or viral infection.
4. Exposure to nephrotoxic drugs and chemicals; aminoglycosides, cephalosporins, amphotericin B, radioiodinated contrasting agents, ethylen glycol, carbon tetrachloride, etc.
5. Malignant hypertension.
6. Metabolic disorders; hypercalcemia, hyperuricemia, hyperoxaluria.
7. Obstructive uropathy and nephro-urolithiasis.

Diminished but stable kidney function in any chronic renal disease, can acutely deteriorate upon the development of acute superimposed infectious, obstructive, metabolic or hemodynamic disorders, or exposure to nephrotoxic drugs. In the event of acute decompensation in chronic renal diseases, immediate correction of these complications may partially reverse the renal failure. Otherwise, the failure may be progressive and permanent. Disorders that are commonly associated with acute decompensation of the existing chronic renal failure are listed in Table 3. While we do not have any specific treatment for many kidney diseases, it is important to identify and treat these concurrent disorders immediately to prevent further failure or to reverse the acute decompensation. The degree and beginning of recovery vary depending on the severity and duration of renal injuries.

2. PATHOPHYSIOLOGY OF CHRONIC RENAL FAILURE

As kidney disease progresses, intricate compensatory and adaptive mechanisms, as well as protean pathologic processes, develop within the kidney and in other organ systems. Because of these remarkable compensatory and adaptive mechanisms, patients with chronic renal failure can be asymptomatic until about 80–90% of their glomerular filtration (generally GFR less than 20 ml/min) is lost. In some patients, however, a compensatory mechanism has beneficial effects on one organ system but deleterious effects on another. Furthermore, some patients may have physical signs of kidney disease, such as hypertension, edema, anemia and acidosis long before they become symptomatic of chronic renal failure. Therefore, the extent and severity of the clinical signs and symptoms of chronic renal failure vary widely depending on the individual patient, etiology of the specific renal disease, rate of development of renal failure, degree of adaptation and details of management.

2.1. Compensatory growth

The kidney has compensatory growth activity when a portion of renal mass is removed. Functional and morphologic characteristics of the compensatory growth have been well studied in both animals and humans, especially in those who underwent unilateral nephrectomy as a kidney donor [29].

After unilateral nephrectomy, GFR and effective renal plasma flow increase 65–85%, averaging 70%, of the prenephrectomy values by as early as one day and at least one week after the procedure. Tubular function also improves but more slowly than improvement of glomerular function. Micropuncture studies in unilaterally nephrectomized rats show that a uniform increase in GFR of 30% occurs in all nephrons of the remaining kidney.

This compensatory growth is not only functional but is also accompanied by anatomical growth. Although anatomical growth begins immediately after acute reduction of renal mass, measurable growth is appreciated much later than functional compensation. The growth is achieved primarily by hypertrophy and hyperplasia of cells in the glomeruli and proximal tubules. During compensatory growth, no new glomeruli or nephrons are formed. A unilateral nephrectomy before adolescence produces growth with much hyperplasia, but afterwards, produces mostly growth with hypertrophy. There is an inverse correlation between age and functional as well as anatomical growth.

In kidney disease that involves only one side, such as unilateral obstructive uropathy, the contralateral kidney develops gradual compensatory growth. Thus, the overall renal function remains near normal levels, even when the affected kidney is totally destroyed. On the other hand, in many kidney diseases, the pathologic process is diffuse and involves both kidneys. In these cases, compensatory growth is limited by the severity of the disease, and functional compensation is not apparent. If the disease activity subsides or is stationary, however, varying degrees of compensatory processes should occur in the remaining nephrons. An acute increment of GFR has been observed in dogs with unilateral renal disease, when the normal contralateral kidney was removed [9].

2.2. Adaptive mechanisms

As kidney disease progresses, a diminishing number of surviving nephrons not only remain responsive to the needs of the patient but undergo

adaptation of extraordinary dimensions [8, 19]. These adaptation processes occurring in a small number of functioning nephrons are essential for survival of the patient.

In the diseased kidney, despite varying degrees of damage at various sites of individual nephrons and markedly decreased glomerular as well as tubular functions, the ratios of glomerular to tubular functions are maintained at almost normal ranges (intact nephron hypothesis). Regarding the nature and significance of the hypothesis, Bricker summarized it as follows [5]:

'In most forms of chronic renal disease associated with marked nephron destruction, the majority of nephrons that contribute to renal function behave, in a regulatory context, as if they were normal. If glomerular or tubular functions are impaired in individual nephrons due to structural damage, there will be simultaneous and proportional changes in other functional systems in the same nephrons. Function in the composite group of surviving nephrons is characterized by relative homogeneity of glomerulo-tubular balance, appropriate continuing responsiveness to the changing needs of the patients as the disease advances.'

2.2.1. Electrolytes and water metabolism

As nephrons are destroyed, each surviving unit must increase its excretory contribution to avert progressive distortion of the composition or volume of body fluids. Indeed, as the number of functioning nephrons decreases, the fractional excretion of sodium or water per nephron gradually increases. This adaptive ability is not solely limited to sodium and water, but is also seen with potassium, chloride, phosphate, magnesium, urate and many other solutes. The mechanism has been called the magnification phenomena by Bricker et al., who defined it as follows [8]: 'the addition or loss from extracellular fluid of any given amount of a substance that is actively regulated by the kidneys will evoke an excretory response per nephron that varies inversely with the number of surviving nephrons.'

As a result of the adaptive processes, these patients can maintain almost normal external balances of sodium, potassium and water until GFR is greatly reduced (usually less than 10 ml/min) or oliguria develops. Since this adaptive ability is not unlimited, the balance can be easily distorted when advanced renal failure is superimposed with other disorders such as heart failure, shock, hypertension, dehydration and septicemia.

On the other hand, some patients may have an inability or marked delay in lowering their urinary sodium excretion when the dietary sodium is abruptly restricted (less than 20 mEq/day). This salt wasting tendency is clinically apparent by weight loss, declining effective plasma

flow and GFR, hyponatremia, and hyperkalemia. In general, patients with tubulo-interstitial diseases (*e.g.*, pyelonephritis, interstitial nephritis, medullary cystic disease, hydronephrosis) are far more susceptible to salt and water wasting than those with primary glomerular or vascular diseases (*e.g.*, glomerulonephritis, nephrosclerosis). It should be emphasized that an adequate salt intake is essential to maintain maximum GFR in patients with chronic renal failure, especially for those who tend to lose excessive amounts of sodium in their urine. The amount of salt required for individual patients can be determined by measuring the amount of sodium lost in a 24-hour-urine sample.

As in sodium balance, most patients with chronic renal failure can maintain a normal external potassium balance until GFR declines below 10 ml/min or until urinary output falls to oliguric range. If renal failure progresses further, most patients develop mild hyperkalemia (5.0–6.0 mEq/l). They can, however, develop acute, severe hyperkalemia whenever a complication is superimposed on chronic renal failure. Conditions that may alter internal or external potassium balance include; 'hypercatabolic state', gastrointestinal bleeding, hypoxemia, acidosis, use of potassium sparing diuretics (spironolactone, triamterene), as well as inadvertent intake of excessive amounts of potassium (high potassium diet, potassium penicillin, salt substitutes). Acidosis, especially when acute in onset, raises serum potassium because of the transfer of the ion out of cells and interference with renal secretion. Whereas, severe tissue hypoxia can cause hyperkalemia by impaired cellular uptake of the ion from extracellular fluid. The initial treatment for hyperkalemia should include the correction of these complicating factors. Treatments for hyperkalemia are described in Chapter 10.

2.2.2. Acid-base balance

The kidney is a key organ that maintains normal acid-base balance. It absorbs the daily filtered load of 3,500–4,000 mEq of bicarbonate and excretes 50–100 mEq of hydrogen ions (approximately 1 mEq/kg/day) in the forms of ammonium, phosphate, and other buffer ions. As renal failure progresses, individual intact nephrons increase both the reabsorbtion of filtered bicarbonate and excretion of hydrogen ions. As a result of this adaptive mechanism, in conjunction with extrarenal compensatory mechanisms (intracellular buffer systems and ventilation), patients with chronic renal failure do not develop acidemia until GFR decreases below 20 ml/min. With further loss of nephrons, especially when GFR falls below 10 ml/min, net acid excretion becomes inadequate to balance the obligatory acid load. Furthermore, the decreased ability of the

tubules to produce ammonia in response to acidosis is responsible for the reduction in bicarbonate generation and is the major factor in the acidosis. Consequently, in advanced renal failure, mild hypochloremic acidosis, with increased anion gap, usually presents and the plasma bicarbonate concentration becomes stable at subnormal levels. As in normal individuals, the salt load and expansion of plasma volume reduces the renal threshold for bicarbonate and may exacerbate metabolic acidosis in chronic renal failure.

A small group of patients, especially those who have primary tubulointerstitial diseases, may develop hyperchloremic acidosis in the presence of even mild renal failure. In this case, the acidosis may be attributable to renal failure plus either proximal or distal tubular dysfunction or hyporeninemic hypoaldosteronism (see renal tubular acidosis).

In general, mild metabolic acidosis (pH $>$ 7.30, plasma bicarbonate $>$ 15 mEq/l) does not require treatment. However, patients with severe acidosis or with acidosis and hyperkalemia, require bicarbonate supplements to maintain the plasma pH at about 7.30 or plasma bicarbonate levels between 15 and 20 mEq/l. In children, long-term use of bicarbonate supplements to avoid severe metabolic acidosis may help to prevent severe, progressive renal osteodystrophy and growth retardation.

In advanced renal failure, the kidney is very slow in excreting excess base. If hydrogen ion loss is in an excess of net acid production (50–100 mEq/day), alkalosis can be readily produced despite renal failure. For instance, patients with renal failure, when on continuous nasogastric suction, may rapidly develop severe metabolic alkalosis. These patients require meticulous planning of fluid therapy with saline or acidic solutions (diluted HCl or ammonium chloride solution) and careful titration of fluid replacement to restore fluid and acid-base balance. Patients with renal failure can also develop iatrogenic metabolic alkalosis, as a result of excessive amounts of bicarbonate supplements or inappropriate use of diuretic drugs.

2.2.3. Calcium and phosphate balance

The kidney plays an important role in the homeostatic mechanisms regulating calcium and phosphate in body fluids. Approximately 20% of the phosphate in plasma is protein bound, and virtually all the unbound phosphate in plasma water is ultrafiltrable at the glomerulus. In normal man, the fractional excretion of phosphate varies from 3–20% of filtered load.

As GFR falls, there is a decreases in the net phosphate excretion by

the kidney which leads, if dietary intake of phosphate remains constant, to hyperphosphatemia. As the serum phosphate concentration rises, a reciprocal fall in the serum ionized calcium concentration occurs which stimulates the parathyroid glands to secrete an increased amount of parathyroid hormone. A secondary increase in parathormone activity promotes a greater phosphate excretion per residual nephron, and tends to normalize both serum phosphate and calcium concentrations. A new state of phosphate balance and consequent calcium balance ensues at the cost of a higher plasma parathormone level. With each stage of decrease in GFR, the sequence recurs resulting in a progressive rise in plasma parathyroid hormone levels [23, 29].

Despite hyperphosphaturia per nephron, eventual phosphate retention and persisting hyperphosphatemia develop when GFR falls to below 30–25 ml/min. As renal failure progresses further, plasma phosphate will rise higher and calcium will decrease to lower levels, despite higher parathormone levels. If the phosphate intake is decreased in exact proportion to the fall in GFR (so called 'proportional reduction of phosphorus'), these sequential changes and resultant renal osteodystrophy can be prevented, at least in the animal model.

When GFR falls to below 30–25 ml/min, decreased conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol in the kidney occurs. Although hyperphosphatemia is the major cause of hypocalcemia and secondary hyperparathyroidism in both early and late courses of chronic renal failure, the superimposed 'apparent' vitamin D deficiency exacerbates the abnormalities further in advanced renal failure. The consequences of chronic hyperphosphatemia, hypocalcemia and hyperparathyroidism, such as renal osteodystrophy, soft tissue calcification and neuromuscular disorders, and treatments for these, are described in Chapter 13.

3. UREMIA

Uremia is a clinical syndrome of systemic disorder involving multiple organs, due to advanced renal failure irrespective of the causes or duration of the renal disease. Although uremic syndrome develops earlier, it becomes clinically apparent when 80–90% of the net function of the total nephron population is lost. The extent of the disease and degree of symptoms of uremia varies depending on the cause, severity and duration of the renal disease. Clinical features in the final stage of uremia are similar among patients and will lead to a fatal outcome

unless procedures such as dialysis and/or renal transplantation are instituted.

3.1. Pathogenesis of uremia

Since the monumental description of uremia by Richard Bright in 1836, research for uremic toxin(s) has been carried on with great enthusiasm. However, no single explanation for all the facets of uremia has been developed until now [38].

The traditional concept about the pathogenesis of uremia has been concerned with the retention of toxic metabolic products, so-called uremic toxin(s), that are normally excreted by the kidney. Harrison and Mayson in 1937 presented a poignant analogy [18].

'The uremic death of the most highly integrated organism is strictly comparable to the most simple organism in an aging bacterial culture. Both are destroyed in an environment poisoned by the products of their own metabolism.'

Besides urea, creatinine, potassium, phosphate, sulfate and uric acid, many other chemical compounds have been found to be in high concentrations in the body fluids of uremic patients. These include; guanidino compounds (methylguanidine, guanidino succinic acid), phenol compounds, amino acids, amines (aliphatic, aromatic and polyamines), myoinositol, hormones (growth, parathyroid and natriuretic hormones, glucagon, gastrin, renin), enzymes (lysozyme, ribonuclease), 'mid-molecules', etc. [2]. Some of these have been incriminated as the toxins responsible for the uremic syndrome. To date, however, none of these compounds retained in the body fluids by virtue of failure of renal excretion, have been shown to unequivocally account for any one of the major stigmata of chronic uremia.

In 1972, Bricker refined and advanced the retention theory to a new concept called the 'trade-off' hypothesis [6, 7]. This hypothesis is extrapolated from the observations of the adaptive mechanisms of the kidney in experimentally produced chronic renal failure. In chronic renal failure, the excretory function of intact nephrons for solutes increases to 2–50 more times than that of nephrons in a normal kidney (magnification phenomenon) [8]. Although the exact intermediary regulatory mechanisms for this phenomenon are unknown, the final modulation of the renal tubular epithelial response is mediated by hormones such as parathormone for phosphate excretion and natriuretic hormone for sodium excretion. Thus, the magnification phenomenon, the adaptive response of intact nephrons to renal failure, is achieved at the expense of higher levels of natriuretic, parathyroid and possibly many other hormones in the plasma.

In the course of chronic progressive renal disease, the concentrations of these hormones rise progressively. Inexorably, there will come a time that the biologic activity of these hormones is sufficiently great to spill over and adversely affect the cells of extrarenal organs. Then, the 'trade-off' for maintaining the external solute balance for a given solute as the renal disease advances, will cause one or more of the abnormalities of uremia. For instance, a prolonged and severe secondary hyperparathyroidism causes some stigmata of uremia, such as osteodystrophy, neuromuscular disorders and impotence. In this view, a uremic toxin would not be a solute retained in the blood owing to failure of its excretion; rather, it would be a circulating humoral factor that serves to prevent the retention of a specific solute.

However neither the retention of uremic toxins nor the consequence of the 'trade-off' alone is sufficient to explain all the aspects of uremic syndrome. Rather, uremia is an end result of the combined failure of excretory, metabolic and endocrine functions of the kidney and intermediary regulatory systems as well.

3.2. Uremic complications

3.2.1. Cardiovascular system

Cardiovascular disorders in uremia include pericarditis, hypertension, accelerated atherosclerosis, cardiomyopathy, congestive heart failure and calcification leading to either arrhythmia or arterial insufficiency. These processes are neither clinically unique nor pathologically specific.

Congestive heart failure and pulmonary edema are among the most common causes of uremic death. Although there are many contributory factors such as anemia, hypertension, arteriosclerosis, pericarditis and cardiomyopathy, the final catalytic event is often salt and water overload rather than primary myocardial failure. Therefore, treatment should be directed to remove excess fluids.

Uremic pericarditis is a common and potentially lethal complication [33]. The incidence of pericarditis in the predialysis era was about 30–50% in patients with chronic renal failure. The incidence has been reduced considerably to less than 20%, since most patients begin dialysis treatment before they develop symptoms of full-blown uremic syndrome. Some patients with stable renal failure may develop uremic pericarditis when they have an acute decompensation of renal failure or when they are in a hypercatabolic state. Uremic pericarditis is usually serofibrinous, but it can be fibrinous, constrictive or hemorrhagic, and

may be associated with cardiac tamponade and pleurisy (uremic polyserositis).

The onset of pericarditis in a patient under conservative medical management indicates the beginning of the final stage of uremia. Aggressive dialysis treatment must be initiated immediately. In general, pericarditis in predialysis patients is rarely associated with cardiac tamponade, readily responds to dialysis and resolves with minimal sequelae, thus obviating pericardiectomy. In contrast, pericarditis in patients on chronic maintenance dialysis has a clinical course that is distinctly different from pre-dialysis patients.

So-called 'dialysis-associated' pericarditis tends to give symptoms such as chest pain, fever and arrhythmia. Effusion is more likely to be hemorrhagic. Hemodynamic compromise and cardiac tamponade is frequent and it can leave sequelae such as adhesive or constrictive pericarditis. Finally, it is rather refractory in responding to dialysis, thus requiring pericardiectomy [1]. The use of antiphlogistic drugs, such as indomethacin and intrapericardial instillation of non-absorbable corticosteroids (triamcinolone), have been used in conjunction with dialysis [31, 10].

Cardiovascular disorders secondary to calcium deposition are described in Chapter 13.

3.2.2. Central and peripheral nervous system

Uremia affects both the central (uremic encephalopathy) and peripheral nervous system (uremic polyneuropathy) [32, 43]. Uremic encephalopathy is seen in both acute and chronic uremia, whereas peripheral neuropathy is seen only in chronic uremia. However, peripheral neuropathy can be associated with acute uremia as a part of systemic diseases such as diabetes mellitus, amyloidosis and vasculitis.

Uremic encephalopathy is within a spectrum of toxic-metabolic encephalopathy. Clinical features of the encephalopathy includes slurred speech, gait imbalance, asterixis, intentional tremor, multifocal myoclonus, delirium, seizures, clouding of the sensorium and coma. The severity of uremic encephalopathy does not correlate with the degree of azotemia but appears to be related to the rate of development of renal failure. The severity of encephalopathy is often profound in acute uremia, whereas it may be of a lesser degree in chronic uremia. Uremic encephalopathy may be due in part to excessive accumulation of small molecular, water-soluble, toxic, organic acids. The rapid clearing of uremic encephalopathy with dialysis supports this hypothesis.

Seizure activity is a common sign of uremic encephalopathy. The

clinical manifestations range from mild twitching to grand mal seizures with a post-ictal phase. There are multiple causes of uremic seizures, all closely related to the biochemical derangements of uremia. (*e.g.*, hyponatremia, hypocalcemia, uremic toxins) and hypertension. Often, it is difficult to point out a single cause of seizures. A combination of multiple metabolic factors and hypertension may reduce seizure thresholds. Although mild seizure episodes are readily reversible by dialysis, patients with recurrent episodes require long-term treatment with anticonvulsant drugs.

Hypocalcemic tetany is a rare phenomenon in uremia, even though severe hypocalcemia frequently occurs. The lack of hypocalcemic symptoms in uremic patients are due to either relatively normal serum levels of ionized calcium, as a result of acidosis or hypoalbuminemia, or by counterbalancing effects of hypermagnesemia. Hypocalcemic tetany can be precipitated by the correction of acidosis without an equivalent rise of serum calcium and after subtotal parathyroidectomy in hypercalcemic patients.

Uremic neuropathy is characterized by a distal, symmetrical, mixed, sensorimotor polyneuropathy, affecting the lower limbs to a greater extent than the upper limbs. Contrary to uremic encephalopathy, the chronicity as well as the severity of renal failure appears to be important to the development of uremic neuropathy. Neurohistological studies have shown that all fiber sizes, both myelinated and unmyelinated, are affected, with axonal degeneration and segmental demyelination. Although the precise mechanism that produces uremic polyneuropathy is unknown, it appears to be related to metabolic failure of neurons due to dialyzable toxins. A transketolase deficiency and excessive levels of parathyroid hormone, myoinositol and 'middle-molecules' have also been postulated to be causes of polyneuropathy.

Clinical features of uremic polyneuropathy include hypesthesia, paresthesia (restless-legs syndrome, burning feet syndrome), paresis, paralysis, muscle cramps and secondary muscular atrophy of the lower limbs. It rarely affects the upper limbs and the autonomic nervous system. Uremic polyneuropathy, especially sensory neuropathy, often responds slowly to dialysis, but resolves rapidly after successful kidney transplantation.

3.2.3. Hematopoietic system

The kidney appears to have a dual erythropoietic function; to act as a major endocrine organ producing erythropoietin and also as an oxygen sensor controlling the rate of erythropoietin release [14]. Erythropoietin

promotes the proliferation and maturation of erythroid precursor cells in the bone marrow, augments the synthesis of hemoglobin within the erythroid cells, and produces a shift of marrow reticulocytes into the circulation. Thus, the kidney plays a pivotal role in erythropoiesis.

Anemia is an invariable finding in chronic uremia. It is characterized by normocytic, normochromic anemia and normocellular bone marrow with normoblastic maturation [27]. Anemia usually presents when GFR falls below 25 ml/min, but it may at a GFR of 50 ml/min. The severity of anemia is variable, but is roughly inversely proportional to the degree of azotemia. Some kidney diseases, such as radiation nephritis, membranoproliferative glomerulonephritis, Goodpasture's syndrome and hemolytic-uremic syndrome, tend to be associated with a severe anemia. In contrast, polycystic kidney disease and obstructive uropathy tend to be associated with lesser degrees of anemia. Rarely, cystic and neoplastic kidney diseases may present with even erythrocystosis.

The cause of anemia in uremia is multifactorial. The decreased production of erythropoietin from the failing kidney and decreased responsiveness of bone marrow to erythropoietin seem to be the major causes. Dialyzable uremic toxins that inhibit erythropoiesis and shorten the life span of circulating erythrocytes (hemolysis) are also important [17, 27, 30]. The removal of toxins via dialysis promotes erythropoiesis and prolongs the life span of erythrocytes, and thus improves anemia. Myelofibrosis secondary to severe renal osteodystrophy is not only a cause of anemia but also of thrombocytopenia [44]. Iron deficiency secondary to bleeding is often a reversible, contributory factor of anemia.

Androgenic hormone has been used for anemia in both dialysis and non-dialysis patients. Although its exact erythropoietic effect has not been well understood, it appears to be mediated by the increased release of erythropoietin, predominantly from the kidney and to a lesser extent from extra-renal sources. Anemia improves with long-term use of androgenic hormone in most uremic and dialysis patients, except in those that are anephric [41].

Uremic patients have both quantitative and qualitative defects in their platelets. Approximately 20% of uremic patients have mild thrombocytopenia. The cause of it is unclear other than its possible relationship with myelofibrosis and splenic sequestration [44]. In general, the hemostatic abnormalities in patiens with uremia are related to acquired defects in platelet function [21]. These defects include impaired platelet aggregation and platelet factor 3 activation and decreased platelet adhesiveness, resulting in prolonged bleeding time and a bleeding diathesis. Although various uremic toxins have been postulated to cause these defects, only

guanidinosuccinic acid, urea and phenolic compounds, have met the criteria as toxins affecting platelet function. Since these toxins are dialyzable, platelet dysfunction in uremia is reversible.

3.2.4. Immune system

Most uremic patients have mild lymphocytopenia. This appears to be related to a shortened life-span of lymphocytes. The ratio of T and B lymphocytes in peripheral blood remains normal. Although B lymphocytes are by and large functionally intact in the uremic state, T lymphocytes have shown diverse functional abnormalities in vivo as well as in vitro. Functional defects of T lymphocytes include decreased responsiveness to antigenic stimulation (phytohemagglutinin, allogeneic lymphocytes and allografts), impaired delayed type hypersensitivity (anergy), and inability to produce interferon [12, 13].

These defective T lymphocyte functions coupled with impaired inflammatory responses of polymorphonuclear leucocytes, monocytes and macrophages, are major causes of increased susceptibility to infection in uremic patients. Similarly, the recent observations of an increased incidence of malignancy in patients on long-term dialysis, has been attributed to impaired immunosurveillance [24].

3.2.5. Gastrointestinal tract

The gastrointestinal tract and digestive organs are frequently affected by uremia. Gastrointestinal manifestations of uremia range from anorexia, nausea, vomiting and uremic fetor to more serious complications such as stomatitis, parotitis, pancreatitis, peptic ulcer and colitis. Most of these symptoms respond to protein restriction alone in the early stages. They respond readily to dialysis in the late stages, suggesting that they are caused by dialyzable toxins that are products of protein metabolism.

The stomach and duodenum are subject to peptic ulceration as well as to multiple superficial erosions causing chronic blood loss or acute severe hemorrhage. It has been postulated that the high incidence of peptic ulcer disease in uremic patients is related to the high serum levels of parathyroid hormone (secondary hyperparathyroidism) and gastrin (due to decreased renal inactivation). Despite the consistent findings of the high serum levels of these hormones in the majority of uremic patients, basal as well as histamin or pentagastrin-stimulated gastric acid secretion, have been variously reported as high, normal, or low [15]. Thus, some other factors, such as disruption of mucosal barriers, might work in concert to produce the ulcerative disorders.

Hyperamylasemia due to decreased renal clearance in uremic patients has been emphasized. However, most uremic patients have normal serum amylase levels, and even if they are elevated, they rarely exceed twice the upper limit of the normal level. Thus, uremic patients with more than a three-fold rise in serum amylase should have causal factors looked at the same as in non-uremic patients.

3.2.6. Endocrine organs

Uremic patients have diverse endocrine disorders which include growth retardation, azoospermia, amenorrhea, infertility, thyroid dysfunction, pancreatic endocrine dysfunction as well as secondary hyperparathyroidism which is discussed elsewhere in the manual (Chapter 13), and earlier in this chapter as well.

Growth retardation. Chronic renal failure in children is often associated with growth delay and retardation in bone age. Undernutrition, osteodystrophy, chronic acidosis and decreased somatomedin (sulfation factor) levels appear to be importantly related to this growth delay [25]. In most children with chronic renal failure and growth delay, somatomedin levels are decreased, whereas growth hormone levels are normal or elevated [36].

Long-term dialysis does not improve growth in these children but kidney transplantation does. The bone age appears to be the most critical factor in predicting growth. Retardation of bone age in proportion to one's height age, gives a higher potential for growth restoration after successful kidney transplantation. Other factors that favorably affect growth after kidney transplantation include higher serum somatomedin activity, higher graft function and lower maintenance doses of steroid hormones.

Reproductive and sexual dysfunction. Decreased libido, impotence, oligospermia and decreased spermatic motility, and infertility, are frequent findings in uremic males. These abnormalities appear to have resulted from a primary testicular dysfunction involving both germinal cells (spermatogenesis) and Leydig cells (steroidogenesis). Thus, testicular dysfunction in uremia is characterized by impaired spermatogenesis (oligospermia or azoospermia) and low plasma testosterone levels, while follicle-stimulating hormone, prolactin and luteinizing hormone levels are normal or elevated [20, 26]. Elevated plasma luteinizing hormone is apparently due to both increased production and reduced metabolic clearance, while elevated follicle-stimulating hormone is due to the

increased production by impairment of feedback control. These dysfunctions are not correctable by dialysis, but are completely reversible by renal transplantation. Since raised prolactin levels are associated with reduced libido and sexual activity, bromocriptin, a dopaminergic agonist which reduces plasma prolactin levels, has been used in male dialysis patients, with an improvement in sexual activity [4].

As in men, decreased libido, hypo or amenorrhea, anovulation and infertility are common concomitants of females with severe renal failure. These patients also frequently have elevated plasma gonadotropin levels in the face of low or lower normal plasma estrogen levels [37]. Although hemodialysis does not improve infertility, it often changes their menstrual pattern from amenorrhea or hypomenorrhea to hypermenorrhea. Nevertheless, there have been several case reports of women on hemodialysis who had a conception and gave normal birth [42]. Kidney transplantation usually restores female reproductive functions completely to normal.

Thyroid function. Because of similarities between the symptoms and signs of uremia and hypothyroidism (low body temperature, cold intolerance, low basal metabolic rate, dry skin, lethargy, hyporeflexia, etc.), there have been extensive studies concerning the thyroid function of uremic patients. The reported results are variable and confusing [15]. The levels of serum free T4 and thyroid stimulating hormone appear to be a more reliable indicator of the true thyroid state [40]. In general, most uremic patients are clinically euthyroid. Laboratory indices which suggest biochemical thyroid dysfunction can often be explained by nonspecific extrathyroidal factors associated with uremia.

Pancreatic endocrine function. Glucose intolerance occurs in over 50% of uremic patients. This abnormality is associated with normal fasting glucose levels, elevated fasting insulin levels, and delayed and reduced falls in blood glucose following exogenous insulin administration. The decreased tissue responsiveness to insulin appears to be most importantly causally related to glucose intolerance. However, other abnormalities such as high plasma levels of glucagon and growth hormone, and decreased sensitivity of pancreatic B-cells to plasma glucose, are all possible contributory factors. Impaired tissue responsiveness to insulin appears to have, at least partially, resulted from uremic toxins, and thus, glucose intolerance improves significantly with hemodialysis.

The normal kidney extracts and degrades about 30–40% of the insulin carried to it [11, 16, 34, 35]. Thus, severe renal failure markedly

reduces renal insulin extraction, its metabolic clearance and prolongs its serum half-life to 5 hours as compared to 2 hours in normals. Accordingly, as renal failure progresses, less insulin is required to control hyperglycemia.

Plasma glucagon levels have also been found to markedly increased (two to six-fold normal) in uremic patients. They are directly correlated with serum creatinine levels [3]. Experimentally, hyperglucagonemia develops immediately after ligation of either the ureters or renal arteries, and disappears within 48 hours after renal transplantation in dogs. At present, neither the cause nor clinical significance of hyperglucagonemia in uremic patients is known. It is not alterable by dialysis.

4. PREPARATION FOR DIALYSIS AND TRANSPLANTATION

As the kidney become progressively damaged to the point where they can no longer function in regulating the homeostasis of the body, every major organ system becomes involved. There is a cascading effect that leads to severe debilitation of the patient and ultimately death, unless procedures like dialysis or transplantation are instituted.

After the serum creatinine levels exceed 10 mg/dl, the median patient survival rate is only two months [28]. At this stage, the survival rate with conservative measures including dietary restriction is 50% for 5 months [22]. However, many factors affect these survival figures. In general, those with polycystic kidneys, pyelonephritis, or obstructive uropathy survive longer. Those with diabetic nephropathy, amyloidosis, or myelomatous kidneys, have a shorter survival rate due to the more rapid progression and less frequent reversibility of the renal failure, in addition to the systemic involvement of the primary disease.

Until two decades ago, uremia was a universally fatal disease. We are now able, partially with dialysis and often totally with transplantation, to reverse not only the uremia but also the renal disease itself. The success of these procedures over the past twenty years, has necessitated a change in our attitude toward the treatment of kidney disease and its progression to chronic renal failure. In the management of chronic renal failure, not only a knowledge of nephrology but also a comprehensive understanding of general internal medicine is necessary so that we can anticipate the subsequent course of the disease and prepare for the consequences in advance. Rather than extending the time so that the involvement of every organ system can produce a cascading effect in debilitating the patient, it is much better to consider dialysis treatment

or transplantation early in the patient's course. Since our aim is to restore the patient completely to normal, we wish to do nothing early in the course of the disease that would seriously complicate his return to total health or jeopardize his survival later in the disease. For instance, steroids are greatly overused in kidney diseases and in many instances may produce irreparable damage that can seriously compromise definitive attempts to treat a patient later on in his course of the disease.

At each stage of renal failure, every attempt should be made to preserve kidney function. Whenever renal failure progresses, reversible factors should be sought diligently, but without undue delay for necessary treatment. When the time comes, the patient should be prepared for eventual dialysis by creating an arteriovenous fistula. This will allow dialysis to be instituted when the patient's symptoms and/or signs indicate that conservative medical therapy alone is no longer sufficient. One should never wait until a major uremic complication develops and use it as the signal to initiate dialysis. It is important to start dialysis earlier than later, so that these complications can be prevented. Dialysis is the immediate life-saving procedure for patients with uremia. Transplantation, however, is an elective but definitive and ultimate procedure and takes a great deal of time and planning to execute successfully.

When GFR decreases to 20–10 ml/min and the patient has only mild uremic symptoms, restricted protein intake (less than 40 gm/day) may be sufficient to relieve the symptoms. The diet should include all the elements of the essential amino acids in high biologic value and provide 2,500–3,000 calories per day. It is not recommended that a protein restrictive diet be instituted at the expense of malnutrition. When GFR falls below 10–7 ml/min, an arteriovenous fistula should be created electively. However, this schedule should be individualized depending on the rate of progression, degree of the subjective symptoms and the extent of the organ involvement of renal failure. At the same time, the possibility of kidney transplantation from either a living related donor or cadaveric donor should be explored. Since the patient's cooperation is essential for the successful management of both dialysis and transplantation, he should be well informed of his status and be encouraged to actively participate in his own medical care.

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12. RENAL HYPERTENSION

BRUCE R. LESLIE

The kidneys play an important role in the pathophysiology of hypertension. In patients with a variety of renal diseases, impaired sodium excretion as well as disturbances in renal vasoactive hormone metabolism may be the stimuli which raise blood pressure (Table 1). It should be recognized that there is no meaningful dividing line between 'hypertension' and 'normotension'. Blood pressure is a quantity, and the risks of organ damage seem to be a direct function of the arterial pressure. Our practice is to regard the patient with a diastolic blood pressure persistently over 95 mm Hg as a candidate for antihypertensive therapy.

Table 1. Renal hypertension

Renal Ischemia
Renal artery stenosis
Renal artery thrombosis
Renal artery embolism
Perinephric compression
Acute Glomerulonephritis
Chronic Renal Insufficiency
Obstructive Nephropathy
Post-Renal Transplantation
Renal Masses
Renin-secreting tumor
Renal artery compression
Renal cortical cyst

1. RENOVASCULAR HYPERTENSION

Production of hypertension in experimental animals by constriction of the renal artery was soon followed by recognition of the association of hypertension and unilateral renal artery stenosis in man. Hypertension resulting from disturbances in renal blood flow is now recognized as the most common form of surgically remediable hypertension.

1.1. Renal artery stenosis

1.1.1. Etiologies

This lesion is most frequently the result of either arterial dysplasia or atherosclerosis.

The arterial fibromuscular dysplasias are a group of disorders characterized by abnormalities of the collagen, smooth muscle, and elastic membrane components of the arterial wall. The lesions can be recognized by their characteristic angiographic appearances [17]. The most common type, medial fibroplasia with mural aneurysms, produces the well-known 'string of beads' appearance (Figure 1). The lesion is bilateral in about 25% of cases. Typically beginning in the middle or distal third of the main renal artery, the stenosis may be localized or may extend into the segmental arterial branches. Neither the etiology nor the pathogenesis of arterial fibromuscular dysplasia is known. The extent and severity of stenosis may progress.

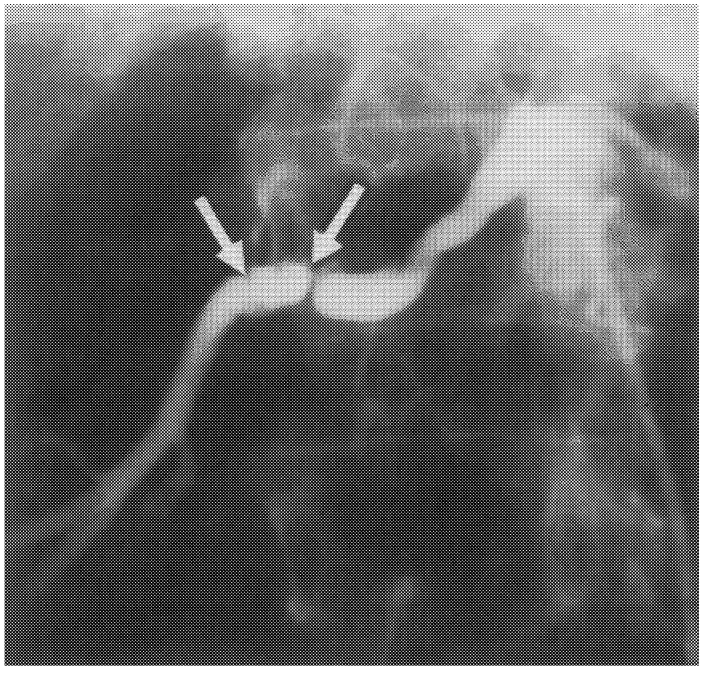

Figure 1. Selective renal arteriogram demonstrating multiple stenoses of the main renal artery. This is characteristic of medial fibromuscular dysplasia.

Atherosclerotic obstruction of the renal artery is most often recognized in patients over the age of 50. They frequently have evidence of extra-renal atherosclerotic disease. Bilateral disease has been reported in 30–60% of cases. The atherosclerotic plaque is usually observed in the proximal third of the main renal artery. The degree of atherosclerotic stenosis is particularly likely to progress with time.

1.1.2. Clinical approach

The clinical approach to the hypertensive patient with possible renal artery stenosis is designed to answer two questions: 1. Is a stenotic lesion present, and 2. Is the lesion physiologically significant in the genesis of hypertension? A diagnostic evaluation should be undertaken only if the discovery of a significant lesion will result in a recommendation for surgery. In certain cases, revascularization or unilateral nephrectomy can restore normal blood pressure or make hypertension easier to control with drugs. Patients may be spared the expense and side-effects of a lifetime of therapy with antihypertensive medications. In selected instances of severe stenosis, glomerular filtration rate may increase following relief of renal ischemia regardless of whether or not blood pressure is reduced. However, morbidity and mortality rates attending renovascular surgery may be unacceptable in older patients with widespread atherosclerotic disease [14]. Antihypertensive therapy should be given to all patients with atherosclerotic renovascular hypertension. Surgery should be reserved for hypertension refractory to medications or when renal function is compromised by a severe reduction in renal blood flow. A recently described 'percutaneous transluminal angioplasty' of a stenotic renal artery (Grüntzig procedure) may be useful in selected cases.

1.1.3. Recognition of renal artery stenosis

Clinical characteristics. Data from the history, physical examination, and routine laboratory survey may help the clinician to suspect the existence of renovascular hypertension. While certain findings may be more frequent in patients with renovascular hypertension than those with essential hypertension, no finding can be relied upon to distinguish between the two groups. Observations recorded with increased frequency in renovascular versus essential hypertensives include: systolic or continuous bruits in the upper abdomen and flanks; bacteriuria; age greater than 50 (atherosclerotic) or less than 30 (fibromuscular dysplasia); low serum K; high serum CO_2 content and high BUN [34]. Renovascular hypertension is also more prevalent in whites than blacks, and

occurs more frequently in patients without a family history of hypertension. Nevertheless, the clinical usefulness of these observations is diminished by the greater prevalence of essential hypertension (in which all these signs also occur) in the general population.

Radiologic investigation. The definitive test for detecting renal artery stenosis is the selective renal arteriogram. The radiologist should be able to distinguish atherosclerotic from dysplastic stenosis. An estimate of the reduction of the luminal cross sectional area may also be made. Lesions producing less than 50% stenosis are not likely to be hemodynamically significant. Rapid sequence intravenous urography and radioisotope renography have been proposed as screening tests for renal artery stenosis, to determine which patients should undergo arteriography. These examinations are designed to reveal disparities in blood flow between the two kidneys. Urographic criteria that suggest reduced renal blood flow include: 1. delayed pyelocalyceal appearance time of the contrast medium in early fims, 2. hyper-concentration of dye in late films, 3. diminished kidney length (1.5 cm or more). Ureteral notching, indicative of collateral blood vessels, is regarded as a minor criterion, as are parenchymal atrophy and renal ptosis. The I^{131}-hippuran renogram is typically judged positive or negative by the radiologist's assessment of whether or not there is reduction of renal blood flow. Both intravenous urography and radioisotope renography have false positive and false negative rates of 20–25%. Renal arteriography is the definitive examination when clinical suspicion is high.

Individual kidney function tests, requiring bladder and ureteral catheterizations, are based on the observation that reduction in renal blood flow results in increased fractional reabsorption of sodium and water. Positive tests show decreases in urine volume and sodium concentration and increases in urinary PAH or creatinine concentration from the ischemic kidney compared to its mate [26]. As an indicator of relative renal ischemia, the split function test has little to offer over the urogram or radioisotope renogram. While positive tests imply a somewhat greater probability of surgical cure, they are not sufficiently reliable to be clinically useful.

1.1.4. Functional significance — prediction of surgical success

The presence of renal artery stenosis does not necessarily mean that this lesion is a cause of the patient's hypertension. Pre-operative evaluation attempts to ascertain the functional significance of the stenotic lesion.

Unilateral renal ischemia leads to an increase in renin secretion from

the involved kidney. Renin is an enzyme that acts on a circulating globulin substrate of hepatic origin to produce the decapeptide, angiotensin I. A dipeptidyl carboxypeptidase, angiotensin-I-converting enzyme, splits a dipeptide from angiotensin I to form the octapeptide, angiotensin II. Angiotensin II acts directly on vascular smooth muscle to produce vasoconstriction. In addition, it may stimulate the sympathetic nervous system at both central and peripheral sites, enhancing norepinephrine release from post-ganglionic neurons. Angiotensin also stimulates increased secretion of the sodium-retaining mineralocorticoid hormone, aldosterone, from the adrenal zona glomerulosa. These actions of angiotensin II result in elevated blood pressure.

Definitive proof of the functional significance of renal artery stenosis is provided by reduction of blood pressure in response to revascularization or unilateral nephrectomy. Pre-operative assessment of functional significance depends on demonstrating enhanced activity of the renin-angiotensin system. Only 40–50% of patients with renovascular hypertension have an abnormally high plasma renin activity (PRA) in peripheral venous blood. Laragh has proposed evaluating peripheral PRA as a function of 24-hour urinary sodium excretion [22]. Increases in this 'renin-sodium index' compared to normal patients may indicate overactivity of the renin-angiotensin system. Increased renin release from the involved kidney is assessed by measurement of PRA in renal venous blood. Selective catheterization of the renal veins is performed percutaneously via the femoral vein. Samples are obtained from both main renal veins and the infra-renal inferior vena cava. Values from the latter site are usually equal to arterial PRA. In cases of stenosis involving a branch of the main renal artery, or of renal neoplasms or segmental infarctions, samples from segmental renal veins may also be obtained. The criteria for a positive test include: (1) a ratio of renal venous PRA greater than 1.5 for the involved compared to the uninvolved kidney; this implies relative hypersecretion of renin (2) venous PRA from the uninvolved side minus vena caval PRA should approach zero; this indicates suppression of renin secretion from the uninvolved kidney.

Failure to meet these criteria may preclude a successful operative outcome. The sensitivity of the renal vein PRA ratio test may be enhanced by measures designed to increase renin secretion. These include: prior sodium depletion by low salt diet and furosemide; upright posture; parenteral hydralazine; intravenous angiotensin-I-converting enzyme inhibitor.

The pathophysiology of hypertension in patients with arterial stenosis

in a solitary kidney differs from the two-kidney model described above. When this one-kidney model is produced in the laboratory, an immediate increase in renin production ultimately gives way to renin suppression due to the development of an expanded intravascular volume. The hypertension of one-kidney renal artery stenosis is 'volume dependent', while the hypertension of unilateral renal artery stenosis in a patient with two otherwise normal kidneys is 'angiotensin dependent'.

In the case of bilateral renal artery stenosis, one or both arterial lesions may produce renal ischemia sufficient to stimulate renal renin production. The absence of unilateral suppression of renin secretion, as reflected by comparison of renal venous and infra-renal vena caval PRA, indicates physiologically significant bilateral disease. Hypertension in these patients is sustained by both the renin-angiotensin system and sodium-volume expansion. It may not be possible to decide from currently available data which side is more severely involved. It is unlikely that unilateral revascularization will restore normal blood pressure. Bilateral revascularization may be undertaken, although this may be attended by higher morbidity and mortality than the unilateral procedure. We prefer a medical approach to the problem of bilateral renal artery stenosis, relying on diuretics and renin-suppressing medications.

In circumstances in which bilateral anatomic disease is present but PRA values indicate unilateral ischemia (suppression of contralateral renin secretion), unilateral revascularization may be undertaken. This decision should be tempered by the understanding that the anatomic lesion on the contralateral side may progress to produce significant renal ischemia in the future.

1.2. Hypertension in other forms of unilateral renal disease

Unilateral excessive renin secretion can also result from other lesions which may interfere with the normal pattern of renal blood flow. Increases in renin secretion have been demonstrated in some hypertensive patients with large renal cortical cysts. Cyst decompression restored normal blood pressure. Hypertension following renal trauma may be associated with renal artery thrombosis or perinephric hematoma. Hypertension due to perinephric masses has been demonstrated in experimental and clinical models to be renin-angiotensin mediated.

Excessive renin secretion may rarely be due to renin producing renal neoplasms. These include juxtaglomerular cell tumors (hemangiopericytomas) and Wilms' tumors. These are usually seen in young adults and children and are detectable by angiography.

2. ACUTE RENAL FAILURE

2.1. Acute glomerulonephritis

Hypertension is a hallmark of the syndrome of acute glomerulonephritis. Cardiac catheterizations in hypertensive children with acute oliguric post-streptococcal glomerulonephritis have provided evidence of hypervolemia. Total peripheral resistances are normal [11]. Low peripheral PRA observed in acute post-streptococcal glomerulonephritis has been thought to be the consequence of physiologic suppression of renal renin secretion due to plasma volume expansion. While extracellular fluid overload with secondary increases in cardiac output may account for the hypertension of post-streptococcal disease, other mechanisms may also be involved in other forms of acute glomerulonephritis. Hypertension in patients with the childhood hemolytic-uremic syndrome, for example, is accompanied by high values for peripheral PRA. This raises the possibility of increases in plasma angiotensin levels contributing to the pathogenesis of the hypertension. Hypertension in acute glomerulonephritis recedes with the diuresis that accompanies recovery. Therapy of moderate to severe hypertension during the oliguric phase should include curtailment of salt and water intake. Acute parenteral administration of diuretics and hydralazine may be helpful if the glomerular filtration rate is not severely compromised. Parenteral methyldopa or nitroprusside may occasionally be necessary. Because circulatory congestion in this setting is the consequence of primary extracellular fluid volume expansion rather than congestive heart failure, digitalis is ineffective in relieving pulmonary edema.

2.2. Ischemic and nephrotoxic acute renal failure

PRA and angiotensin blood levels are typically elevated during the oliguric phase of acute renal failure, falling during the diuretic phase [7]. Nevertheless, there is no correlation between these renin or angiotensin levels and blood pressure. This may be the result of severe decreases in effective plasma volume which preceded the onset of acute renal failure. Hypertension in acute renal failure usually occurs in the setting of increases in total body sodium. Antihypertensive therapy therefore is directed toward normalizing extracellular fluid volume by restriction of salt and water intake, and dialysis when necessary.

2.3. Obstructive uropathy

Several reports have appeared of hypertension accompanying both unilateral and bilateral obstructive uropathy [36]. In cases of unilateral hydronephrosis, relative increases in ipsilateral renal vein PRA with suppression of contralateral renin secretion, analogous to renal artery hypertension, have been documented. Relief of hypertension has followed either corrective ureteral surgery or unilateral nephrectomy. With ureteral obstruction in a solitary kidney, analogous to the one-kidney model of renal artery stenosis, hypertension in the chronic phase is sustained by an expanded plasma volume which acts to suppress renin production.

3. CHRONIC RENAL FAILURE

Hypertension is common finding in most forms of chronic renal parenchymal disease. Approximately 80% of patients presenting for chronic hemodialysis have a history of hypertension [23]. Mechanisms causing high blood pressure may operate early in the course of chronic progressive renal disease, resulting in hypertension in the presence of minimal increases in serum creatinine concentration [6]. The physiologic variables that have been most frequently suggested as contributing to hypertension in chronic renal insufficiency are discussed below.

3.1. Sodium-volume factors

Increases in total-body exchangeable sodium as well as plasma and extracellular fluid volumes are observed early in the course of chronic renal disease. These increases frequently persist to the time chronic dialysis is initiated, and have been shown to correlate with elevated blood pressure [9, 12].

The importance of sodium-volume factors in the regulation of blood pressure is reflected in the management of hypertension in patients with chronic renal insufficiency. Even before dialysis is required, blood pressure may be reduced by the use of diuretic drugs [2]. In the majority of hypertensive dialysis patients, blood pressure reduction can be achieved by dialysis-mediated removal of excess salt and water coupled with appropriate dietary restrictions.

Because hypertension is such a common finding in chronic progressive renal disease, the finding of a normal blood pressure in an untreated patient should prompt consideration of the possibility of

extracellular fluid volume depletion induced by gastrointestinal fluid losses or 'salt-losing nephropathy'. Replacement of salt and water losses may have the undesirable effect of restoring hypertension, but more importantly may eliminate a 'pre-renal' component of worsened renal function. Most patients with chronic renal disease can maintain sodium balance except at the extremes of sodium intake (less than 20–30 mEq/day). However, some patients may incur negative salt and water balance at normal or only modestly restricted sodium intakes [27]. The renal diseases in these patients are characterized by significant interstitial damage. The resultant tubular dysfunction may lead to inadequate tubular sodium reabsorption. These patients may remain normotensive because of persistent deficits of salt and water. Hypertension may develop in such patients when terminal renal failure supervenes and the defect in tubular sodium reabsorption is overshadowed by the decrease in glomerular filtration rate. The etiologies of this form of chronic renal disease include medullary cystic disease, obstructive nephropathy, and other tubulo-interstitial diseases.

3.2. Vasoconstrictor factors

Increases in total peripheral resistance play a major role in sustaining hypertension in chronic renal disease [12, 19]. The role of the renal renin-angiotensin system has been emphasized in analyses of vasoconstrictor forces.

A significant minority of dialysis patients fails to achieve satisfactory blood pressure control despite vigorous removal of sodium and water. This group may include some patients whose blood pressure is observed to rise in response to plasma volume reduction during dialysis. The 'volume-resistant' patients have been observed to have higher levels of plasma renin activity (PRA) and total peripheral resistance than volume-responsive patients. Presumably, high blood pressure in these patients is in part the result of arteriolar vasoconstriction mediated by angiotensin II. Decreases in blood pressure can be obtained by therapy designed to reduce PRA and angiotensin II levels. Bilateral nephrectomy may result in dramatic decline of elevated blood pressure associated with decreases in PRA and total peripheral resistance. Drugs such as propranolol may reduce blood pressure in part by suppression of renal renin secretion. Angiotensin converting enzyme inhibitors, such as captopril, may also prove useful in these patients.

4. TRANSPLANTATION

Hypertension in patients who have received renal allografts has been reported with a prevalence of 40–50% [1, 32]. The potential etiologic factors are multiple, and more than one may operate in a given patient (Table 2).

Table 2. Causes of post-transplant hypertension

Persistence of pre-transplant hypertension
Acute rejection
Corticosteroids
Transplant renal artery stenosis
Chronic rejection
Hypercalcemia
Acute ureteral obstruction
Acute parenchymal renal failure
Recurrence of original disease

4.1. Persistence of pre-transplant hypertension — The role of the recipient's kidneys

Approximately three-quarters of renal transplant recipients have a prior history of hypertension. Among those patients surviving for longer than six months with a functioning allograft, the prevalence of hypertension is reduced by as much as 40% [32]. Post-transplant hypertension appears to be less frequent in those patients who have undergone bilateral native nephrectomy prior to transplantation [8]. In addition, hypertensive patients treated by bilateral native nephrectomy subsequent to transplantation have experienced blood pressure reductions. Elevation of native renal vein PRA compared to peripheral or transplant vein PRA has been said to predict the hypotensive response to native nephrectomy [24]. Other groups, however, have failed to demonstrate a correlation between native renal vein PRA and blood pressure reduction following native nephrectomy; some patients with non-elevated native vein PRA experiencing reduction in blood pressure and others with increased values failing to have a hypotensive response to operation [32].

4.2. Acute rejection

An increase in arterial blood pressure is a hallmark of acute rejection. The decrease in GFR results in sodium and water retention. Furthermore, acute rejection is associated with increases in PRA and the consequent increase in plasma angiotensin II concentration may exacer-

bate the hypertension. However, the changes in PRA during acute rejection may be seen in the absence of a rise in blood pressure.

4.3. Corticosteroids

Several mechanisms have been invoked to explain the increase in blood pressure associated with the administration of large doses of glucocorticoids. While prednisone and methylprednisolone have minimal mineralocorticoid activity, some sodium retention may result from the massive doses used in transplantation. Elevations in aldosterone secretory rates have been observed in hypertensive allograft recipients. Reduction in steroid doses has been associated with a decreased prevalence of hypertension and a fall in aldosterone secretion rate. Rises in plasma renin substrate concentration and plasma renin activity have been reported in rats receiving large doses of methylprednisolone.

Steroids are likely to play a significant part in the genesis of blood pressure during the first few weeks after transplantation when doses are high [31]. Blood pressure has not been found to correlate with steroid dose in those patients with functioning allografts longer than six months after surgery [32].

4.4. Transplant renal artery stenosis

Transplant renal artery stenosis has been demonstrated angiographically in 5–47% of patients with post-transplant hypertension [21]. It is regarded by some investigators as the most common cause of 'refractory hypertension' in the allograft recipient. Perhaps because of variations in salt and water balance among the patient groups, or the coexistence of other factors which increase renin secretion such as chronic rejection, PRA measurements have not consistently reflected the presence of transplant renal artery stenosis or predicted a salutary response to revascularization. While transplant renal artery stenosis is most commonly discovered in patients with hypertension, it may be present in patients with normal blood pressure. Certain proof of the functional significance of transplant renal artery stenosis can be provided only by a return toward normal blood pressure after restoration of normal renal blood flow. Severe stenosis may be associated with a reduction in GFR, and the combination of hypertension and a rise in serum creatinine may be mistaken for rejection. The clinical distinction between transplant renal artery stenosis and chronic allograft rejection may be further complicated by similar reductions in total and renal cortical blood flow and,

under appropriate sodium-balance conditions, similar increases in plasma renin activity from the transplant renal vein [4]. In one reported series, no case of transplant renal artery stenosis was detected in the absence of a bruit over the allograft [35]. Exceptions to this 'rule' have been reported [28]. The only reliable method for diagnosing transplant renal artery stenosis is renal arteriography.

4.5. Hypercalcemia

Hypercalcemia may occur in as many as 30% of patients after transplantation [10]. The most common cause is hyperparathyroidism due to slow regression of secondarily hyperplastic parathyroid glands. Hypercalcemia may contribute to elevation of blood pressure by incompletely understood mechanisms that may include an increase in total peripheral resistance.

4.6. Chronic rejection

The progressive decline in GFR associated with chronic rejection is frequently associated with the appearance or worsening of hypertension. Increases in total-body sodium and water as in patients with chronic renal failure of other etiologies plays an important role. In addition, the renin-angiotensin system may be activated by a decrease in renal cortical blood flow induced by the rejection process [4]. Intimal fibrosis and thickening, provoked by antibody-mediated endothelial damage, leads to vascular narrowing and renal parenchymal ischemia.

5. PHARMACOLOGIC THERAPY OF HYPERTENSION IN RENAL DISEASE

Drug therapy of hypertension in patients with renal disease may be necessary when more 'conservative' measures such as restriction of dietary sodium, elimination of obesity, and intensive salt and water removal by dialysis (where applicable) have failed to reduce blood pressure.

5.1. Diuretics

Increases in body sodium and water are present in the majority of hypertensive patients with both acute and chronic renal insufficiency.

The antihypertensive effect of diuretics is a consequence of their natriuretic properties [3]. They are not likely to be effective as antihypertensive agents in patients whose glomerular filtration rate (GFR) is less than 5 ml/minute. Patients with these severe reductions in GFR require dialysis to effect salt and water removal. Patients who are apparently 'refractory' to antihypertensive drugs may have pre-existent or acquired plasma volume expansion. They may regain responsiveness to antihypertensive medications when diuretics are added or administered in increased doses [13].

Patients with GFR's greater than 25 ml/minute usually respond to maximum doses of a thiazide (*e.g.* chlorothiazide 1 gm/day; hydrochlorthiazide 100 mg/day) or an equivalent diuretic (*e.g.* chlorthalidone 100 mg/day). Side effects of these diuretics include hyperuricemia, hypercalcemia, glucose intolerance, and hypokalemia. In addition, acute renal failure due to allergic interstitial nephritis has been reported with administration of thiazides and furosemide [25].

In patients whose GFR is 5–25 ml/min, thiazides will not produce a diuretic response. Some of these patients may respond to the new diuretic agent, metolazone [5]. The more potent 'loop diuretics', furosemide and ethacrynic acid, are usually necessary under these circumstances. Because of reports of irreversible nerve deafness occurring after administration of ethacrynic acid to patients with renal insufficiency [30], furosemide is the preferred agent (although reversible deafness has been reported with this drug as well).

So-called 'potassium-sparing' diuretics such as spironolactone may exert mild antihypertensive effects in patients with renal insufficiency. Nevertheless, spironolactone is ineffective at GFR's less than 25 ml/min and may subject the patient with renal insufficiency to the risk of fatal hyperkalemia. This potential danger outweighs any benefit from the use of this drug.

5.2. Beta-adrenergic blockers

The most frequently used agent in this group is propranolol. Chronic oral administration of propranolol may decrease elevated blood pressure by a variety of mechanisms including: decline in cardiac output; decreased renal renin secretion; central inhibition of efferent sympathetic nervous system activity with consequent fall in total peripheral resistance [18]. The drug should not be administered to patients with congestive heart failure, asthma, or heart block, and is relatively contraindicated in patients with peripheral arterial insufficiency, Raynaud's phe-

nomenon, and those at risk of insulin-induced hypoglycemia. In doses up to 640 mg/day, and occasionally higher, propranolol has been effective in reducing blood pressure in patients with chronic renal disease. It may be particularly useful in patients whose hypertension is mediated by over-activity of the renin-angiotensin system. Abrupt cessation of propranolol therapy may provoke severe angina pectoris and malignant ventricular arrhythmias in patients with ischemic heart disease.

5.3. Drugs acting on the central nervous system

Clonidine and alpha-methyl norepinephrine, the principal metabolite of methyldopa, stimulate alpha-adrenergic receptors within the brainstem medullary vasomotor center. This results in decreased efferent activity of the sympathetic nervous system. The consequences include decreases in total peripheral resistance, cardiac output, and renal renin production. Renal blood flow and GFR are not diminished. Clonidine reduces blood pressure in both supine and standing positions, with few problems with orthostatic or exercise-induced hypotension. Side-effects of clonidine include sedation, constipation, xerostomia, xerophthalmia. Male sexual dysfunction is said to occur less frequently than with methyldopa. Most disturbing is the occurrence of rebound hypertension with abrupt cessation of medication. This is characterized by rises in blood pressure to levels higher than pre-treatment, associated with a hyper-adrenergic state (tachycardia, diaphoresis, increased plasma and urinary catecholamines)[16]. Because of the risk of rebound hypertension from sudden interruption of therapy, clonidine should not be offered to unreliable patients. Preliminary investigations suggest substantial removal of clonidine by hemodialysis, but rebound hypertension has not yet been reported in this setting.

Methyldopa's side effects include drowsiness, postural hypotension, impotence, hepatitis, drug fever, and Coombs positive hemolysis. In addition, several cases of rebound hypertension following abrupt discontinuation of therapy have been reported[15]. Substantial amounts of methyldopa are removed by hemodialysis, and a rise in blood pressure may occur after this procedure[38].

5.4. Vasodilators

Hydralazine decreases total peripheral resistance by direct action on arteriolar smooth muscle. By itself, hydralazine is a weak antihypertensive agent because it elicits reflex compensatory increases in cardiac

output. This may provoke angina pectoris in some patients. When this reflex response is inhibited by beta-blockers or centrally active agents, the antihypertensive response is potentiated. Hydralazine is not removed by dialysis. Acute parenteral administration of hydralazine may be particularly effective in treating hypertension associated with acute glomerulonephritis. This may be a consequence of the increased renal blood flow that attends acute administration. Side effects of hydralazine include: nausea and vomiting: this may be a problem when large doses are employed at the start of therapy (we begin with a dose of 40 mg/day with successive increments at intervals of 2–3 days; drug-induced lupus syndrome: most frequently seen with daily doses exceeding 200 mg; neuropathy due to pyridoxine deficiency (infrequent).

Prazosin decreases total peripheral vascular resistance primarily as a result of its blockade of peripheral alpha-adrenergic receptors. Because this blockade is relatively specific for the post-synaptic vascular receptors (α_1), the unopposed stimulation of the pre-synaptic neuronal receptors (α_2) limits norepinephrine release during sympathetic firing. This indirect inhibition of adrenergic neuron activity may prevent reflex increases in cardiac output in response to prazosin, and thereby potentiates its antihypertensive effect. Plasma prazosin levels are not affected by dialysis. A small proportion of patients receiving prazosin may experience transient severe orthostatic hypotension upon receiving the first dose. Therefore, prazosin therapy should be initiated with the smallest dose size available. The first dose should be administered either under observation in the physician's office, or upon retiring in the evening. Patients with renal insufficiency have been noted to be particularly sensitive to the hypotensive effect of prazosin.

Minoxidil is a potent vasodilator which acts directly on arteriolar smooth muscle by an unknown mechanism. It may be useful in control of hypertension refractory to conventional medications. Because it elicits a hemodynamic reflex response similar to hydralazine, minoxidil must be combined with adequate doses of a beta-adrenergic blocking drug [29]. In addition, large doses of furosemide are typically required to counteract sodium and water retention that attends its use in patients with preserved renal function. Hirsutism is a side effect that may be particularly troublesome in females.

5.5. Parenteral drugs for hypertensive emergencies

A discussion of the pathogenesis and treatment of malignant hypertension is beyond the scope of this chapter, but has been the subject of

recent reviews [20]. A hypertensive emergency exists when severe high blood pressure is accompanied by one or more of the following: hypertensive encephalopathy, intracranical hemorrhage, left ventricular failure, dissecting aortic aneurysm. An immediate reduction in blood pressure is mandatory. In addition, the patient with sustained diastolic blood pressure above 140 mm Hg is at risk of serious cardiovascular morbidity and should receive prompt therapy. Accelerated hypertension may be associated with a decrease in GFR, which may decline further with hypotensive therapy. Dialysis may be necessary. Nevertheless, sustained therapeutic blood pressure reduction may promote 'healing' of the renal vascular changes of malignant nephrosclerosis. Renal function may slowly improve, sufficient to support life without dialysis. For this reason, aggressive pharmacologic antihypertensive therapy should be undertaken in seriously hypertensive patients, even though their renal function appears to be 'end stage'.

Patients with chronic renal insufficiency appear to be quite sensitive to the hypotensive effect of intravenous diazoxide. This may be a consequence of decreased protein binding of the drug in renal failure. With this in mind, we initiate treatment with a bolus of 75–150 mg injected rapidly, instead of the 300 mg prescribed for patients with normal renal function. The initial dose may be repeated at 5–10 minute intervals two or three times if necessary. As a direct-acting arteriolar vasodilator, diazoxide elicits reflex tachycardia and increases in cardiac ouput. This may be deleterious in patients with coronary insufficiency. In addition, abrupt reduction of elevated blood pressure to normal may precipitate coronary and cerebrovascular insufficiency in predisposed patients. Diazoxide is cleared by hemodialysis.

Nitroprusside can produce a more controlled reduction in blood pressure. Cyanide, a byproduct of nitroprusside degradation in vivo, is metabolized to thiocyanate. Thiocyanate accumulates in patients with reduced renal function. Thiocyanate toxicity may be manifested as anorexia, nausea, vomiting, myoclonus, convulsions, psychosis, hypothyroidism. Toxicity is especially prevalent at plasma thiocyanate levels above 10 mg/100 ml. Nitroprusside should not be used for longer than 48 hours in patients with renal insufficiency. If such use is necessary, plasma thiocyanate levels should be measured. Thiocyanate is dialysable.

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13. DIVALENT ION METABOLISM AND RENAL OSTEODYSTROPHY

DAVID S. DAVID

1. INTRODUCTION

Disordered divalent ion metabolism in renal failure contributes to many of the signs and symptoms of uremia [7]. There are three major hormones that regulate calcium and phosphorus homeostasis. These are parathormone, Vitamin D and calcitonin. Parathormone helps to maintain ionized serum calcium by increasing bone resorption, increasing renal tubular reabsorption of calcium and increasing renal excretion of phosphorus. Parathormone is also essential for normal bone formation and remodelling. Vitamin D and its active metabolites help to maintain both the serum calcium and phosphorus levels by increasing their intestinal and renal absorption. Vitamin D may also be essential for normal feedback inhibition of parathormone secretion, muscle function and bone formation and resorption. The functional role of calcitonin in man has not been fully defined, but it acts to antagonize the effects of Vitamin D on the intestine and the kidney, thus leading to a decrease in intestinal absorption of calcium and to an increase in urinary losses of calcium and phosphorus. It also antagonizes the effects of parathormone and Vitamin D on bone and leads to a decrease in bone formation and resorption.

2. METABOLISM OF VITAMIN D

The metabolism of Vitamin D is now thought to involve 25 hydroxylation in the liver to form 25-hydroxycholecalciferol (25 Vit D) which is the main circulating form of the vitamin. The 25 Vit D is further hydroxylated in the kidney to form 1,25 dihydroxycholecalciferol (1,25 Vit D) or 24,25 dihydroxycholecalciferol (24,25 Vit D). Although 1,25 Vit D is synthesized exclusively by the kidney, there is a possibility that some 24,25 Vit D may be formed elsewhere as well. The 1,25 Vit D is the main active hormone accounting for the intestinal and bone effects

of Vitamin D. Parathormone appears to increase the synthesis of 1,25 Vit D by the kidney, possibly through its effect on the kidney and serum phosphorus. The 24,25 Vit D was initially thought to be inactive, but recent work suggests that this compound or one of its metabolites may possess significant Vitamin D activity [11]. Knowledge of these major Vitamin D metabolites is still far from complete.

3. PATHOGENESIS OF ABNORMALITIES IN DIVALENT ION METABOLISM IN CHRONIC RENAL FAILURE

3.1. Phosphate retention

Phosphate retention appears to be the major stimulus to secondary hyperparathyroidism seen in patients with renal failure [19]. In mild renal failure, while there is still enough residual renal function to respond to the phosphaturic effect of parathormone, the serum phosphorus may be normal. However, in advanced renal failure, hyperphosphatemia is almost always present. The presence and severity of associated hypocalcemia depend in part on the severity and duration of hyperphosphatemia and the degree of compensatory parathyroid hyperplasia.

3.2. Bone resistance to the calcemic effect of parathormone

Patients with renal failure have skeletal resistance to the calcemic effect of both endogenous and exogenous parathormone. This skeletal resistance also contributes to secondary hyperparathyroidism but its mechanism remains controversial.

3.3. Abnormalities in Vitamin D metabolism

As renal failure progresses, renal synthesis of 1,25 Vit D decreases. This decrease results from both a reduction in functional renal mass and from the effect of hyperphosphatemia in inhibiting 1,25 Vit D production. The decrease in 1,25 Vit D synthesis further aggravates secondary hyperparathyroidism by decreasing intestinal absorption of calcium, further increasing skeletal resistance to parathormone, and possibly by preventing the normal feedback inhibition of parathormone by Vitamin D. Numerous other factors, including calcitonin, magnesium, acidosis, underlying disease, age and sex, may also contribute to the abnormalities in bone and mineral metabolism in renal failure.

4. CLINICAL CONSEQUENCES OF ABNORMAL CALCIUM AND PHOSPHATE METABOLISM

The effects of abnormal calcium and phosphate metabolism on patients with renal failure can be divided into two major categories, skeletal (renal osteodystrophy) and non-skeletal complications.

Table 1. Skeletal lesions in renal disease.

Type	Contributing Factors
Osteitis fibrosa	Secondary hyperparathyroidism
Osteomalacia	Dietary or actinic Vit D deficiency Specific disease states (nephrotics, renal tubular defects) Drugs (anticonvulsants, phosphate binders) Fluoride or other toxins in water ? low parathyroid hormone and high calcitonin
Osteosclerosis	Second hyperparathyroidism and hyperphosphatemia
Osteoporosis	Dietary protein restriction Negative calcium balance Toxins in water Age and sex Drugs Underlying disease
Retarded growth in children	Diet 1,25 Vit D_3 deficiency Drugs (anticonvulsants, corticosteroids)

4.1. Skeletal abnormalities (Table 1)

4.1.1. Osteitis fibrosa

Osteitis fibrosa is the most common skeletal lesion found in patients with renal failure. The increased bone resorption and bone turnover most frequently seen in phalangeal bones and distal clavicles, results from secondary hyperparathyroidism.

4.1.2. Osteomalacia

The reported incidence of this abnormality in bone mineralization is much higher in Europe than in the United States, suggesting that it is not due solely to the effect of diminished production of 1,25 Vit D by the kidney. There are several factors that may contribute to the osteomalacia. A relative deficiency in dietary or actinic Vitamin D intake may explain some of the geographical differences in the frequency of

this skeletal lesion. Certain disease states, such as nephrotic syndrome and renal tubular disorders, may contribute to osteomalacia. Osteomalacia may occur in nephrotic patients secondary to large losses of protein-bound Vitamin D and 25 Vit D in the urine [1]. Severe acidosis accompanying some renal tubular disorders may also cause this lesion [13, 17]. In the proximal tubular disorders, abnormal production of 1,25 Vit D and chronic hypophosphatemia may contribute to osteomalacia. Chronic hypophosphatemia, whether due to phosphate-binding antacids or decreased intestinal absorption of phosphorus, can cause osteomalacia. Anticonvulsant drugs interfere with Vitamin D metabolism and lead to osteomalacia [10]. Fluoride or other elements and toxins in water may contribute to osteomalacia in some dialysis patients. A very small subgroup of dialysis patients have been noted to have almost 'pure' osteomalacia and a severely depressed bone turnover [6]. They have severe bone pain with normal or elevated serum calcium and only slightly elevated serum parathormone. Their parathyroid glands show minimal hyperplasia. These patients are usually refractory to all present forms of therapy. This syndrome is sometimes also seen in patients after subtotal parathyroidectomy [6]. Although the mechanism is not known, it is possible that this is due to a low parathormone to calcitonin ratio.

4.1.3. Osteosclerosis

An increase in total mass of cancellous bone occurs in some patients with renal failure, due to a combination of secondary hyperparathyroidism and hyperphosphatemia.

4.1.4. Osteoporosis

A decrease in total bone mass was rarely seen in patients with untreated renal failure in the past, but several factors in the modern therapy of uremia may contribute to an increased incidence of this lesion. Severe dietary protein restriction may lead to osteoporosis by at least two mechanisms: negative nitrogen balance and low calcium content of restricted diets. The upsurge of osteoporosis in patients in the early days of hemodialysis was probably due to a negative calcium balance associated with the use of dialysates having only 2.5 mEq/l of calcium. In certain localities, however, it was due to toxins in the main water supply. Since older patients with markedly curtailed activity are also being dialyzed, more involutional and post-menopausal osteoporosis is now being recognized. The common use of corticosteroids in many immunological renal diseases has also contributed to an increase in

osteoporosis. The use of heparin in hemodialysis may also play some role in dialysis osteoporosis. Underlying systemic diseases such as diabetes mellitus may be associated with osteoporosis, irrespective of renal involvement.

4.1.5. Retarded growth in children

Children with renal disease may develop these same skeletal abnormalities. However, these lesions are much more devastating in growing children. Osteomalacia and secondary hyperparathyroidism cause severe bone deformities. The retarded growth of children with renal failure is probably multifactorial. Children require a high intake of protein and calories for growth. If protein intake must be restricted to less than 1 g/kg/day in a child to control uremic symptoms, then the child should be placed on dialysis or transplanted. Recently, the administration of 1,25 Vit D has been shown to improve growth in a uremic child [4]. This therapy, if confirmed by others, holds great promise for the future.

Table 2. Non-skeletal complications of abnormal mineral homeostasis in uremia

1. Hypercalcemia
2. Soft tissue calcification
3. Myopathy
4. Peripheral neuropathy
5. Disorders of the central nervous system
6. Others? (see text)

4.2. Non-skeletal complications (Table 2)

4.2.1. Hypercalcemia

Clinically symptomatic, persistent hypercalcemia may develop in the course of chronic renal failure. There are many iatrogenic causes for this hypercalcemia. These include the use of such drugs as thiazide diuretics, calcium-exchange resins, Vitamin D or calcium supplements (orally or by dialysis) and hypophosphatemia (usually due to phosphate-binding antacids). Prolonged bed rest in these patients can also cause hypercalcemia. Rarer causes, such as hyperthyroidism, Addison's disease, and tumors, must also be considered. However, the most common cause of hypercalcemia in renal failure is severe hyperparathyroidism.

4.2.2. Soft tissue calcifications

Soft tissue calcification, especially involving the vasculature, are common in uremia. They may be asymptomatic, but they also may cause life-threatening disorders. Among the latter are calcifications in the heart causing arrhythmias, in the lungs leading to respiratory insufficiency, and in the vessels of the skin and muscle causing livedo reticularis, necrosis and ulceration of the skin and ischemic myopathy.

4.2.3. Myopathy

Severe proximal myopathy can occur secondary to the abnormal Vitamin D metabolism or to the secondary hyperparathyroidism.

4.2.4. Neuropathy

Secondary hyperparathyroidism may contribute, in part, to the peripheral neuropathy and some of the central nervous system disorders seen in uremia [7, 15].

4.2.5. Miscellaneous

Whether the secondary hyperparathyroidism may in some way also contribute to some of the other signs and symptoms of uremia, *i.e.*, pancreatic abnormalities, impotence, anemia, and hyperlipidemia still requires further documentation [15].

5. MANAGEMENT

5.1. General guidelines for therapy

Up to the present time, the management of the abnormalities in mineral metabolism in chronic renal failure has been corrective rather than preventive. The biochemical indices one monitors are: serum calcium, phosphorus and magnesium, the serum (calcium X phosphorus) solubility product and the serum bone alkaline phosphatase. Newer biochemical assays that, if adequately perfected, may help guide preventive therapy, are parathormone and Vitamin D metabolite blood levels. In addition, the patient's symptoms and signs, including various radiographic techniques must also be closely followed.

5.2. Control of phosphorus

Control of serum phosphorus is achieved through dietary restriction and phosphate-binding antacids. However, to avoid negative nitrogen bal-

ance, protein restriction should not be less than 0.6 g/kg/24 hours in an adult or 1 g/kg/24 hours in children. The general problems with currently available phosphate-binding antacids are their relative unpalatibility, their tendency to constipate, and the fear that the aluminum they contain may contribute to dialysis dementia.

Although it is easy to guide control of phosphorus therapy when clinical hyperphosphatemia is present, the difficulty lies in the therapy of patients with mild renal failure who have normal serum phosphorus but elevated parathormone levels. Proper management of these patients requires parathormone determinations.

During therapy, it is important to avoid development of hypophosphatemia. Hypophosphatemia in patients with severe hyperparathyroidism can cause hypercalcemia, and, if chronic, may lead to osteomalacia.

5.3. Vitamin D therapy

Vitamin D therapy in renal failure is usually used only in patients with overt osteomalacia, hypocalcemia with a normal or low serum phosphorus (especially post subtotal parathyroidectomy), and in children with severe bone disease. However, with the recent advances in the knowledge of Vitamin D metabolism, the ability to measure blood levels of the active Vitamin D metabolites, and the availability of 1,25 Vit D (Rocaltrol®), these indications will probably be broadened.

They may include:

A. Normocalcemic patients with advanced renal failure and predominant hyperparathyroidism, in an attempt to control or reverse secondary hyperparathyroidism.

B. Patients with moderate renal failure in whom the only detectable abnormality is an elevated serum parathormone, in an attempt to prevent the development of severe secondary hyperparathyroidism.

C. Certain patients with kidney disease but without renal failure in whom Vitamin D metabolism may be abnormal such as patients with nephrotic syndrome, patients with proximal renal tubular defects, and those receiving anticonvulsants or corticosteroids [1, 3, 10]. Therapy in these conditions is at present limited by the unreliability and unavailability of parathormone and Vitamin D metabolite determinations.

Since injudicious use of Vitamin D therapy can cause many problems, including deterioration of renal function [5], the use of any analogue of Vitamin D in patients with renal disease should be closely

monitored. With few exceptions, no Vitamin D analogue should be started before the serum phosphorus is decreased below 6 mg%. The serum calcium, corrected for serum albumin, should not be allowed to consistently exceed 11 mg%, and the (calcium X phosphorus) solubility product should not exceed 65.

The dose of Vitamin D analogue should be started at the lowest dose recommended for patients with renal failure and not increased more frequently than every 1–2 months. The starting dose for dihydrotachysterol is 0.2 mg a day and for 1,25 Vit D (Rocaltrol®) 0.25 mcg a day.

The parameters to follow for a therapeutic effect are a change in serum calcium, phosphorus, bone alkaline phosphatase, parathormone, Vitamin D metabolites, patient's symptoms, and other clinical findings, including bone X-rays, osteodensinometry and bone biopsies. If there is improvement in any of these, the same dose of Vitamin D should be continued, even if serum calcium levels have not increased.

When therapeutic doses of Vitamin D are employed, the elemental calcium in the diet (including oral calcium supplements) should not exceed 1 g/24 hours. Also, the dialysate calcium should not exceed 3–3.25 mEq/l. The only exception to this is in patients following subtotal parathyroidectomy who may require massive doses of supplemental calcium initially to prevent severe hypocalcemia.

Patients not treated with dialysis who have an indication for Vitamin D therapy must have their renal function measured frequently for evidence of accelerated renal insufficiency secondary to hypercalcemia. At present, Vitamin D therapy should not be used routinely for prophylaxis in non-dialyzed patients.

5.4. Calcium supplementation

Calcium supplementation for uremics may be given in two forms, by diet and via dialysis.

5.4.1. Dietary calcium

Because 1,25 Vit D production is deficient in renal failure, intestinal absorption of calcium is diminished. This situation is aggravated by the low calcium content of restricted diets. To prevent the negative calcium balance which might occur in some patients, dietary calcium supplementation of 1–2 g of elemental calcium per day has been necessary in the past. However, with the ready availability of 1,25 Vit D and the demonstration that Vitamin D metabolites tend to decrease secondary hyperparathyroidism more than calcium supplementation alone, the die-

tary intake of calcium must be reevaluated. The daily oral calcium intake of most patients on therapeutic doses of dihydrotachysterol or 1,25 Vit D should be between 400–800 mg per day. This is to prevent excessive calcium absorption.

5.4.2. Dialysate calcium

A dialysate calcium of 3–3.5 mEq/l is required to prevent a negative calcium balance during dialysis. The use of dialysate calcium concentrations of 3.5–4 mEq/l induces positive calcium balance during dialysis. Most dialysis centers use a dialysate calcium concentration of 3.5 mEq/l. However, dialysate calcium concentration in most patients receiving 1,25 Vit D should remain between 3.25–3.5 mEq/l.

5.5. Other medical therapy

Control of chronic acidosis ($pH < 7.3$) in children improves osteomalacia [13, 17]. The importance of control of acidosis in adults is controversial.

Hypermagnesemia should be avoided because of its adverse effects on bone mineralization and visceral calcification. Mg-containing antacids and cathartics should be avoided and low Mg dialysates used. However, hypomagnesemia should also be avoided, since it is also detrimental to normal mineral homeostasis.

The content of minerals and other ions and toxins in the central water supply must be measured, especially if patients being dialyzed have an inordinately high incidence of bone disease. Deionizers or the use of distilled water may be necessary in certain localities.

As much physical activity as possible should be encouraged in dialysis patients, since inactivity, especially in patients with severe secondary hyperparathyroidism, leads to accelerated bone resorption.

5.6. Subtotal parathyroidectomy

Subtotal parathyroidectomy should be reserved for patients in whom all medical therapy has failed. Three major indications for subtotal parathyroidectomy are:

A. Significant hypercalcemia that persists for more than 3 months after removal of other causes of hypercalcemia, such as high dialysate calcium, oral calcium supplements, Vitamin D therapy, hypophosphatemia, or immobilization.

B. Progressive, severe secondary hyperparathyroidism with osteodystrophy and/or soft tissue calcification.

C. Ischemic necrosis of skin and muscle (calciphylaxis).

With the exception of the usual surgical complications, there are two serious side-effects of subtotal parathyroidectomy; hypocalcemia and osteomalacia.

Severe hypocalcemia with tetany may occur at any time post-operatively. It may occur much earlier (within the first few hours post-operatively) than in surgery for primary hyperparathyroidism. This is most likely due to the greater bone demineralization in renal failure. The immediate post-operative requirement of calcium may reach as high as 3–4 g of elemental calcium (33–45 ampules containing 10 ml of 10% calcium gluconate) parenterally per 24-hours. Large doses of 1,25 Vit D (as much as 2 micrograms per day) and 2–3 g of oral elemental calcium supplements may be required for several weeks post-operatively. These patients should be dialyzed against a calcium concentration of 4 mEq/l until their serum calcium is stabilized. The serum calcium may have to be measured as frequently as every 4–6 hours in the first 48-hours post-operatively. Tetany may lead to multiple fractures. Occasionally, in some patients, hypocalcemia may be delayed by several days or weeks post-operatively. This is thought to be due to early mobilization of soft-tissue calcium stores that have temporarily maintained the serum calcium.

Rarely, patients, at some time post-subtotal parathyroidectomy, develop severe refractory bone disease, characterized by 'pure' osteomalacia and a low bone turnover state.

One modification in surgical technique that has the potential for decreasing the incidence of post-parathyroidectomy osteomalacia is the autotransplantation of parathyroid tissue into the forearm [20]. With the present technique, about three and one-half to three and seven-eights of the hyperplastic glands are removed. If this happens to be too much, then osteomalacia may develop. If too little is removed or if the remnant becomes hyperplastic, reexploration of the neck may be required. It has been suggested that 3 glands be removed and an estimated 150 mg of the remainig parathyroid gland left in the neck and the remainder autotransplanted to the forearm. Such a maneuver, although leaving too much parathyroid tissue in most patients, may avoid osteomalacia. The residual hyperparathyroidism may be reversed by the medical therapies discussed above. If it cannot be reversed, then more parathyroid tissue can be removed from the forearm.

6. POST-TRANSPLANT MINERAL HOMEOSTASIS

The most common abnormalities in mineral metabolism following successful renal transplantation (serum creatinine <2.0 mg%) are hypercalcemia and hypophosphatemia [8].

Mild hypercalcemia (<12 mg%) occurs at some time following successful transplant in about 30% of patients. It can occur from a few days to as long as several months post-transplant. It probably results from slow involution of hyperplastic parathyroid glands, and is associated with elevated serum parathormone. It is usually asymptomatic and rarely requires any therapy other than correction of the associated hypophosphatemia. Rarely, severe hypercalcemia (>12.5 mg%) may occur in the first post-transplant month. This may be associated with an acute hypercalcemic nephropathy and renal failure mimicking rejection [18]. These patients require emergency subtotal parathyroidectomy.

Hypophosphatemia is noted in about one-third of post-transplant patients. It is usually due to decreased renal tubular reabsorption of phosphorus and to antacid therapy. If the serum phosphorus is below 2 mg%, and especially if associated with hypercalcemia, it should be treated. Therapy consists of oral phosphorus supplements and the use of phosphajel as the antacid.

Almost all the skeletal lesions of renal osteodystrophy improve after successful transplant. The major exception is osteoporosis, which may progress or appear de novo [9]. This is due to corticosteroid therapy. The growth abnormality in children may improve if the dose of corticosteroids can be sufficiently reduced to below 4 mg of Prednisone/m^2 of body surface area. The recent demonstration of the effects of corticosteroids on 1,25 Vit D [3] suggests the possibility that administration of 1,25 Vit D to patients post-transplant may prevent some of these effects of corticosteroids on post-transplant bone disease.

Avascular necrosis may occur post-transplant. This is most likely related to the combined effect of corticosteroids and secondary hyperparathyroidism [7, 15].

7. MINERAL HOMEOSTASIS IN ACUTE RENAL FAILURE

Acute renal failure is usually associated with markedly elevated serum phosphorus and decreased serum calcium. This results from excessive release of phosphate due to hypercatabolism and the lack of adequate

parathyroid hyperplasia. However, Vitamin D and calcium therapy is rarely indicated. Furthermore, if these patients are not taking anything by mouth, phosphate-binding antacids via the naso-gastric tube is only indicated for prevention of gastritis and is of little help in lowering the serum phosphorus. Early dialysis is required because of the marked catabolism usually associated with acute renal failure. Dialysis should be performed against a dialysate calcium of 3.25–3.5 mEq/l. Lowering the serum phosphorus usually raises the serum calcium, so that despite correction of acidosis, tetany does not usually occur during dialysis. However, one must also measure serum Mg, since it may be low and could therefore contribute to development of hypocalcemia and tetany.

Rarely, in the diuretic phase of acute renal failure, hypercalcemia may occur. This is especially likely to occur following acute rhabdomyolysis [12]. The hypercalcemia is usually transient and asymptomatic and does not require any specific therapy. If the hypercalcemia is severe, symptomatic or prolonged, one can use saline diuresis, furosemide or calcitonin for its control.

8. MINERAL REPLACEMENT THERAPY

8.1. Calcium and magnesium

Calcium must often be administered to patients with renal disease, as described above. Table 3 lists the elemental content of calcium in the most commonly used preparations. The intestinal absorption of calcium varies depending on the patients' Vitamin D status and on the calcium preparation being used. For instance, the intestinal absorption of calcium appears to be better from calcium gluconate than from calcium carbonate. Calcium Cl contains 18 mEq of chloride per gram. Large doses or chronic use, especially in patients with even mildly compromised renal function, may lead to the development of hyperchloremic acidosis.

Magnesium supplementation is rarely needed in uncomplicated chronic renal failure patients, except during hyperalimentation.

8.2. Phosphorus

Phosphorus replacement may be required in some renal disorders, such as the Fanconi syndrome, in post-transplant patients and rarely in

Table 3. Content of elemental calcium and magnesium of commonly used replacement preparations.

Calcium

Preparations	Dose	Elemental calcium (mg)
Whole cow's milk (O)	1 ml	1.2
Calcium carbonate (O)	1 g	400
Calcium lactate (O)	1 g	130
Calcium glubionate (O) (Neo-Calglucon®)	1 ml	23
Calcium gluconate (O, IV)	1 g	90
Calcium chloride (O, IV)*	1 g	272

Magnesium

Preparation	Dose	Elemental magnesium	
		(mg)	(mEq)
50% magnesium sulfate (IV)	1 cc	97	4.1

O = oral preparation
IV = intravenous preparation.
g = gram.
* = 1.0 gm of calcium chloride contains 18 mEq of chloride.

chronic renal failure patients, especially during hyperalimentation. Table 4 lists the elemental phosphorus content, as well as the sodium and potassium content, of commercially available phosphate preparations.

Table 4. Content of elemental phosphorus, sodium and potassium of commericially available phosphate preparations.

Preparations	Dose	Elemental phosphorus (mg)	Sodium (mEq)	Potassium (mEq)
Whole cow's milk (O)	1 ml	0.9	.03	.04
Neutra-phos (O)	1 ml	3.3	0.1	0.1
Neutra-phos K (O)	1 ml	3.3	0	0.2
Phospho-soda (O)	1 ml	129	5	0
Na phosphate (IV)	1 ml	93	4	0
K Phos (IV)	1 ml	93	0	4.4

O = oral preparation.
IV = intravenous preparation.

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14. DIALYSIS TREATMENT

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1. INTRODUCTION

Maintenance dialysis as a method of therapy for patients with end-stage renal failure became available in 1960. In that year, Scribner and his colleagues devised a method of maintaining permanent access to the patient's circulation that made maintenance hemodialysis possible. Following the introduction of soft silastic permanent péritoneal catheters by Tenckhoff in 1968 and the development of automated peritoneal dialysis machines in 1970, peritoneal dialysis also became a method of maintenance dialysis therapy. Hemodialysis is the most widely used method of dialysis. In 1979, the population of patients treated with dialysis throughout the United States was approximately 50,000. Of this number, only about 3% were being maintained on peritoneal dialysis. Historically, the majority of patients reaching end-stage renal failure have been started on hemodialysis because of the greater efficiency of the technique and the shorter treatment period involved. However, peritoneal dialysis is the preferred dialysis technique in the following situations: inability to maintain elderly patients on hemodialysis because of unstable cardiovascular status; loss of permanent vascular access; bleeding diathesis; diabetic patients who would do poorly on hemodialysis because of vascular and cardiac disease and severe retinopathy with potential vitreous and retinal hemorrhage.

2. HEMODIALYSIS

2.1. Principles of hemodialysis

2.1.1. Dialyzing membrane

During hemodialysis, solutes are removed from the patient by diffusion from the patient's blood through a semi-permeable membrane into the

dialyzing solution. The most commonly used membrane is cuprophan, which can be manufactured in sheets, coils or hollow fibers. Other materials currently used for dialyzer membranes include cellophane, cellulose acetate, polycarbonate and polyacrylonitrile.

2.1.2. Diffusion of solutes

The effective removal of solutes from the blood depends on the pore size of the membrane, surface area of the membrane in contact with blood as it flows through the dialyzer, and the concentration gradient of the solute between blood and dialyzing fluid. In general, the smaller the molecular weight of the solute, the more efficient the diffusion through the membrane. Proteins or substances bound to protein do not pass through the membrane.

2.1.3. Blood flow

A blood pump is required to propel the patient's blood through the dialyzer. The greater the blood flow through the dialyzer, the more efficient the clearance of low molecular weight solutes. In general, the most practically efficient blood flows during dialysis are 250–350 ml/min.

2.1.4. Ultrafiltration and transmembrane pressure

Ultrafiltration during dialysis refers to the removal of fluid from the blood as it passes through the dialyzer. This may be accomplished by exerting hydrostatic pressure on the blood passing through the dialysis membrane. The volume of fluid transferred from the blood through the membrane is directly proportional to the amount of transmembrane pressure exerted. This pressure is the sum of the positive pressure (resistance to blood leaving the dialyzer) and negative pressure (partial vacuum created on the dialysate side of the membrane).

2.1.5. Dialyzing fluid

The dialyzing fluid is an aqueous solution of electrolytes similar to that of normal extracellular fluid. The composition of the fluid is variable but usually consists of: Sodium 135 mEq/l, Potassium 0–2 mEq/l, Calcium 3.5 mEq/l, Magnesium 1.5 mEq/l, Chloride 104 mEq/l, acetate 38 mEq/l. Since the dialyzing fluid contains none of the solutes that accumulate in uremia, there is a steep concentration gradient from blood to dialysate, allowing the transfer of these substances into the dialysate. Acetate is metabolized to bicarbonate and corrects acidosis.

2.2. Indications for dialysis

2.2.1. Uremic symptoms

The clinical state of the patient with chronic renal failure is the main guide to when dialysis is required. Nausea, vomiting, anorexia, lethargy, pruritus, and fatigue are strong indications that the patient requires dialysis. Progressive peripheral neuropathy, pericarditis and severe acidosis are absolute indications for dialysis.

2.2.2. Overhydration

The presence of intractable peripheral edema, unresponsive to high doses of potent diuretics such as furosemide, is another indication for dialysis. While digitalis may aid in managing the patient in congestive heart failure with uremia, no lasting benefit will occur if the diseased kidneys are unable to increase the urine volume.

2.2.3. Residual renal function

When the glomerular filtration rate falls to a level of 5–6 ml/min, most patients will require hemodialysis. This usually corresponds to a serum creatinine of 10–12 mg% and a BUN of 100–150 mg%. Nonetheless, one should not establish a limit or a level of creatinine, or urea that must be reached before dialysis is instituted. Older patients, diabetics, and patients with colagen vascular diseases often require dialysis before their blood chemistries reach these levels.

2.2.4. When to create vascular access

Patients with chronic renal disease should have vascular access created when their renal function reaches a creatinine clearance of 10–15 ml/min. This enables the arterio-venous fistula to mature (with dilatation of the veins to facilitate needle puncture) over a period of months.

2.3. Type of dialyzer

2.3.1. Coil

The most common disposable dialyzer is a coil dialyzer. This consists of a long tube of cuprophan wrapped tightly around a plastic core with plastic mesh separating the coils of membrane. The surface area may vary from 0.6–1.2 m^2. Coil dialyzers are immersed in the dialyzing fluid, usually in a tank or canister.

2.3.2. *Parallel plate*
This dialyzer consists of narrow sheets of cuprophan pressed tightly between thin layers of plastic. The dialyzing fluid enters this closed dialyzer and flows counter-current to the blood flow. This is a 'negative pressure' dialyzer. This refers to the reduced or 'negative pressure' which is created on the dialysate side of the membrane. This is the method of producing ultrafiltration in this dialyzer. The surface area of these dialyzers varies from 0.4–2.0 m^2. The smallest of these dialyzers are useful for performing hemodialysis on infants or very small children.

2.3.3. Hollow fiber
Hollow fiber dialyzers consist of 10,000–15,000 thin hollow fibers (200 micron in diameter) enclosed in a tight casing and are prepared from cuprophan or cellulose acetate. Blood volume of the dialyzer is usually less than 150 ml. Surface area can be varied from 0.6 m^2 to 2.5 m^2, depending on the clinical needs of the patient. These fibers have very low compliance and the interdynamic blood volume does not change appreciably during dialysis.

2.4. Fluid delivery systems

2.4.1. Recirculating dialysis fluid
In this system, all of the dialysis fluid in a 100 liter bath is continuously recirculated around the coil dialyzer that is immersed in the dialysis fluid. The bath may be changed during the dialysis procedure if desired.

2.4.2. Recirculating-single pass system
This method of fluid delivery allows some fresh dialyzing fluid to enter the dialyzing cannister throughout the dialysis procedure, usually at a rate of 500 ml/min. At the same time a similar volume of 'used' dialysate leaves the cannister. This system is slightly more efficient than the recirculating bath.

2.4.3. Single pass fluid delivery
This fluid delivery system combines a dialysate concentrate mixed with tap water within the machine and pumped through the dialyzer for only a single pass across the dialyzing membrane. This creates a continuous, optimum gradient for the removal of solutes from the blood.

2.5. Acute problems during dialysis treatment

2.5.1. Hypotension

During hemodialysis, because of ultrafiltration, the blood pressure usually declines gradually. However, sudden drops in blood pressure should be provided or corrected. Some of the causes of such hypotension are:

1) Excessive fluid removal due to a high level of ultrafiltration: Treatment consists of reducing the transmembrane pressure (which lowers the ultrafiltration rate), laying the patient flat in the chair or bed, and administering physiologic saline as required to adjust the blood pressure. Occasionally an infusion of salt-poor albumin may be useful in correcting persistent hypotension secondary to volume depletion.

2) Secondary to antihypertensive medications such as alpha-methyldopa or hydralazine. This may sometimes be alleviated by withholding short acting antihypertensive drugs within 6 hours before dialysis is scheduled.

3) Rupture of the dialysis membrane resulting in sudden blood loss or internal hemorrhage: Immediate cessation of dialysis and replacement of fluid and/or blood is required.

4) Autonomic neuropathy (amyloidosis, diabetes mellitus).

2.5.2. Arrhythmias

Occasionally, near the end of dialysis, various arrhythmias (atrial fibrillation; flutter or premature ventricular contractions) may occur. This is often related to atherosclerotic heart disease in these patients. It may be precipitated by hypokalemia because of a low potassium concentration in the dialysate. This can be corrected by raising the dialysate potassium to 2.5 or 3.0 mEq/l. Patients receiving digitalis preparations may experience sudden arrhythmias if dialyzed against low potassium dialysate.

2.5.3. Cramps

The rapid removal of fluid during dialysis may provoke severe leg and abdominal cramps. Low sodium concentrations in the dialysate may also cause cramping. By adjusting the ultrafiltration rate to a low level and with the cautious use of hypertonic saline, the cramps can be eliminated. In general, the use of dialysate sodium concentrations of 135–140 mEq/l will ensure more comfortable dialyses for the patients.

2.5.4. Chest pain

Hypotension may produce chest pain during dialysis, resembling angina, that quickly abates with restoration of normal blood pressure. Occasion-

ally, the rapid flow of blood into the dialyzer may produce chest pain. This is treated by simply slowing the blood pump. However, some patients experience persistent chest pain. If the above maneuvers do not eliminate the chest pain within 10–15 minutes, the dialysis should be terminated and the patient evaluated for possible myocardial damage.

2.5.5. Dialysis disequilibrium

This syndrome is manifested during dialysis by increasing headache, rising blood pressure, anxiety, occasional blurred vision, nausea, and may produce seizures. It appears to be related to rapid changes of urea, electrolyte concentrations and pH changes in the peripheral blood during dialysis that are not reflected in the central nervous system tissue because of the blood brain barrier. It may be prevented by dializing the patient slowly (slow blood pump setting) and for frequent but short periods (2 1/2–3 hrs) during the initial stages of hemodialysis treatment. If a high level of blood urea nitrogen is present (>200 mg/dl), great care should be taken to assure a slow and gradual dialysis. Small amounts of diazepam (Valium®) intravenously (2.5–5 mg) are often helpful in irritable and severely uremic patients undergoing their first hemodialysis to prevent seizures.

2.5.6. Heparinization

Heparin is required to prevent clotting of the blood in the dialyzer. Clotting times should be done on each new patient to determine the minimal amount required for a dialysis. In general, when heparin is given as a bolus, approximately 100 units of heparin per kilogram of body weight is required at the start of dialysis with about 1000–2000 units required in the third or fourth hour. When a heparin pump is used, 2000 units at the start of dialysis and 750–1500 units per hour are usually sufficient to prevent clotting. The dose of heparin should be reduced to low levels and clotting times monitored when an unusual situation occurs, such as gastrointestinal bleeding, bleeding from tooth extraction, menstrual periods or recent surgery. Heparin requirements may change when a patient is switched from a coil or plate dialyzer to a hollow fiber dialyzer.

2.5.7. Pruritus

Pruritus is one of the most troubling symptoms in the dialysis patient. The cause is usually obscure and the various treatments proposed are of limited value. The use of oral diphenhydramine HCl (Benadryl®)

(25–50 mg) may produce some relief but seldom eliminates the itching. The use of intravenous lidocaine (100 mg of lidocaine in 100 ml of saline) has produced relief in many patients during dialysis. Rarely, a patient may be allergic to the heparin and switching from beef to pork heparin (or vice versa) may be of help. Patients tend to be more comfortable and have less pruritus when the room is cooler, but this is an individual reaction.

2.5.8. Seizures

In general, seizures are uncommon during hemodialysis. However, some patients demonstrate seizure activity when their blood pressure drops suddenly during dialysis. These are usually limited in duration to 10–30 seconds and disappear with restoration of blood pressure. There are seldom any sequelae and the patients do not become incontinent. This may be prevented by administering small amounts of saline on an hourly basis during dialysis to prevent drastic falls in blood pressure. These patients do not require long-term anticonvulsant medications. Some dialysis patients do have an irritable focus in the central nervous system and may have occasional seizures during dialysis. These patients should have a thorough neurological evaluation to rule out possible subdural hematomas. In most cases, however, the seizure disorder is idiopathic and patients respond quite well to conventional anticonvulsant medications.

2.5.9. Dialysis accidents

During hemodialysis, serious complications can occur as a result of accidents.

Lack of salts in the dialysate: This produces immediate hemolysis and is manifested in the patient by cramps, hypotension, anxiety, and chest pain. It is fatal if not immediately noticed and the dialysis terminated. The blood remaining in the dialyzer should be discarded and the patient transfused as soon as blood can be obtained. The patient may require dialysis within a few hours because of hyperkalemia resulting from potassium released by the hemolyzed blood. Most fluid delivery systems now have conductivity meters that prevent this problem. However, 100 l batch type tanks do not have such a meter and these dialysate baths should be tested with a hand meter.

Concentrated dialysate: This occurs when a double dose of dialysate concentrate is placed by error in 100 l tank, and results in a dialysate concentration of sodium in excess of 260 mEq/l. Patients dialyzed against this fluid experience cramps, extreme thirst, hypertension fol-

lowed by hypotension and a general feeling of uneasiness. If discovered within 15–30 minutes, there is seldom any lasting neurological damage. But if a longer period of time elapses, irreversible brain damage may occur due to intracranial hemorrhage. The dialysis should be immediately stopped. A new dialysis bath should be mixed and the sodium concentration adjusted to about 145–150 mEq/l. The patient should be dialyzed against this new bath for 1–2 hours. The bath should be then changed again for the remainder of the dialysis to the normal dialysate concentration.

Air embolus: Because of a leak in the blood tubing or because of the entry of air through the intravenous side-arm, air may enter the patient. This can also occur from excessive amounts of foam which may not be detected by the air detector alarm. For this reason, the venous bubble catcher should always be observed. In the event of an embolus, the dialysis should be immediately terminated and the patient turned on his left side.

Fever and chills: These may indicate a leak in the dialyzer or an infection in the area of the fistula, especially if they occur only after dialysis is started. Careful examination of the dialyzer for leaks and the area of the fistula for infection should be performed. Blood cultures should be drawn immediately from the blood lines.

2.6. Chronic problems in hemodialysis

2.6.1. Hypertension

This remains one of the major problems in maintenance hemodialysis. The majority of dialysis patients have some degree of hypertension. This may be controlled by dialysis with ultrafiltration and dietary sodium restriction in the majority of patients (volume dependent hypertension). Approximately 15–20% of dialysis patients with hypertension are refractory to ultrafiltration alone and require some antihypertensive medications (renin dependent hypertension). The most common medications are alphamethyldopa, propranolol, hydralazine, prazocin, metaprolol tartrate and clonidine. Because of the danger of sudden hypotension during the dialysis procedure, alphamethyldopa and hydralazine should be withheld within 4 to 6 hours before hemodialysis.

A small percentage of patients remain refractory to all methods of blood pressure control and become candidates for bilateral nephrectomy. This becomes necessary when patients, despite being maintained at their dry weight and receiving large doses of antihypertensive medications, still have persistent diastolic blood pressures of over 115 mm Hg.

In general, if these patients are not nephrectomized, they often develop cardiac hypertrophy, angina, and congestive heart failure.

2.6.2. Anemia

With few exceptions, most maintenance dialysis patients have some degree of anemia. After a short time on dialysis, patients stabilize their hematocrits to 18–21%, or occasionally higher. The shortened life span of red blood cells in the uremic individual as well as bone marrow depression induced by uremic toxins and decreased production of erythropoietin from the kidney contributes to this anemia. There is a small (5–10 ml) but regular loss of blood following each dialysis because of residual blood remaining in the dialyzer.

Treatment of the anemia includes oral or intravenous iron whenever the serum iron or ferritin levels indicate iron deficiency. The use of weekly nandrolonedecanoate (Deca-durabolin®) or testosterone enanthate intramuscularly in dialysis patients may elevate the hematocrit into the 26–34% range.

Transfusions of fresh packed red cells should be used whenever indicated, especially in patients over the age of 50 years. Other indications for transfusion include severe dyspnea on exertion, chest pain, and tachycardia after slight exertion.

2.6.3. Renal osteodystrophy

See details in Chapter 13.

2.6.4. Peripheral neuropathy

Uremia may cause demyelinization of peripheral nerves in patients prior to the start of hemodialysis. The peripheral neuropathy is characterized by paresthesia, foot drop, and a marked slowing of nerve conduction velocity. This can be reversed by intensive hemodialysis. The frequency of dialysis must be increased to 4 or 5 times a week or the time of dialysis must be increased to as much as 6 hours per treatment.

2.6.5. Central nervous system

Subdural hematomas: Because of the increased tendency of bleeding as well as the intermittent heparin required during dialysis, patients are at risk to develop subdural hematomas, even without trauma to the head. Sudden changes in personality, bizzare neurological signs, sudden development of persistent headaches, and gait disturbances should alert the physician to the possibility of a subdural hemorrhage. After craniotomy

for a hematoma, the patient should be placed on peritoneal dialysis for at least 2 weeks in order to avoid heparinization.

Dialysis encephalopathy (dialysis dementia): This is a rare but distinct clinical syndrome seen in long-term dialysis patients, characterized by speech disturbances, dementia, facial grimacing, myoclonus, asterixis and convulsion. Once developed, it usually progresses relentlessly, although a few patients have recovered. The EEG changes in this syndrome are also distinctive and consist of diffuse multifocal slow (delta) waves interrupted by bilaterally synchronous, high voltage complexes. The etiology of the encephalopathy appears to be excessive amounts of aluminum in the dialysate. The use of reverse osmosis or deionization techniques may prevent this problem. There is no known effective treatment of dialysis encephalopathy once it develops.

2.6.6. Pericarditis and pericardial effusion

Uremic pericarditis may appear prior to starting a patient on a dialysis treatment. This type of pericarditis usually responds to dialysis. A second type of pericarditis occasionally develops in patients on chronic maintenance dialysis. This type appears to be related to prior infections or other complications. In some patients, the pericarditis may not only progress but also be complicated by pericardial effusion, despite intensified dialysis. This may be diagnosed with the use of echocardiography when the patient develops an enlarged cardiac silhouette on chest X-ray. While the effusion occasionally disappears with daily hemodialysis, in the majority of cases the pericardial effusion slowly becomes more extensive and compromises the patient's cardiac output. These patients require immediate pericardiectomy. Occasionally, with varying success, pericardial effusions in dialyzed patients have been treated with instillation of non-absorbable steroids or air into the pericardial sac. The use of repeated pericardiocentesis has also been reported to be helpful in managing this complication.

2.6.7. Heart disease

The greatest cause of morbidity and mortality in dialysis patients is related to cardiovascular and cerebrovascular disease. Patients receiving dialysis for a period of years appear to have accelerated atherosclerosis. This may be related to prolonged hypertension as well as lipid abnormalities. The contribution of vascular calcification to heart disease secondary to secondary hyperparathyroidism has not been completely evaluated.

Congestive heart failure may appear in patients who have been on

dialysis for many years and this is an ominous sign. These patients may require digitalis and their hematocrits should be maintained between 25–30%. It is essential that they be maintained as close to their dry weight as possible.

2.6.8. Overhydration

Overhydration remains a serious problem in patients who are unable to limit the amount of fluid they gain between dialysis. The removal of more than 4 kg during dialysis usually results in an uncomfortable dialysis for the patient. Treatment of chronic overhydation includes a careful review of the patient's diet and an increased amount of ultrafiltration during dialysis. In selected patients, an increase in the frequency of dialysis to every other day until the patient reaches his dry weight may be beneficial. The use of ultrafiltration without dialysis should be considered in patients who develop hypotension during the early part of their dialysis (sequential dialysis).

2.6.9. Hepatitis

Serum hepatitis remains an ever present problem in patients on hemodialysis. Because of the continued need of transfusion in some patients as well as the persistance of the hepatitis antigen in many patients who have had serum hepatitis, the potential for new cases of hepatitis is always present. The ideal method of preventing hepatitis is to segregate positive and negative patients in separate units. If this is not possible, then machines should be designated for use with only hepatitis antigen positive or negative patients to reduce the risk of contamination. Patients with elevated levels of antibodies against the Hepatitis B virus may also be dialyzed on those machines designated for hepatitis antigen-positive patients.

Careful attention by the dialysis staff to technique is essential in reducing the incidence of hepatitis. Gloves should be used by all staff when performing any function around a patient that could produce contact with the hepatitis antigen. The gloves should then be removed when other tasks are to be performed. Separate blood pressure cuffs, chairs, sinks, and eating utensils should be used. Patients should be warned that they should use these same precautions at home to protect their family.

In staff members who stick themselves with a contaminated needle, the use of hyperimmune gamma globulin is recommended. A new hepatitis vaccine is currently being evaluated in dialysis patients and staff.

2.7. Options in types of hemodialysis

A dialysis center should be able to provide various options such as full care, self care or home dialysis. The full care unit provides total care for the patient who cannot become involved in his or her care. The self care unit allows the patient to be involved with his regular dialysis treatments, including needle puncture, monitoring of dialysis, fluid administration and termination of dialysis. These patients also participate in active discussion of their chemistries and the evaluation of their course on dialysis.

From self care dialysis, it is a small step to home dialysis. This is the ideal form of dialysis, allowing the patient to maintain considerable control over his treatment and to fit dialyses into his life activities. It also reduces contact with hepatitis virus. In operating a successful home program, it is essential to have close communication between the patient and the center staff of physicians and nurses. This reassures the home patient that, although they are relatively independent, they have a close bond to the center for follow-up care and in case of any emergencies. All home patients should be seen every 4–6 weeks to evaluate their course of dialysis.

In the training of home dialysis patients, it is essential that the training be done by a small selected team of nurses, so that the patient is not confused by different teaching techniques. The training area should be separated from other areas of the dialysis center. The training should be regulated and guided by the ability of the patient learning the technique. While considerable time is devoted to teaching the patient, the partner also is carefully instructed in dialysis techniques.

Home dialysis should make treatments easier, more comfortable and less stressful for the patient and his family. If it creates difficulties for the patient and his family, then the patient would perhaps be better handled in self or full care facilities.

2.8. General management of hemodialysis patients

Dialysis should be instituted when the creatinine clearance is less than 4–7 ml/min and the patient develops uremic symptoms. Assuming that the arterio-venous fistula has been created previously, the first 2–3 dialyses should be brief and at low blood flow rates. The frequency of dialysis should be at least twice a week and ideally, three times a week. This allows better control of the uremic syndrome and blood chemistries and prevents the accumulation of excessive amounts of fluid.

The amount of dialysis should be individualized. Various formulas have been proposed to accomplish this. Since products of protein catabolism appear to be important in the development of the uremic syndrome, Gotch and Sargent proposed a definition of minimal acceptable dialysis therapy based on the removal of a constant load of the easily measurable end-product of such metabolites as urea. According to Gotch and Sargent, the minimum dose of dialysis (dialyzer urea clearance, treatment time and frequency) sufficient to result in mean predialysis BUN values of 80 mg/dl with documented dietary protein intake equal to or greater than 1.0 g/kg/day and measured protein catabolic rate equal to dietary protein intake is acceptable with respect to the well being and the clinical stability of the patient on dialysis. By this definition, dialysis schedules can be modeled based on a patient's urea generation rate and the particular dialysis characteristics.

The final designation of the amount of dialysis must eventually depend on the patient's response. If a patient is not thriving on what appears to be adequate dialysis and a search for non-dialysis causes is unrevealing, then a therapeutic trial of either more or less dialysis should be initiated. In our experience, patients have seldom, if ever, suffered from too much dialysis.

Usually with a dialyzer having a surface area of 1–1.5 m^2, the average patient requires between 4–5 hours of dialysis. For patients with greater muscle mass or those with special problems related to excessively high BUN or creatinines and severe complications such as neuropathy or pericarditis, a larger surface area dialyzer should be selected, the time on dialysis should be extended, or more frequent dialyses should be performed.

The patient's residual renal function usually diminishnes with time. In addition, the patient may gain in dry weight. If the patient is to remain in good health, dialysis time should be increased or a dialyzer with a larger surface area should be used.

2.9. Medication for dialysis patients

Since phosphate is poorly dialyzable, all dialysis patients require phosphate binders to control serum phosphorus levels. These come in various forms. The best ones contain aluminium hydroxide or aluminum carbonate without any magnesium. Use of the aluminum containing antacids does not apparently lead to dialysis encephalopathy in the absence of high aluminum concentrations in the dialyzing fluid. These should be taken after meals for maximum effect. The amount must be

determined empirically for each patient. As these compounds are often constipating, stool softeners should be used if the patients complains of this symptom.

Multivitamins containing all the water soluble vitamins should be given to replace the amount lost during dialysis. Particularly, supplementary doses of folic acid (1 mg/day) and pyridoxine (10 mg/day) should be given to all dialysis patients. However, it is not necessary to give additional supplements of vitamins A, E or K.

Iron may be given as an oral preparation 2 or 3 times a day, or by the intravenous route at predetermined intervals. Serum iron, iron binding capacity and ferritin levels should be followed.

Vitamin D preparations and calcium supplementation are discussed in the Chapter on Renal Osteodystrophy.

Hypertensive medications have been described above.

The Chapter on 'Drug Metabolism and Dose Adjustment in Patients with Renal Failure' should be consulted when any medication is prescribed for these patients.

2.10. Acute hemodialysis

Indications for an acute hemodialysis include acute renal failure and acute intoxication with dialyzable drugs or chemicals.

Accurate blood chemistries and hematocrit must be determined prior to dialysis for acute renal failure. Comatose uremic patients often require a lumbar puncture to be certain that subarachroid hemorrhage has not occurred. Because of the likelihood of increased bleeding in acute uremia, the patient should be typed and cross-matched for several units of blood in the event of excessive blood loss. This is especially important if the vascular access is to be established via a percutaneous femoral catheter. If the patient is semi-conscious and agitated, and the blood urea nitrogen is excessively elevated (>150 mg%), a small amount of intravenous diazepam (Valium®) (2–5 mg) may prevent seizures.

Acute hemodialysis for drug introxication or poisoning should only be performed if there are elevated levels of drugs or toxins present in the blood, and then only if they can be extracted via hemodialysis in sufficient amount. The use of charcoal or resin hemoperfusion should also be considered when dialysis is contemplated for a drug overdose as this is a more efficient method of removing many drugs from the blood (see Chapter 19 for a list of dialyzable drugs).

Heparinization should be done cautiously in all acute dialyses. Fol-

lowing an initial clotting time, only small doses of heparin 500–1500 units should be administered. The clotting time of the blood leaving the dialyzer should be kept between 20–30 minutes. Occasionally, regional heparinization is used when the patient is actively bleeding. Heparin is infused into the arterial blood before it enters the dialyzer; the blood leaving the dialyzer receives a neutralizing dose of protamine before being returned to the patient. In most instances, however, small doses of heparin with careful monitoring of clotting times will suffice to carry out a dialysis. Occasionally, because of excessive bleeding at the end of dialysis (especially when the clotting time is prolonged) an intravenous bolus of 5–10 mg of protamine may be required. For patients who bleed for a prolonged period from the needle puncture sites, the use of topical thrombin may hasten hemostasis.

Hypotension may occur in acute hemodialysis because of bleeding, sepsis, or other causes related to the etiology of the renal failure. Blood, salt poor albumin and vasopressor agents should be available during dialyses.

It is sometimes necessary to alter the dialyzing solution for acute hemodialysis. There is increasing evidence that critically ill patients receiving dialysis may benefit from replacing acetate with bicarbonate. In addition, the amount of potassium in the dialysate should be adjusted for the individual patient. A patient with a serum potassium of 7.2 mEq/l should not be dialyzed against a potassium free bath. Instead, an initial dialysate of 2–3 mEq/l should be used for the first 1–2 hrs and then the bath changed and potassium reduced, if desired. Dextrose should be added to the dialysate of patients receiving acute hemodialysis.

3. PERITONEAL DIALYSIS

3.1. Peritoneal membrane characteristics

When two liters of dialysis solution are introduced into the peritoneal cavity, uremic solutes diffuse from capillaries through the peritoneal membrane into the dialysate. Urea diffuses rapidly during the first 30 minutes and equilibration between blood and dialysate is reached at 120 minutes. Urea is the most rapidly diffusable solute. The diffusion of other substances, expressed as a percentage of urea diffusion (100%), is: potassium 90%, phosphate 62%, creatinine 61%, bicarbonate 67%, and uric acid 62%.

The peritoneal membrane is more permeable to higher molecular weight substances such as vitamin B_{12} and inulin compared to hemodialysis membranes because of its larger pore sizes. It is also permeable to large molecules such as proteins.

The surface area of the peritoneal membrane is approximately 1.0 m^2. The effective surface area for peritoneal clearance is only that part of the peritoneal membrane that is in close contact with capillaries. The peritoneal clearance of urea is 20–30 ml/min and that of creatinine is 15–20 ml/min. Hemodialysis clearances of urea and creatinine are five to six times higher. Thus, peritoneal dialysis has to be carried out for longer periods of time to obtain comparable results. Factors affecting peritoneal clearance include dwell time, dialysate composition, temperature and flow rate and intra-abdominal conditions.

The period of time that the dialysate remains in contact with the peritoneal membrane (dwell time) influences the amount of solute removed. The optimal dwell time for adequate solute removal is 10 minutes. Peritoneal clearance is higher with a dialysate warmed to 37° than at room temperature. The higher the concentration gradient between blood and dialysate, the greater the solute removal. A high concentration gradient can be achieved by using large volumes of dialysate or by inducing very rapid exchanges. However, dialysate volumes above 2 liters and flow rates above 4 liters/hr are impractical. A flow rate of 3–4 liters/hr with 2 liter exchanges results in optimal peritoneal clearance. The use of hypertonic dialysate solution (4.25 g/dl dextrose) increases peritoneal clearance. This is probably due to larger volumes of fluid removed and to the solvent-drag effect. The addition of vasodilators especially nitroprusside can produce a 20% increase in peritoneal clearance.

Factors that decrease peritoneal clearance include ileus, vascular disease, small abdominal cavity and thickened peritoneal membrane from previous episodes of peritonitis.

3.2. Peritoneal dialysate

The composition of the dialysate solutions is as follows:

Na	132–140 mEq/l
Cl	99–102 mEq/l
Acetate	35– 45 mEq/l
or Lactate	35 mEq/l
Ca	3.5–4.0 mEq/l
Mg	1.5 mEq/l

These solutions are available in two liter plastic bags or glass bottles. Acetate may have some advantage over lactate because it appears to be bacteriostatic at concentrations of 35 mEq/l. A potassium-free dialysate is employed in most patients undergoing maintenance peritoneal dialysis because the peritoneal membrane clears potassium slowly. Potassium can be added to the dialysate if a patient is receiving digitalis or undergoing peritoneal dialysis for a long period of time (over 24 hours). The dextrose concentration of the dialysate is either 1.5 or 4.25 g/dl.

3.3. Permanent peritoneal catheters

Permanent catheters are made of silastic with dacron cuffs. The catheter is inserted surgically (see Chapter 18 for details concerning insertion). One hour prior to catheter insertion, the following antibiotics are given as a single dose: Gentamicin 1.5 mg/kg intravenously or intramuscularly; cephalothin 1.0 g intravenously; or Cefazolin 1.0 g intramuscularly.

After the permanent catheter has been introduced in the operating room, peritoneal dialysis should start immediately to avoid clotting of blood in the catheter and should continue for 48 hours. The dextrose concentration of the dialysate should be 1.5 g/dl to prevent dehydration during the 48-hour period of dialysis. The dialysate should contain heparin 500 units/l, cephalothin 50 mg/l and KCl 3 mEq/l.

For the first 24 hours, dialysis is performed without dwell time, using one liter exchanges. During the second day, dialysis continues allowing for 10 minute dwell times with two liter exchanges if tolerated. If the permanent catheter is functioning well, peritoneal dialysis can be performed with an automated machine at least during the second dialysis day.

At the end of this dialysis, 500 ml of fluid is left in the abdomen and 3000 units of heparin are instilled into the catheter. Daily until the next regular dialysis day, the new catheter should be irrigated with 50 ml of normal saline, followed by instillation of 3000 units of heparin.

3.4. Automated peritoneal dialysis devices

An automatic peritoneal dialysis cycler may be used to instill and drain the dialysate solution. Eight 2-liter plastic bags of dialysate are placed on the cycler. The cycler has two timers; one determines the duration of the 'fill cycle' (time for the fluid to run into the peritoneal cavity and remain there) and the other for the duration of the 'drain cycle' (time during which the fluid drains out of the peritoneal cavity). The desired

dialysate volume flows from the eight containers into a warming device. 'Fill cycle' and 'drain cycle' proceed automatically. During the 'drain cycle', the fluid empties into a weighing bag that sounds an alarm and stops the dialysis if a preset volume has not drained out within a given period. Bags of dialysate are replaced every five to six hours.

Automated peritoneal dialysis can also be performed with a reverse osmosis device. This is a closed system utilizing a concentrated solution and a reverse osmosis water purification process. The deionized and sterile water is proportionally mixed with a concentrated solution of dextrose and electrolytes to make the dialysate that is then pumped into the patient. The fluid drains out from the peritoneal cavity by gravity.

3.5. Management of peritoneal dialysis patients

Most patients require over 40 hours of dialysis per week. This is divided into approximately 20 hours twice a week. The majority of patients tolerate 2 liter exchanges. Each exchange usually lasts 40 minutes (20 minutes filling time, 20 minutes draining time). Many patients, however, drain out completely within 10–15 minutes. The drain time should then be decreased appropriately and the time saved used for dialysis. The best peritoneal clearances can be obtained with a volume of 2 liters per exchange at a rate of 1.5 to 2 exchanges per hour (flow rates 3–4 liters/hour).

A strict aseptic technique should be utilized to start and terminate dialysis. If ascites is present, a sample is taken for culture before the catheter is connected to the dialysis tubing. Many patients on peritoneal dialysis tend to form fibrin clots in the peritoneal cavity. To prevent catheter obstruction, heparin (500 units/l) is added to each dialysate exchange for the first three months after catheter insertion. Each 20-hour peritoneal dialysis is usually performed with potassium-free dialysate. When the patient is receiving digitalis, however, potassium is added (depending on serum potassium levels), especially during the initial dialyses. It may not be needed thereafter. Prophylactic antibiotics are not required.

Dry weight is the post-dialysis weight at which the patient is free of edema and congestive heart failure. Within a short time after starting maintenance peritoneal dialysis, the patient's dry weight should be achieved. As the patient is stabilized on dialysis and gains tissue weight, dry weight should be adjusted upward, especially if hypotension occurs at the previous dry weight. The patient's fluid balance is maintained by

removing during dialysis the volume of fluid that is gained between dialyses.

A simple guide for fluid removal is as follows:

Interdialysis Weight Gain	*Dextrose Concentration in 8 Bags*	
	4.25 g/dl	*1.5 g/dl*
0–0.9 kg	*0*	*8*
1–1.9 kg	*1*	*7*
2–2.9 kg	*2*	*6*
3–3.9 kg	*3*	*5*
>4.0 kg	*4*	*4*

These approximate figures must, of course, be adjusted appropriately for each patient.

Patients treated with maintenance peritoneal dialysis lose approximately 30–100 g of protein/week. To compensate for this loss, dietary protein intake should be in the range of 1.5 g/kg of body weight/day.

3.6. Complications of peritoneal dialysis

Catheter obstruction is the most common complication and it is usually one-way obstruction. The dialysate runs in the peritoneal cavity but does not drain out. This usually occurs when the catheter is dislodged from the pelvis to one of the upper abdominal quadrants or when the catheter becomes covered with omentum. Vigorous bowel movements with a cathartic may free the obstruction. Permanent catheter obstruction may be caused by fibrin clots, adhesions due to previous peritonitis or may follow one-way obstruction. In most instances this requires replacement of the catheter. Bloody effluent is common after catheter implantation. It usually clears spontaneously. Leakage around the catheter may occur in the period immediately following catheter insertion. It is treated by temporary cessation of dialysis.

Rectal or suprapubic pain may occur during the first four to five weeks after catheter implantation. It is usually inconsequential. Abdominal pain may occur with prolonged use of dialysate with 4.25 g/dl dextrose concentration. Abdominal distension may develop by inadvertent overfilling with dialysate. The fluid should be drained immediately. If the permanent catheter is not functioning properly, dialysis should be instituted through a stylet catheter.

Overheating of dialysate, although a rare complication, may occur with the automated machines. Dialysate should be drained immediately. Dehydration may be induced by the excessive use of 4.25 g/dl solutions. Hypokalemia may develop when patients are dialyzed for long periods with potassium-free dialysate. When dialysis is planned for more than 24 hours, potassium should be added to the dialysate (2–3 mEq/l).

Peritonitis is the most important complication of peritoneal dialysis. Its incidence varies between 0.1 to 1.5% of dialyses performed. Peritonitis is manifested clinically by abdominal pain, cloudy effluent, rebound abdominal tenderness, and sometimes fever, vomiting or ileus. When peritonitis is suspected, the following steps should be undertaken immediately.

Cell count and gram stain examination of the peritoneal effluent should be done. If the Gram stain reveals Gram-positive organisms, usually staphylococcus aureus or staphylococcus epidermitis, cephalothin is added to the dialysate. If Gram-negative organisms are identified, gentamicin is the drug of choice. The antibiotic can be changed after culture and sensitivity results are available. The desired concentrations of intraperitoneal antibiotics are listed in Chapter 19. Peritoneal dialysis should be continued with no dwell time and with one liter of dialysate containing heparin (500 units/l), potassium (2–3 mEq/l), 1.5 g/dl dextrose, as well as the appropriate antibiotic. To compensate for the very high protein loss during peritonitis, 2–4 units of albumin should be administered intravenously. The peritonitis should clear with appropriate treatment within 24 to 48-hours. Dialysis is continued until at least two consecutive daily cultures are negative. If the dialysate culture remains positive, one should suspect either contaminated catheter, intraperitoneal abscess or perforated bowel. For the three weeks following an episode of peritonitis, heparin and antibiotics should be added to the dialysate during regular twice weekly peritoneal dialysis. In addition, oral antibiotics should be administered during this period.

Treatment for positive cultures of peritoneal fluid without clinical peritonitis is controversial. Repeatedly positive cultures may be treated by adding the appropriate antibiotics to the dialysate at the time of the patient's regular dialysis. Antibiotics are continued until two consecutive negative cultures are obtained.

Prevention of peritonitis is the key to successfully maintaining patients on peritoneal dialysis. Peritonitis can be prevented if strict aseptic techniques are used when handling connections and inserting needles into fluid containers. In addition, the introduction of the auto-

mated machines contributes significantly to the prevention of peritonitis.

3.7. Continuous ambulatory peritoneal dialysis

Continuous ambulatory peritoneal dialysis (CAPD) is a 24-hour-per-day, seven-day-per-week dialysis. CAPD uses the continuous presence of dialysate in the peritoneal cavity except for brief periods of drainage and instillation of fresh dialysate four or five times per day, seven days per week.

The technique of CAPD is simple and is performed by the patient at home. It consists of exchanging two liters of dialysate four times a day at approximately 8:00 A.M., 2:00 P.M., 8:00 P.M., and 12:00 A.M. This results in two 6-hour dwell times, one 4-hour dwell time and one 8-hour dwell time. At the time of each exchange, strict aseptic techniques should be utilized. The dialysate is available in 2 liter plastic bags. The bags are connected to the permanent catheter by a short plastic tube. After infusion of 2 liters of dialysate, the bag is carried rolled up in a cloth waist purse under the clothing. At the end of the dwell time, the dialysate is drained into the same bag which is then changed and a new dialysate bag is attached to the same connection tube for fluid instillation. The connection tube is changed once a month.

Patients maintained with CAPD have continuous steady-state control of blood chemistries including serum creatinine, urea nitrogen, potassium and uric acid levels, and adequate salt and water removal. In addition, CAPD offers more efficient clearance of high molecular weight substances, such as inulin and vitamin B_{12} when compared to hemodialysis and intermittent peritoneal dialysis.

The disadvantages of CAPD are:

Increased protein loss (10 to 20 g/day). This loss should be compensated by a high dietary protein intake.

Higher incidence of peritonitis than with the intermittent peritoneal dialysis.

4. CONCLUSION

Both hemodialysis and peritoneal dialysis are efficient methods of controlling uremia in patients with chronic renal failure.

It is important to remember that a dialysis center should be able to

provide both types of dialysis because the feasibility of hemodialysis or peritoneal dialysis may vary according to the age or clinical status of the uremic patient. In addition, patients may be transiently switched from hemodialysis to peritoneal dialysis because of a temporary clinical situation that may render hemodialysis hazardous. These include vascular access infection or bleeding, severe state of overhydration with ascites, intractable congestive heart failure, central nervous system bleeding and pericarditis and/or pericardial effusion. On the other hand, some patients may be transferred from peritoneal dialysis to hemodialysis because of peritoneal catheter problems, extensive abdominal surgery, repeated episodes of peritonitis, or failure to thrive with that mode of therapy.

Rehabilitation in patients treated with hemodialysis varies according to the age of the patient. Patients under 50 years of age are often able to resume occupations of a sedentary nature or requiring moderate physical exertion. Older patients have difficulty in returning to any type of work. Rehabilitation in patients treated with peritoneal dialysis was found to be comparable to hemodialysis patients in most centers where similar patient populations were treated with both therapies. Overall, mortality rate in dialysis patients is about 5% to 15% per year. Most deaths are due to cardiovascular disease and cerebral vascular accidents. Mortality rates in peritoneal dialysis patients may be higher than hemodialysis patients, but comparable groups have yet to be adequately studied.

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15. KIDNEY TRANSPLANTATION

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1. INTRODUCTION

The ability to replace both excretory and endocrine functions of diseased kidneys by renal transplantation has made this approach a very attractive alternative method of treatment for patients with end-stage renal disease. Though initially successful only in closely related donor-recipient combinations, clinically acceptable patient and graft survival rates have been achieved with kidneys obtained from cadaveric donors. Since the first successful transplantation between monozygotic twins in 1954 in Boston, more than 30,000 transplants have been performed in multiple transplant centers. Based on a sample size of 19,631 transplant recipients in whom follow-up information was available to the transplant registry, 13,384 (68.18%) were alive with or without functioning grafts at the time of the 13th report of the Human Transplant Registry. Of these patients, 8,893 (45.3%) had functioning grafts and 4,491 (22.88%) had grafts that were non-functioning or that had been removed [1].

2. DONORS AND RECIPIENTS

Two types of donors, living related and cadaveric donors, have provided the kidneys for transplantation. In forty percent of transplants performed in the United States, and in fifteen percent of the transplants in Europe, kidneys have been obtained from living related donors. Superior patient and graft survival rates can be expected when kidneys are obtained from living related donors rather than from cadaveric donors.

2.1. Living Related Donors

Potential donors must be carefully investigated to insure the absence of any significant disease and they must be in excellent health [25]. They

should have no evidence of renal disease or any other risk factors such as hypertension or diabetes that might predispose them to renal disease in the future. The consent for donation must be an informed one with full knowledge of risks and benefits. The situation becomes quite complex when children are potential donors and it is preferable to restrict such transplants to unavoidable circumstances [13]. Usually, the risks are minimal. Complications such as wound infection or lower urinary tract and pulmonary problems might arise occasionally. Very infrequently, more serious complications such as the development of deep vein thrombophlebitis and pulmonary embolism might occur [26]. On the benefit side, the donor usually derives tremendous satisfaction from being responsible for saving or prolonging the life of a loved one. The routine donor evaluation procedure is summarized in Table 1.

Table 1. Donor evaluation procedures.

1.	Pre-admission screening interviews with the nephrologist, psychiatrist, urologist, and social worker.
2.	Admission history and physical examination.
3.	Laboratory: CBC; BUN, Two-hour post prandial blood sugar; cholesterol; triglycerides; Na; K, CO_2; Mg; Ca; P; liver chemistries; uric acid; creatinine; creatinine clearance; urinalysis (twice); urine culture (twice); and 24-hour urine for protein.
4.	Radiology:
	a. Chest x-ray
	b. Intravenous pyelography
	c. Renal arteriogram
5.	ECG
6.	Special studies as indicated (e.g., cystoscopy; catheterized urine specimens; cultures for AFB, etc.).
7.	Consultation(s) as indicated (e.g., cardiology, etc.).
8.	Review and final approval by the urologist or donor's surgeon.

2.2. Cadaveric Donors

The majority of transplants are performed with kidneys obtained from donors with brain death [6]. The diagnosis of brain death is made on clinical grounds and often confirmed by electroencephalography. Cadaveric donors are generally between five and fifty-five years of age and are usually victims of accidents without any significant past medical history. There should be no evidence of renal disease and they should not suffer from malignancy or any infectious disease, such as hepatitis, septicemia or urinary tract infection.

2.3. Recipients

Every patient maintained on chronic intermittent dialysis is a potential candidate for transplantation. The best results are obtained in recipients between 10 and 50 years of age with primary renal disease and without other medical problems such as diabetes, arteriosclerosis, or cardiovascular disorders. Certain primary renal diseases, however, might recur in the allograft. Failure of a previous transplant is not a contraindication in itself for re-transplantation. Usually, the longer the period of survival of the first graft, the better the chances for the success of the second graft. The presence of outlet obstruction in lower urinary tract or severe vesicoureteral reflux is not in itself a contraindication either. However, these patients require a corrective procedure, such as urinary diversion (e.g., ileal conduit) or ureteronephrectomy prior to transplantation. Pre-transplant bilateral nephrectomy is also indicated in patients with pyelonephritic kidneys, large polycystic kidneys, renin-dependent refractory hypertension, bleeding kidneys and glomerulonephritis with anti-GBM antibodies (see Chapter 18).

3. IMMUNOLOGICAL ASPECTS OF RENAL TRANSPLANTATION

In all vertebrate species investigated thus far, a single chromosomal complex codes for antigens of greatest importance in the rejection of tissues and organs. In man, the genes coding for these important transplantation antigens are located on the short arm of chromosome six (Figure 1) and constitute the major histocompatibility complex (MHC) [2, 29].

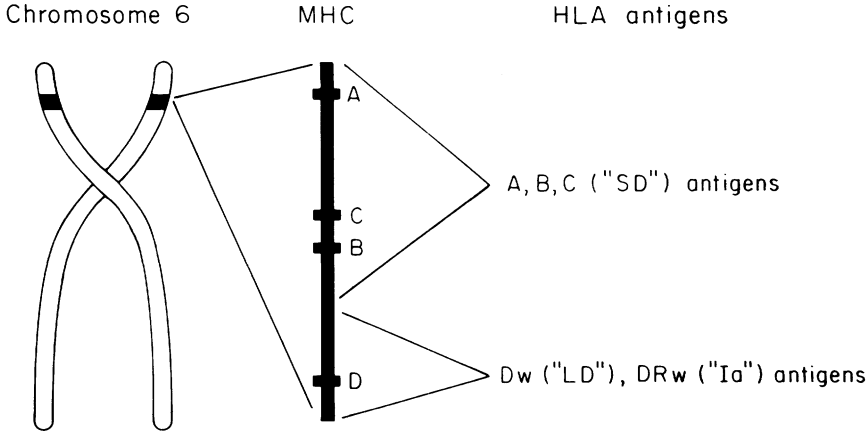

Figure 1. Schematic representation of human MHC.

3.1. Human Major Histocompatibility Complex

Four distinct but closely-linked loci are currently recognized in the human MHC, and are designated A, B, C, and D (Figure 1). The gene products of the A, B, and C locus are expressed on virtually all nucleated cells and are termed 'SD' antigens, since these antigens are easily defined by serological methods. The molecular structure for these antigens consists of a β_2-microglobulin light chain (mol. wt. 12,000 daltons) and a heavy chain with a mol. wt. of 33,000 daltons. The gene products of the D locus antigens have a more restricted tissue distribution and are preferentially expressed on B lymphocytes, monocytes, and endothelial cells but not on resting T lymphocytes or platelets. The molecular structure of D locus antigens is different from that of HLA-A, B, C antigens. They contain two polypeptide chains of similar size (mol. wt. 23,000 and 30,000 daltons). Currently, 45 antigens of the A, B, C, and 7 D antigens are recognized. In addition to HLA- A, B, C and D antigens there is now impressive evidence that the genes located in the human MHC code for a B cell antigenic system analogous to the I region products detected in the mouse. These 'Ia' specificities, determined by serological assays on B lymphocytes, are designated as DRw antigens and DRw_1 through DRw_7 specificities have been defined. It is unclear at this stage whether the Dw antigens and DRw antigens are identical or closely-related gene products.

3.2. Genetic and Inheritance Patterns of the MHC

Each of the A, B, C, and D series of HLA antigens act as if the corresponding antigens are controlled by multiple allelic genes at distinct but closely-linked loci. This means that there should be no more than one antigen from each series on a single haplotype.

The haplotypes, the units of inheritance, from each parent, are inherited *en bloc* and in an autosomal fashion. It can be predicted from simple Mendelian genetics that 25% of siblings will be HLA identical, 25% completely non-identical, and 50% will have one haplotype identical. In the event of recombination during meiosis in one of the parents, a new haplotype can result.

3.3. Identification of HLA- A, B, C Antigens

The complement dependent microcytotoxicity assay (CDC) is the standard technique utilized to detect HLA- A, B, C antigens. The major

components of the system are purified lymphocytes of the subject to be tested, well characterized typing sera, standardized rabbit complement and a vital dye such as trypan blue or eosin. Lymphocytes, isolated from peripheral venous blood from the individual to be tissue typed, are incubated with operationally monospecific typing sera in individual wells of microtiter plates. The lymphocytes are used as targed cells since HLA antigens are well expressed on them and these cells are relatively easy to purify. The HLA phenotype of the individual is identified by noting the typing sera that mediate cell death. Cell death occurs in the presence of appropriate target antigen on the cell surface and is complement dependent. A, B, and C locus antigens can be detected by this technique.

The CDC assay is also used to detect preformed complement dependent cytotoxic antibodies in transplant recipients' sera. Serum obtained prior to transplantation from the potential recipient is incubated with the donor's cells in the presence of rabbit serum which serves as the complement source. Cell death occurs if the recipient's sera contains antibodies directed against donor cells. A positive pretransplant CDC (positive crossmatch), indicating the presence of preformed cytotoxic antibodies against the donor, is an absolute contraindication to transplantation. Seventy to 80% of grafts fail immediately when transplantation is performed across a positive CDC [20].

3.4. Identification of DRw Antigens

The standard microlymphocytotoxicity assay has been successfully modified to detect DRw antigens. Since DRw antigens are expressed on B lymphocytes and not on resting T cells, purified B lymphocytes are used as targets instead of peripheral blood lymphocytes. Prior to testing, sera are absorbed with platelets to remove antibodies directed at HLA-A, B, C antigens. Platelets or T cells can be utilized for absorption of sera since only HLA- A, B, C antigens are well expressed on these cells.

3.5. Mixed Lymphocyte Culture

The mixed lymphocyte culture (MLC), reflects the compatibility between donor and recipient for D locus-determined antigens. In the MLC, lymphocytes from the potential recipient are mixed with donor cells and left for four to five days, after which the proliferative response

is assayed by measuring the incorporation of ^{3}H-thymidine into the responding lymphocytes.

To make the MLC unidirectional, untreated recipient cells (responder cells) are mixed with irradiated donor cells (stimulator cells). The irradiated cells do not incorporate thymidine and all the thymidine incorporated represents the proliferative response of the recipient's cells. The MLC response can be quantitated and within a given family can be correlated with the number of haplotypes by which individuals differ.

3.6. Role of HLA Antigens in Renal Transplantation

Current evidence suggests a differential role for HLA- A, B, C, and D antigens in the initiation of alloimmune responses and in the development of both cellular and humoral immune responses [10] (Figure 2). HLA- D locus antigens seem to activate a subset of T cells (T helper cells) to proliferate; these in turn provide help to another subset of T cells to differentiate into cytotoxic T cells (cellular immune effector mechanisms). Target determinants for the cytotoxic T cells (CTL) thus generated can be either HLA- A, B, C, or D antigens or even non-HLA antigens. The T helper cells also provide help and amplify the production of antibodies by B cells (humoral immune effector mechanisms). The target determinants for the antibodies might again be HLA- A, B, C antigens or D locus-determined antigens. It is clear that the rejection of renal allografts results from a complex interplay of both cellular and humoral immune effector mechanisms directed at the antigens encoded

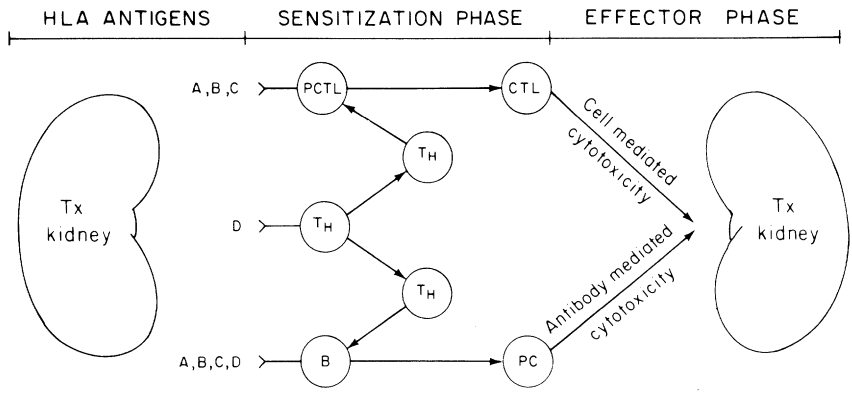

Figure 2. Schema of relative roles of HLA antigens in the initiation of alloimmune responses, (PCT: precursor of cytotoxic T cells; TH: T helper cells; B-B cells; PC-Plasma Cells; CTL-cytotoxic T cells).

for by the MHC. However, other antigen systems (e.g., endothelial cell antigens and major and minor blood group antigens) might initiate unfavorable alloimmune responses that might be detrimental to renal allograft function and survival. Graft survival rates are clearly related to matching for HLA antigens between the donor and the recipient in living related donor transplants. However, a role for HLA- A, B, and C antigens, in influencing graft survival, is less impressive in cadaver renal transplants. Some recent observations suggest a more significant role for DRw antigens in cadaver renal transplantation.

3.7. Role of ABO Blood Group Antigens in Renal Transplantation

The principles applicable to transfusion apply equally well to transplantation since blood group products are well expressed on the endothelial cells of the graft. Besides the ABO blood groups, RhD antigens and Lewis blood group antigens may influence renal transplant outcome [19].

3.8. In Vitro Techniques to Detect Alloimmunity

The sensitivity of the in vitro technique to detect alloimmunity has been augmented by labeling target cells with ^{51}chromium and using the release of the chromium label as an index of cell death in various cytotoxicity assays.

3.8.1. ^{51}Chromium Release Complement-dependent Cytotoxicity Assay

The principles of this assay are identical to the standard CDC. Cell death is assessed by the release of ^{51}chromium rather than by the ability of cells to exclude a vital dye.

3.8.2. Antibody Dependent Cell-mediated Cytotoxicity Assay (ADCC)

This sensitive technique detects the presence of IgG antibodies. Cell death is mediated by complement independent mechanisms. Donor's cells, labeled with ^{51}chromium, are incubated with the recipient's sera and lymphocytes from 3–5 normal individuals (non-presensitized effector cells). The Fab portion of the antibody binds to the target cells and the Fc piece is bound by the Fc receptor bearing cells in the effector population. The cytotoxicity is mediated by the effector cell but is dependent on the antibodies present in the serum and is independent of complement.

3.8.3. Lymphocyte-mediated Cytotoxicity Assay (LMC)

Cytotoxic T cells (CTL) are detected by the LMC. Cellular presensitization, as well as the development of CTL in the post-transplantation period, can be detected by this technique. Lymphocytes obtained from the recipients are incubated with ^{51}chromium-labeled donor's cells (target cells). Target cell death occurs in the presence of CTL and results in the release of the ^{51}chromium label. By measuring the amount of the ^{51}chromium released from the target cells, the presence of CTL can be ascertained. Though the precise mechanism mediating cytotoxicity is unknown, it is thought to be independent of complement and cytotoxic antibodies.

Since the humoral and the cellular immune effector mechanisms that might be operative in allograft rejection can be measured by CDC, ADCC, and LMC, these tests can be used for assessing pre-transplant sensitization and for monitoring the immunologic reactivity of the transplant recipient. These assays tend to be reasonable correlates of rejection activity and can be utilized as predictive and diagnostic indices.

4. MEDICAL MANAGEMENT OF THE TRANSPLANT RECIPIENT

4.1. Pre-transplant Evaluation

Recipients of living related grafts are admitted a few days prior to surgery. The potential cadaveric graft recipient is admitted to the hospital when an appropriately-matched and initial crossmatch negative cadaveric kidney becomes available. The transplant recipient should undergo a thorough physical and laboratory evaluation with particular attention being paid to acid-base status, serum electrolytes, and hematocrit. Transfusion is indicated if the hematocrit is $<18\%$ and dialysis can restore optimum preoperative fluid and electorlyte status. An intensive search for active infection is mandatory. The routinely recommended preoperative laboratory tests are summarized in Table 2.

4.2. Immunosuppressive Therapy

Azathioprine and corticosteroids are the cornerstones of immunosuppressive therapy used in renal transplantation despite the availability of multiple drugs with potent immunosuppressive properties [4].

Table 2. Preoperative laboratory tests for kidney transplantation.

1. *Blood tests:*
   a. CBC with differential count and platelet count.
   b. Na; K; Cl; CO_2; Blood sugar; BUN; Uric Acid; Ca; and P.
   c. Creatinine.
   d. Bilirubin (direct and total); SGOT; SGPT; Alkaline phosphatase; and SH antigen.
   e. Cold agglutinins.
   f. Cytomegalovirus antigen and antibody titre.
   g. Red cell type and crossmatch.
   h. Leukocyte crossmatch with donor cells and recipient's serum.
   i. Serum complement: C_3.
   j. Protime and partial thromboplastin time.
2. *Radiology:*
   a. PA and left lateral chest.
   b. Other as indicated.
3. *Optional studies:*
   a. Radiologic bone survey.
   b. Eye consultation.
   C. Nerve conduction.

4.2.1. Azathioprine

Azathioprine is an analogue of 6-mercaptopurine. Its ability to inhibit both deoxyribonucleic acid and ribonucleic acid synthesis is thought to be responsible for its immunosuppressive properties. The antimitotic effect, resulting from inhibition of DNA synthesis, can potentially prevent the expansion of relevant immunocompetent cell clones. Treatment with azathioprine is generally initiated 12–48 hours preceding transplantation and continued indefinitely in the post-transplantation period. Though retention of metabolites occurs with severe renal failure, it is primarily metabolized by the liver and minimal alterations in dosage are required with renal impairment. Leucopenia, anemia, thrombocytopenia, and alopecia can all occur with neutropenia being the most common side effect. The total and absolute neutrophil count should be determined frequently and azathioprine should be decreased or even temporarily discontinued with the onset of neutropenia. Hepatitis is a less frequent complication of azathioprine and alternate drug therapy with cyclophosphamide is indicated under such circumstances. Since hemorrhagic cystitis, azospermia and leucopenia are all potential complications of cyclophosphamide therapy, extreme caution is required when it is used as an alternate drug for azathioprine.

4.2.2. Corticosteroids

Prednisolone is the most common steroidal preparation used in renal transplantation. Therapy with steroids is usually initiated at a dose range of 100–200 mg/day along with azathioprine. The dose can then be tapered to maintain levels of 10–20 mg/day over a varying time interval. It is highly desirable that the recipient be maintained with minimal steroids since both poor wound healing and infectious complications might be causally related to high dose steroid therapy. A bolus of prednisolone consisting of 100–1000 mg/day for 1–5 days is recommended for the management of acute rejection crisis [3]. Following such pulse therapy, the dosage can and should be rapidly tapered to pre-pulse dosages.

4.2.3. Antithymocyte Globulin

Antithymocyte globulin (ATG) is prepared by sensitizing rabbits or horses with human lymphocytes. The rationale for the use of ATG is its ability to suppress cellular immunity. Despite its potent immunosuppressive properties as indicated by prolonged survival of allogeneic grafts in animal models, no clear-cut benefit from administration of ATG to renal allograft recipients has yet been demonstrated.

4.2.4. Retroplacental Gamma Globulin

Retroplacental gamma globulin (RPGG) is prepared from pooled human retroplacental blood [24]. RPGG seem to contain alloantibodies directed at the gene products of the MHC and can suppress both alloantigen and mitogen-induced proliferative responses of lymphocytes. Though the mechanism of action is unknown, RPGG has recently been shown to prolong cadaveric graft survival rates in controlled clinical trials.

4.2.5. Other Techniques

Local irradiation to the allograft in three or four doses of 150 rads has been used to manage rejection crisis or as a routine post-transplant treatment protocol. Thymectomy and splenectomy, as well as thoracic duct drainage to deplete lymphoid populations, have all been attempted to improve graft survival rates. Irradiation, as well as the surgical procedures mentioned above, have contributed very little to ultimate graft success and as such have not found wide usage in the transplant community. Fractioned total lymphoid irradiation [28], based on protocols used in Hodgkin's patients, seems to be a promising approach for the future and has been shown recently to improve graft survival in certain animal transplantation models.

4.3. Post-transplant Management

Most living related donor kidneys produce urine within minutes of restoring circulation during transplantation. Only about 20–50% of cadaveric transplants, however, function immediately. The circulatory status of the cadaver prior to death and the warm and total ischemic times of the graft account in part for this high incidence of acute renal failure.

The degree and duration of the immediate post-operative diuresis depends on the preoperative state of the recipient and the cadaveric organ. When patients are underdialyzed and/or hypervolemic prior to transplantation, there may be a massive post-operative diuresis of 10–20 liters of urine daily for the first two–three days. Several factors may be responsible for this including an osmotic diuretic effect caused by high blood urea nitrogen levels, hypervolemia, or renal tubular abnormalities associated with ischemic injury to the graft.

Proper replacement of fluid and electrolyte losses prevents the complications of hypovolemia, hyponatremia, and hypokalemia. This is accomplished by measuring hourly urine output, urine electrolytes, serum electrolytes, and by monitoring vital signs and the central venous pressure. The electrolyte composition of the replacement fluid, as well as its rate of administration, depends on analysis of all these factors.

The immediate post-transplant diuresis usually does not last more than several days. During this time, renal function, as measured by creatinine clearance, gradually improves and reaches levels of 40 to 80 ml/min. In spite of such function, and even in the absence of overt rejection, patients often demonstrate renal injury manifested by tubular proteinuria and renal tubular acidosis. When urine flow is established, inversion of the normal circadian urinary rhythm is frequently observed.

A significant number of cadaveric transplants do not form urine within the immediate post-operative period. A systematic approach to determining the cause of oliguria should be outlined and followed. Factors which have been shown to produce anuria or oliguria are listed in Table 3. Acute tubular necrosis is the most common cause of post-operative oliguria and is a diagnosis of exclusion. It should be suspected in a cadaveric recipient when the circulatory status of the donor, prior to death, was compromised. Acute tubular necrosis may also follow acute rejection. Determination of urea and sodium concentration in the urine may be helpful prior to the onset of anuria, but many times, such patients are anuric from the time of transplant.

Table 3. Causes of anuria or oliguria in the post-transplant period

1. Acute tubular necrosis.
2. Urinary tract obstruction.
3. Hypovolemia.
4. Vascular accidents.
5. Urine extravasation.
6. Hyperacute rejection.
7. Acute rejection.
8. Metabolic insult (e.g., hypercalcemia).

Kidney biopsy may not distinguish between acute tubular necrosis and acute rejection as the cause of renal failure since there is evidence of both in most patients. Data from immune monitoring studies and serial measurements of renal blood flow with renal scans may provide information that can help to differentiate acute tubular necrosis from rejection.

Outlet tract obstruction, caused by blood clots and accompanied by bladder spasms, can be remedied or ruled out as a cause of anuria by bladder irrigation through a Foley catheter.

Cessation of urine output, usually gradual in onset and coincidental with a fall in arterial and venous pressure, suggests hypovolemia. This is seen following a massive diuresis or consequences of accumulation of lymph or plasma in the intestine or at the operative site. A plasma expander is usually given until the etiology of the hypovolemia is discovered.

Total arterial occlusion of the transplanted kidney is rare. It can be diagnosed by radionuclide studies or by renal angiography. Venous thrombosis of the allograft is also a rare event and difficult to demonstrate. Local pain is a feature of both, while massive proteinuria and leg edema may accompany the latter.

Extravasation of urine from the bladder or an obstructed ureter can cause decreased or absent urine flow. A cystogram can demonstrate extravasation of urine from the bladder but leakage of urine or obstruction proximal to the bladder may be difficult to diagnose. Routine cystoscopy and retrograde catheterization of the transplanted ureter is not advisable. The site of neo-uretero-cystotomy is usually edematous, and repeated attempts at catheterization may compromise or perforate it. Sonography is becoming extremely helpful in making the diagnosis of significant urinary tract obstruction.

Infrequently, electrolyte imbalances such as hypercalcemia, hyponatremia, and hypokalemia can also be responsible for renal impairment in the immediate post-transplant period.

4.4. Immunologic Problems

4.4.1. Hyperacute Rejection

Irreversible hyperacute rejection with cortical necrosis results from adverse presensitization and is usually diagnosed at the operating table. Acute cessation of urine flow accompanied by a bluish or mottled discoloration of the kidney and lack of swelling on renal vein compression strongly suggest this diagnosis. After surgery, acute onset of fever, anuria, enlarged kidney, local pain, and a generalized toxic appearance of the recipient are compatible with this diagnosis. Poor to rapidly decreasing perfusion characteristics on renal scans are seen.

Early biopsies of hyperacutely rejected kidneys show a linear localization of IgG and C_3 on the glomerular and peritubular capillary lumina. While infiltrating mononuclear cells are rare, neutrophilic polymorphonuclear leucocytes can be found lining the capillary walls. Fibrinoid necrosis and microthrombi block most of the capillaries and arterioles, and cortical necrosis ensues.

Exploration of the graft is usually indicated and nephrectomy is performed unless a biopsy proves the kidney to be unexpectedly viable. A repeat lymphocyte crossmatch, using donor cells, may sometimes reveal a cytotoxic antibody directed against the donor tissue, and antibodies directed at donor HLA antigens can invariably be demonstrated in recipient's serum with more sensitive techniques.

4.4.2. Acute Rejection

The diagnosis of acute rejection is first made by a constellation of clinical findings, and fortified by immunological and pathological studies. Fever, local pain, swelling, and declining urinary output are usually prominent with increase in serum creatinine. Weight gain and hypertension might also occur. Urinary findings include proteinuria, lymphocyturia, natriuresis, and defects in concentrating and acidifying mechanisms. Renal biopsy usually reveals evidence of both cellular and humoral immunity. Frequently, one immune mechanism may predominate over the other. Microscopically, the outstanding feature is mononuclear cell infiltration in interstitial tissue. Specific cytotoxic T cells and B cells, as well as macrophages and null cells, can all be found infiltrating the graft. Initially, the infiltration might be focal but later it is diffusely distributed throughout the interstitium. The hallmark of humoral immunity is vasculitis and necrotizing glomerulitis. The vascular endothelium bears the brunt of the attack, and IgG and C_3 can be detected in the graft.

Antibodies directed as donor HLA antigens can be eluted from some irreversibly-rejected allografts. Generally, the prognosis is poor when the biopsy indicates significant humoral rejection. Both cytotoxic T cells and alloantibodies directed at the donor transplantation antigens can usually be detected with the aid of LMC, ADCC, and CDC assays. Management of acute rejection involves the exclusion of other causes for deterioration of renal function, such as obstruction, volume depletion, infection and acute tubular necrosis. When rejection is diagnosed, steroid dosage should be increased. No unanimity exists regarding the dose employed for treating acute rejection episodes, but most centers use 100–1000 mg/day of prednisolone for 3–5 days.

4.4.3. Chronic Rejection

Chronic rejection can be visualized as the end result of repetitive immunologic insults to the vascular endothelium. Renal function gradually deteriorates several months or years after transplantation [23]. Clinically, azotemia, proteinuria and hypertension, progressive in nature, are the prominent features. Nephrotic range proteinuria might occur in few patients. Severe narrowing of a variable number of arteries (obliterative arteriopathy) and thickening of glomerular basement membrane can be found in the biopsy of the kidney. The arterial narrowing is usually accompanied by ischemic tubular atropy and interstitial fibrosis (ischemic nephropathy).

Immunoglobulins, more frequently IgM than IgG and complement, can be detected by immunofluorescence studies and subendothelial deposits can be seen with the electron microscope. Both antibodies and cytotoxic T cells can be eluted from the rejected kidneys and specificity to the donor's HLA antigens can be demonstrated. Chronic rejection of the kidney is usually managed symptomatically without alterations in immunosuppressive therapy at the present time.

4.5. Results and Factors Affecting Transplantation

Both patient and graft survival rates are better when kidneys are obtained from living related donors. The single best explanation for this phenomenon is the better tissue compatibility in donor-recipient combinations when kidneys are obtained from living related donors. Though some variability exists between individual transplantation centers with respect to patient and graft survival rates, reasonable expectations for patient survival rates for both living related and cadaveric transplants are 90–80% at 1 year following transplantation. Graft survival rates are

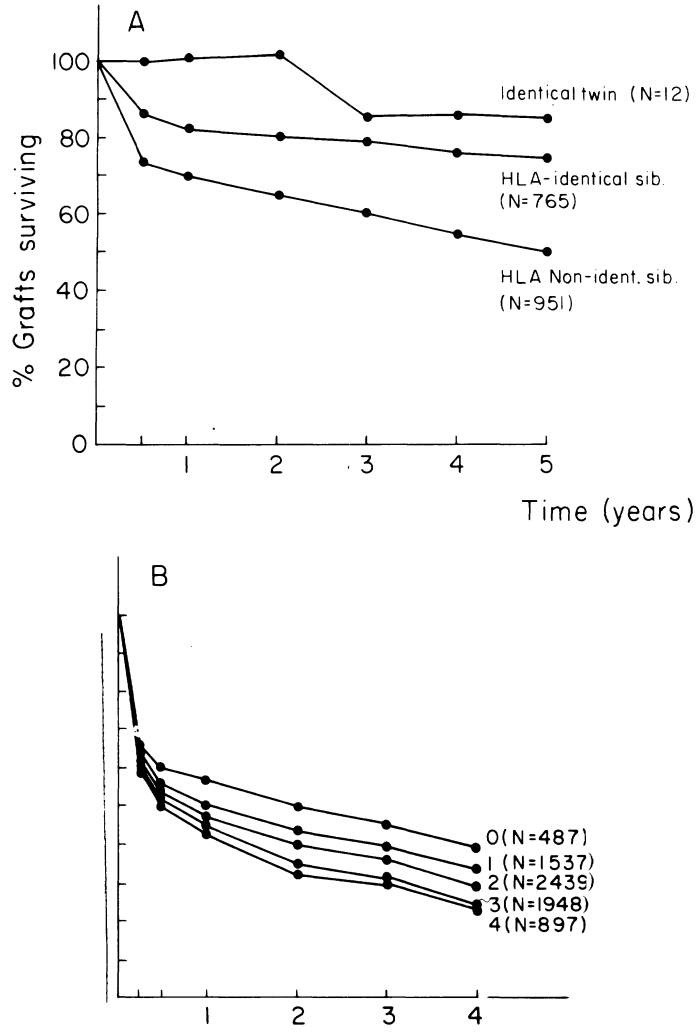

Figure 3. Graft survival rates for related donor kidney grafts by donor category (3A) and first cadaver-donor kidney transplants by the number of mismatched HLA-A,B, antigens (3B). Graft survival rates are significantly better at all time intervals tested in both groups (data from Opelz and Terasaki).

clearly related to HLA compatibility in living related transplants (Figure 3A) and 1 year graft survival rates are 100% in identical twins, 85% in HLA identical sibling transplants, and 69% in 1 haplotype-matched donor-recipient combination [15]. The superior graft survival rates in identical twin transplants, as compared to HLA identical sibling transplants, and the requirement for immunosuppressive therapy in the latter

situation brings into focus other non-MHC determinants that may influence transplant outcome. This possibility is further strengthened by the findings of a lack of clear-cut discernible differences in cadaveric graft survival rates based on matching for HLA- A, B antigens alone. However, there is a certain trend now reaching statistical significance of improved graft survival rates with better matching in cadaveric transplantation [18] (Figure 3b).

The most immediate benefit that results from successful transplantation is the freedom from dialysis with its attendant restrictions. Though salt restriction must be continued, especially during high dose steroid therapy, a much liberalized diet can be enjoyed by the recipient. Not infrequently, the patient develops a better appetite and taste for his food. Improvement in anemia with return to normal hemoglobin levels, as well as diminished debilitation from neuropathy and bone disease, can reliably be expected following successful transplantation. Gonadal functions improve and pregnancy has been carried to full term with functioning allografts.

Multiple factors appear to determine the outcome of transplantation, though much controversy exists regarding the relative contribution of each factor. Donor specific presensitization to HLA- A, B antigens, as determined by a crossmatch, is accepted universally as an absolute contraindication [20]. Presensitization to B cell antigens, as well as to a panel of normal lymphocytes, is associated with variable graft outcome. Pretransplant blood transfusions seem to have a salutary effect on cadaveric graft survival [17] but the risks of donor specific sensitization, leading to non-transplantability, is a potential one with indiscriminate use of transfusions.

4.6. Immunologic Monitoring of the Renal Allograft Recipient

The ultimate aim of monitoring the transplant recipient with a battery of immunologic tests is to provide predictive and prognostic information that can help the clinician to intervene prior to functional and structural impairment of the allograft secondary to rejection [9]. Better understanding of the mechanism of rejection is an additional bonus from such an approach.

Though the criteria, such as urine volume, serum creatinine and peripheral leucocyte count, have provided excellent guidelines for the individualization of immunosuppressive regimens, they fail to take into consideration the immunologic reactivity of a particular recipient when therapeutic decisions are made. The immunologic protocols, therefore,

have been developed to overcome some of the shortcomings and have led to the development of a variety of test systems that can detect both cellular and humoral immunity. Donor specific tests, such as LMC, ADCC, and CDC are often positive during rejection episodes, especially when done sequentially in the post-transplantation period. Cytotoxic T cells and donor specific antibodies can be detected preceding or in association with rejection and, as such, can serve as reasonable correlates of rejecion [11]. Non-donor specific tests, such as spontaneous blastogenesis, E rosette levels, and mitogen-induced blastogenesis, can also provide additional guidelines for therapeutic intervention.

It should be stressed that no individual test or even a comprehensive battery can substitute for clinical assessment of the patient. The best benefit, of course, is realized when the results of these tests, done with particular attention to technical details, supplement rather than supplant clinical judgment.

5. COMPLICATIONS

The list of potential complications related to transplantation is summarized in Table 4. It should be stressed that of the many complications in the post-transplantation period, only some are clearly attributable to the transplantation procedure per se. Certain other complications, such as bone disease, lipid abnormalities, and hypertension, may simply represent progression of the original disease processes, albeit augmented in part by the immunosuppressive drugs.

5.1. Primary Non-function

Anuria or oliguria, persistent for more than one month post-transplantation, suggest non-viability secondary to severe ischemic injury, major vessel occlusion or irreversible rejection. Potentially reversible causes of non-function, such as outlet obstruction, must always be excluded before advocating nephrectomy. Serial renal scans and biopsy can provide useful therapeutic guidelines.

5.2. Urinary Leakage

Careful surgical technique, with preservation of ureteral blood supply, has resulted in the reduction in the incidence of urinary leaks leading to fistula formation to less than five percent. Prompt provision of adequate

Table 4. Complications related to transplantation.

I. *Operative period:*
1. Iatrogenic damage of the graft.
2. Coagulopathies.
3. Respiratory depression.
4. Atelectasis.
5. Electrolyte abnormalities.
6. Blood volume and pressure alterations.

II. *Post-operative period:*
1. Wound:
   a. Infection.
   b. Bleeding and hematoma.
   c. Dehiscence.
   d. Lymphocele.
2. Renal:
   a. Acute tubular necrosis.
   b. Rejection.
   c. Rupture.
   d. Infection.
   e. Recurrence of the original disease.
3. Renal vascular:
   a. Arterial and venous thrombosis.
   b. Aneurysm.
   c. Stenosis.
   d. Disruption of arterial anastomosis site.
4. Urological:
   a. Obstruction.
   b. Stenosis.
   c. Fistula and sinus tracts.
   d. Infection.
5. Cardiovascular:
   a. Hypertension.
   b. Atherosclerosis and atherosclerotic heart disease.
6. Pulmonary:
   a. Bacterial, fungal and viral infection.
   b. Atelectasis.
   c. Pulmonary edema.
   d. Transplant lung (?)
7. Gastrointestinal:
   a. Hepatitis.
   b. Pancreatitis.
   c. Peptic disease.
   d. Bowel perforation.
8. Hematologic:
   a. Coagulopathy.
   b. Leukopenia and thrombocytopenia.
   c. Erythrocytosis.
   d. Microangiopathic hemolytic anemia.

drainage of urine is mandatory to avoid infection and early spontaneous closure of fistulas. Reimplantation of ureter or other reconstructive procedures might occasionally be necessary.

5.3. Lymphocele

Interruption of lymph channels, at the time of surgery, may lead to inadequate drainage with consequent collection of lymph around the graft. All visible channels must be ligated meticulously at the time of surgery to prevent the development of lymphoceles. Once formed, they may be drained externally or internally. Very rarely, nephrectomy might become necessary for the management of intractable lymphocele.

5.4. Infections

Defects in the immunological integrity, resulting from intensive immunosuppressive therapy, is responsible for the transplant recipient's undue susceptibility to fungal, bacterial, and viral infections. Impaired T cell immunity has been reported to be responsible for fungal and viral infections. Pulmonary infections, with a variety of unusual organisms, including pneumocystis, candida, aspergillus, nocardia, and cytomegalovirus occasionally occur, especially in recipients treated with high dose steroid. Urinary tract infections occur in about 70 percent of recipients. In the absence of reflux, conventional antibiotic treatment can be expected to eradicate the infection. The morbidity and mortality witnessed in the earlier years of transplantation has been significantly reduced by a more conservative approach to the use of immunosuppressive drugs. A high index of suspicion, early initiation of appropriate antibiotics, and even temporary discontinuation of immunosuppressive therapy have all contributed to the recent declining morbidity and mortality associated with infectious complications in the post-transplantation period.

5.5. Hypertension

Hypertension occurs in 50 percent of recipients some time during the post-transplantation period. Hypertension can result from renal artery stenosis, just distal to the anastomosis or due to intrarenal vascular disease secondary to chronic rejection. Native kidneys might also be a contributory factor. Acute rejection is also associated with hypertension, and is amenable to successful anti-rejection therapy. Sudden onset of

severe hypertension or a loud bruit at the transplant site, with minimal alteration in renal function, are signs of transplant renal artery stenosis. Renal vein renin studies may provide some diagnostic information. However, peripheral renin levels are less informative since they are often normal or low even in the presence of severe transplant renal artery stenosis (one-kidney Goldblat hypertension). Surgical correction or percutaneous dilation of the stenosis may alleviate the hypertension and may also improve renal function in selected cases (see Chapter 12).

5.6. Lipid Abnormalities

The abnormal lipid profiles observed in patients on hemodialysis may continue despite excellent graft function. Daily corticosteroid administration may be responsible for the perpetuation of the lipid abnormalities, and alternate day steroid therapy has been advocated to mitigate this problem. Low levels of high density lipoprotein and increased very low density lipoprotein, plasma triglycerides, and cholesterol have been reported in transplant recipients.

5.7. Gastrointestinal System

Recurrent peptic ulceration is not uncommon, and bleeding and perforation is associated with a high mortality rate. Hence, prophylactic vagotomy and pyloroplasty or antrectomy before transplantation is recommended for patients with peptic ulcer disease. Duodenal ulcer has been found after transplantation in 8 percent of recipients. Pancreatitis, sometimes attributed to high doses of corticosteroids, may also be a prominent problem. Liver disease is usually secondary to hepatitis B virus. Sometimes, cytomegalovirus may also be responsible. Azathioprine has been implicated in a minority of patients with abnormal liver function tests. Temporary discontinuation or substitution with cyclophosphamide may solve the problem.

5.8. Bone Disease

Although renal osteodystrophy usually improves after successful renal transplantation, hyperparathyroidism may persist (tertiary hyperparathyroidism) for years. Subtotal parathyroidectomy may be necessary to correct the hypercalcemia, hypophosphatemia and high phosphate clearance. Decreased amounts of cancellous bone formation and a low rate

of mineralization resulting from high dose corticosteroids may act as contributory factors in the pathogenesis of aseptic necrosis observed in 20% of transplant recipients. Some patients with progressive aseptic necrosis and intractable pain may require hip joint replacement with prosthesis.

5.9. Malignancy

The risk for the development of malignancy is 35 times higher in transplant recipients as compared to normal individuals [21]. The most common malignancies include skin and cervical cancers and lymphoma, particularly reticulum cell sarcoma in the brain. Surgical intervention with reductions in immunosuppressive therapy is effective for managing patients with tumors of the skin, lip, or uterine cervix. However, the prognosis of those patients with malignant lymphoma or visceral neoplasm is poor, even if immunosuppressive therapy is discontinued. The incidence of cancer recurrence after transplantation in those who have a history of malignancy before transplantation is unknown. A period of observation of at least a year between nephrectomy and transplantation is recommended for patients with primary renal tumors. Total withdrawal of immunosuppressive drugs and transplant nephrectomy is indicated for accidental transplantation of tumor cells along with the graft.

5.10. Recurrence of the Original Disease in Renal Grafts

Some renal diseases may recur in the renal grafts days to years after transplantation [8]. The renal diseases that can recur in renal grafts include immunological (membranoproliferative, anti-GBM antibody nephritis, focal segmental sclerosis, IgA nephropathy, etc.), genetic (hereditary nephritis) and metabolic renal diseases (diabetic nephropathy, amyloidosis). Although the precise incidence of recurrence of such a disease is unknown, it is seen in approximately 10 to 20% of long-surviving renal grafts. The clinical course of the recurrent disease is variable ranging from only pathologic changes in the graft without clinical manifestations to rapid progression of the disease to end-stage. It is interesting to note that recurrence occurs despite long-term use of immunosuppressive drugs that are often recommended for the management of such diseases. In contrast, membranous nephropathy and lupus nephritis, prototype immune complex renal diseases, rarely recur in the renal graft.

5.11. Miscellaneous Complications

Other complications, such as diabetes, cataracts, alopecia and obesity, have been frequently observed after transplantation and have been attributed to the immunosuppressive therapy.

6. FUTURE PROSPECTS

Much has been achieved in the last two decades of experience with renal transplantation. Morbidity and mortality, associated with non-specific immunosuppressive therapy, have been reduced to a rate quite comparable to or better than alternate methods of management of end-stage renal disease. Immunologically, it is no surprise that histoincompatible grafts fail; it is more surprising that they function in such a high percentage of recipients. Matching for additional gene products of the MHC, such as DRw antigens [22, 23], avoidance of adverse presensitization and immunologic monitoring of the graft recipient [11], can all be expected to boost graft survival rates. Newer drugs such as cyclosporin A [7], biological agents like retroplacental gamma globulin [24], thoracic duct drainage, and fractionated total lymphoid irradiation [28] all hold promise. Extension of many enhancement protocols, including the induction of anti-idiotypic antibodies [5] and suppressor cells from animal models to clinical settings have the potential to help attain the elusive goal of donor specific immunosuppression. More importantly, newer insights into mechanisms of many disease processes have already started to unfold with the detailed study of the MHC, a complex that was originally studied for the sole purpose of transplantation.

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16. DIALYSIS AND TRANSPLANTATION: DIETARY MANAGEMENT

JACQUELINE CHAMI

Dietary therapy of patients with renal disease is of prime importance in their medical management. Many patients with chronic renal failure or undergoing maintenance dialysis are undernourished. This chapter outlines principles of management of nitrogen and caloric intake designed to minimize uremic toxicity and provide optimal nutrition.

1. DIETARY MANAGEMENT FOR PATIENTS WITH CHRONIC RENAL FAILURE NOT TREATED WITH DIALYSIS

1.1. General principles

In advanced renal failure, dietary therapy is concerned with the management of protein and caloric intake and the maintenance of fluid, electrolyte and acid-base homeostasis. Severe reduction in renal function leads to an accumulation of metabolites in the plasma as a result of protein catabolism. These nitrogenous waste products are responsible for some of the symptoms and signs of uremia [7]. Limiting protein breakdown diminishes the concentration of these substances in the plasma and improves the uremic syndrome. Minimum protein breakdown can be achieved by prescribing a diet for the patient containing just enough protein to replace endogenous protein loss. This loss amounts to approximately 20 to 25 g protein per day [9] when adequate calories are supplied from carbohydrate and fat. The type of protein ingested should be primarily of high quality * to include the daily requirements of essential amino acids plus histidine [22]. A high proportion of essential amino acids is necessary in a protein restricted diet to provide these minimal requirements. In 1948, Borst wrote '... the basic principles of the dietetic treatment in uremia is the restriction of protein and the energy requirements being supplied from carbohydrate and fat' [5].

* High quality proteins are those sources of protein containing a high proportion of essential amino acids.

1.2. Protein intake

In chronically uremic patients, many of the signs of uremic toxicity, such as anorexia, nausea, vomiting, and twitching, usually occur when the serum urea nitrogen (SUN) level rises above 90 mg/dl. Dietary protein restriction should be instituted for patients with advanced renal failure (SUN >90 mg/dl, serum creatinine >7 mg/dl and creatine clearance <10 ml/min) to maintain the SUN below 90 mg/dl and to improve symptoms of uremia.

There is a direct relationship between the ratio of SUN to serum creatinine and protein intake in chronically uremic patients [15]. The level of protein intake related to the SUN/creatinine ratio is illustrated in Figure 1. This relationship provides a simple tool for the prescription of appropriate amounts of dietary protein to maintain a given degree of azotemia at different levels of serum creatinine. For instance, assume that a patient has a serum creatinine of 10 mg/dl and it is desired to maintain SUN at approximately 70 mg/dl with a SUN/creatinine ratio of 7. From Figure 1, it can be predicted that a dietary protein intake of 50 g/day will maintain this ratio. In addition, by measuring the SUN/creatinine ratio in a patient, the degree of adherence to dietary protein prescriptions can be assessed. It is, however, not always possible to accurately relate the protein intake to the SUN/creatinine ratio, especially in patients with a very small lean tissue mass.

In general, the level of protein intake in relation to renal function should be as follows:

> When the GFR is 5 to 10 ml/min, protein intake should be 40 to 50 g/day.
>
> When the GFR falls below 4 to 5 ml/min, protein intake should be 20 to 25 g/day.

This level of protein intake often controls uremic toxicity.

When the uremic patients are given low-protein diets, it is important that they ingest high biological value proteins; that is, those in which 40% or more of the amino acids are essential amino acids. This prevents poor protein utilization and negative nitrogen balance. A list of foods containing protein of high quality is given in Table 1.

An adequate supply of calories is of major importance for uremic patients ingesting restricted amounts of protein. In the absence of an adequate caloric intake, protein is utilized as a source of energy and negative nitrogen balance ensues. The caloric supply from carbohydrate and fat should be approximately 2500 Kcal/day to allow proper utilization of a low protein diet. High carbohydrate intake of more than

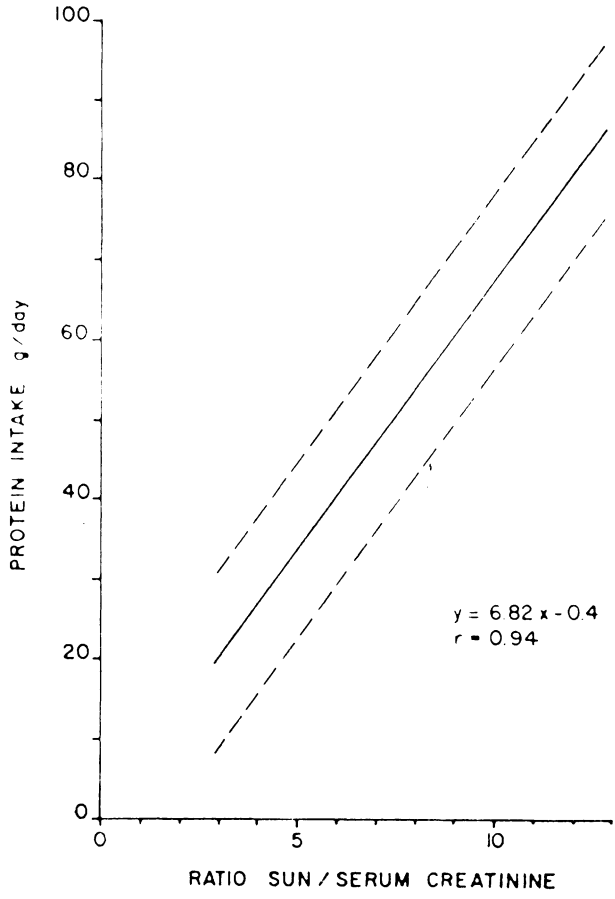

Figure 1. This figure is reproduced from Shaul G. Massry, M.D. and Alvin L. Seller, M.D. (eds), Clinical Aspects of Uremia and Dialysis, 1976. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.

Table 1. Foods containing protein of high biological value

Cheese:	Fish:	Meat:
Cheddar	Cod	Beef
Parmesan	Flounder	Ham
Swiss	Halibut	Pork
Chicken	Shrimp	Veal
Egg	Tuna	Milk

300 g/day given simultaneously with protein helps provide the calories for energy and also stimulates insulin production that is required for efficient utilization of the proteins. Diabetic and obese patients may require a lower calorie intake.

Present evidence suggests that diets that provide adequate calories and 40 g of protein (0.55 to 0.6 g/kg/day) (primarily of high biological value), maintain neutral or positive nitrogen balance and control uremic toxicity in patients with GFR between 5–10 ml/min [14].

When the GFR falls below 4 or 5 ml/min, the safety and the effectiveness of dietary therapy becomes controversial. Some evidence indicates that if the caloric supply is adequate, many patients respond well to a daily intake of 20–23 g of high quality proteins (Giordano-Giovanetti Diet) [2, 3]. Other studies, however, have shown that uremic patients become catabolic on such a diet [17]. Diets that provide 20 g of protein and that are supplemented with 20 g of essential amino acids significantly improve nitrogen utilization [1]. This dietary regimen requires a team of doctors, nurses and dietitians that is particularly devoted to its success as well as a very cooperative patient. It should be recognized, however, that the benefit/risk ratio of maintaining patients with GFR's below 4 ml/min on low-nitrogen diets compared with treatment by maintenance dialysis and more liberal protein intake has not yet been established.

1.3. Caloric supply

In uremic patients ingesting 40 g protein/day or less, the optimal caloric intake of at least 2500 Kcal (45 Kcal/kg/day) must come from carbohydrate and fat. Major sources of carbohydrate calories (bread, potatoes, pasta, cake) are also rich in proteins, so they cannot be given unmodified in renal failure. Low-protein breads and pasta (Aproten) are now available, and with the help of a skillful dietitian, their taste can become acceptable. Low protein wheatstarch cookies are tasty and appreciated by uremic patients. A pure carbohydrate calorie source is de-ionized liquid glucose (cal power). It is not sweet and does not have an osmotic effect when given in large amounts. Vegetable oil and margarine represent sources of calories that are low in electrolytes and protein-free. A list of high-calorie, low-protein, low-electrolyte foods is given in Table 2.

Table 2. High calorie, low protein, low electrolyte supplements*.

Product	Protein† (gm)	Sodium† (mg)	Potassium† (mg)	Kilo-calories†	Brand Name of Manufacturer
Low protein starches					
Wheatstarch	0.1	10	2	107	Cellu® from Chicago Dietetic Supply Paygel P® from General Mills Chem.
Cornstarch	0.1	0	0	105	Any brand.
Tapioca	0.2	1	5	105	Any brand.
Low protein bread	0.2	12	7	110	Dietetic Paygel® from General Mills Chem. Bavarian Specialty Foods. San Pedro, CA. Jolly Joan® from Ener-G Foods, Inc.
Low protein bread mix	0.1	16	3	123	Dietetic Paygel Baking Mix® from General Mills Chem. Jolly Joan—Low Protein Baking Mix, from Ener-G Foods, Inc.
Low protein rusks	0.3	9	12	126	Aproten®. manufactured in Italy by Carlo Erba. Distrib. in USA by General Mills Chem. Inc.
Low protein macaroni, noodles and spaghetti	0.2	6	3	102	Aproten®, manufactured in Italy by Carlo Erba. Distrib. USA by General Mills Chem. Cellu®—Low Protein Macaroni. Chicago dietetic Supply Co.
Wheatstarch cookies	0.1	5	3	113	Bavarian Specialty Foods, San Pedro, Calif.
Fats					
Butter, unsalted	0.2	2	6	200	Any brand.
Margarine, unsalted	0.2	2	6	200	Any brand.
Vegetable oil	0	0	0	252	Any type.
Lard	0	0	0	252	Any brand.
French dressing, low sodium	0	2	20	176	Cellu, from Chicago Dietetic Supply Co.
Fruit Drinks					
Cranberry juice	0.1	0.3	3	20	Any brand.
Grape Tang®	0	2.0	0.3	15	Post® beverages, from General Foods Kitchens
Kool Aid®, regular and pre-sweetened	0	2.0	0.1	11	General Foods Kitchens.
Lemonade	0	0.1	4	13	Any brand.
Limeade	0	0.1	1	12	Any brand.
Special food supplements					
De-ionized liquid glucose	0	3.8	0.4	72	Cal Power®, from General Mills Chemicals, Inc.
Hydrolysate of cornstarch and vegetable oil	0	2.9	1.1	143	Controlyte®, from Doyle Pharmaceutical Co.
De-ionized liquid glucose polymers	0	4.0	0.2	74	Hycal®, from Beecham Messangill. Pharmaceuticals.
Corn oil emulsion	0	20	0.8	180	Lipomul Oral®, from Upjohn Company.
Sweets—Polysaccharides					
Cranberry sauce	0.1	1	9	44	Any brand.
Sugar, white	0	1	1	125	Any brand.
Jams and Jellies	0.1	3	27	83	Any brand.
Honey	0	1	15	96	Any brand.
Gum drops	0	11	2	104	Any brand.
Jelly beans	0	4	1	110	Any brand.
Plain hard candy	0	9	1	116	Any brand.
Danish dessert	0.1	3	1	27	Junket® from Salada Foods.
Fruit and water ices	0.1	1	1	18	Any brand.

* Per 30 g portion unless otherwise stated. (Bowes and Church, in C.E. Church and H.N. Church (eds.). *Food Values of Portions commonly Used,* 11th ed. [Philadelphia, J.B. Lippincott. 1970]).

† Data are from manufacturers' reports or food tables and have not been confirmed analytically by the author.

Table 2. (continued)

Product	Protein† (gm)	Sodium† (mg)	Potassium† (mg)	Kilo-calories†	Brand Name of Manufacturer
Nondairy Creamers and Whipped Toppings‡					
Collee Rich®	0.2	24	27	94	Rich Products Corporation.
Cool Whip®	0.2	4	1	60	General Foods Kitchens.
Desert Whip®	0.6	40	20	164	Presto Food Products, Inc.
Mocha Mix®	0.2	60	35	86	Presto Food Products, Inc.
Rich's Whip Topping® (Whipped)	0	7	1	32	Rich Products Corporation.

‡ In portions of one-fourth cup.

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1.4. Fluid, sodium and potassium intake

The amount of sodium, potassium and water intake must be adjusted for each patient. Dietary sodium recommendations depend primarily on urinary losses along with factors such as blood pressure, state of hydration and serum sodium concentration. Uremic patients with creatinine clearance of 5–10 ml/min tend to retain potassium and to be in positive H^+ balance. Dietary potassium should not exceed 50–60 mEq/day and all potassium rich foods should be restricted. A list of such foods is given in Table 3. Sodium exchange resins, such as Kayexalate to control hyperkalemia and sodium bicarbonate to control acidemia can only be given if the patient can excrete the sodium load.

Table 3. Potassium-rich foods

Fruit:	Miscellaneous:
Apricot	Artichoke
Avocado	Beets
Banana	Broccoli
Cantaloupe Melon	Brussels Sprouts
Citrus Fruits	Chick Peas
Coconut	Chocolate
Dates	Green Leafy Vegetables
Honeydew Melon	Lentils
Mango	Lima Beans
Papaya	Milk (low-sodium)
Peaches	Mixed Nuts
Prunes	Mushrooms
Pumpkin	Potatoes/Yams
Raisins	Rhubarb
Tomatoes	Soy Beans
	Squash
	Sunflower Seeds

The administration of lasix in large amounts (1 g/day) may help increase urinary volume and salt excretion in patients who have a tendency to retain salt and water. The total fluid intake per 24 hours should equal the maximum amount the kidneys can excrete without weight gain or the development of congestive heart failure plus 400 cc for insensible losses. Table 4 outlines data useful in sodium and potassium management in renal failure.

Table 4. Conversion of grams to milliequivalents

1 gm Na	= 43 mEq Na
1 gm NaCl	= 17 mEq Na
1 gm Na HCO_3	= 12 mEq Na
1 gm K	= 25 mEq K
1 gm KCl	= 13 mEq K

Drugs' Sodium and Potassium Content

Potassium penicillin G has 1.7 mEq K per million units.
Cephalothin has 2.3 mEq Na per gram.
Carbenicillin has 4.7 mEq Na per gram.
Kayexalate 1 gm orally gives 2–3 mEq Na.
Salt substitute: one (1) packet (1 gm) = 12 mEq K.

1.5. Vitamin supplements

Low-protein diets may lead to inadequate vitamin intake. These diets should therefore be supplemented with preparations providing minimum daily requirements of water soluble vitamins including folic acid. The daily requirement of pyridoxine may be as high as 10 mg in renal failure patients.

1.6. Mineral requirements

The major mineral supplements that are used are calcium and iron. Because of decreased intestinal absorption of calcium, dietary intake should be supplemented with calcium gluconate to provide the minimum daily requirements of 1–2 g/day of elemental calcium. A low plasma calcium level in the presence of a normal plasma albumin level should be treated with 1,25-dihydroxycholecalciferol (Rocaltrol®) to increase intestinal absorption of calcium. Iron may not be absorbed efficiently in uremia. Several factors may contribute to poor iron absorption. Some patients have a high gastric pH that impedes iron absorption. The concomitant ingestion of bicarbonate or antacids and the ingestion of iron pills with meals to reduce gastric irritability, may both contribute

to poor iron absorption. Anemia is almost universal in renal disease; but, the major defect is probably a lack of erythropoietin. Nevertheless, iron deficiency has been frequently documented in renal failure. Routine administration of iron supplements has been recommended; Ferrous sulfate, 300 mg three times daily one-half hour after meals, may be used. Zinc concentrations in serum and hair may be low. Preliminary data indicate that abnormal taste and impotence in uremic patients may improve with zinc supplementation.

In summary, patients with severe renal failure (creatinine clearance 5 to 10 ml/min) can be maintained successfully on a diet which consists of 40 g of protein primarily of high biological value and 2500 calories supplied from carbohydrate and fat, always with supplemental vitamins.

For patients with more advanced renal failure (creatinine clearance below 4 ml/min), it is probably preferable to initiate dialysis therapy.

2. DIETARY MANAGEMENT FOR PATIENTS WITH CHRONIC RENAL FAILURE TREATED WITH DIALYSIS

Many patients undergoing maintenance hemodialysis or peritoneal dialysis are undernourished and some clinical and laboratory findings resemble those found in patients with protein-calorie malnutrition. These include decrease in strength, body weight and skin fold thickness, muscle wasting, increased extracellular fluid volume and decreased intracellular water and body fat, low concentrations of plasma proteins, and low essential to non-essential plasma amino acid ratios [6, 25]. This wasting syndrome frequently occurs in dialysis patients secondary to inadequate nutrient intake. Requirements for protein, calories, and certain vitamins may be higher than normal in dialyzed patients, because of losses during dialysis, the metabolic stress of uremia itself and frequent intercurrent illnesses. In addition, poorly dialyzed patients have a greater tendency to be undernourished because of more prominent uremic symptoms and anorexia.

Kopple [13] evaluated protein and energy intake during a 12 months period in 35 men on maintenance hemodialysis. He found that the average daily protein intake for the 12 month period was about 1 g/kg of body weight/day. This intake of protein was similar to that commonly prescribed for hemodialysis patients. On the other hand, many dialysis patients had caloric intakes of less than 75% of the recommended daily allowance for normals (35 Kcal/kg/day). In addition, marked

decreases in protein and energy intake were frequent in individual patients during and immediately after dialysis and during intercurrent illnesses. Holliday and Chantler[11] reported that uremia causes an exaggerated catabolic response to stress. Uremic rats had greater protein breakdown than control rats following a 36 hour fast. Frequent episodes of fasting prior to laboratory procedures, inadequate intake during illnesses and anorexia associated with the dialysis procedure may all be detrimental to the uremic patient. Evidence of protein-calorie malnutrition was found to be more common in dialysis patients who had fluctuating food intakes[23]. Dialysis patients should be encouraged to have frequent and regular feedings. The dialysis process may perturb the patient's nutritional status. Approximately 5 to 8 g of free amino acids and 3 to 4 g of small peptides are removed during a four-hour hemodialysis in fasted patients. Ingestion of food increases the loss slightly. Adding glucose to dialysate reduces amino acid losses since glucose lowers plasma concentrations of amino acids[19]. Significant quantities of protein, mainly albumin, can be removed during peritoneal dialysis. The amount of protein removed varies from 0.3 to 2 g during each two-litre exchange. With acute peritonitis, protein losses can exceed 10 g during each two-litre exchange.

Glucose losses during hemodialysis with glucose-free dialysate may enhance gluconeogenesis and if the patient is fasting or poorly nourished, the glucose generated to replace that lost during dialysis (approximately 50 g) may be largely derived from protein. To minimize perturbations caused by losses of amino acids and glucose during hemodialysis, it may be advisable to administer glucose intravenously or in dialysate in patients with poor food intake and who are malnourished.

Because of the frequent occurrence of wasting syndromes, careful attention to dietary intake of protein and calories is of prime importance in the management of dialysis patients.

2.1. Dietary protein intake for patients treated with hemodialysis

When uremic patients are treated with dialysis, there is no need for severe dietary protein restriction. Protein intake should be sufficient to combat the added loss of amino acids in the dialysate, but not so great as to cause worsening of the uremic syndrome or increase in the SUN level above 90 ml/dl. With a more liberal protein diet, the biological value of protein is somewhat less important, since in such protein diets the essential amino acid content of lower quality protein often satisfies the minimum daily requirements. However, the minimum daily requi-

rements of essential amino acids (6 to 12 g in normals) may be higher in dialysis patients. It is, therefore, recommended that most of the protein intake of dialysis patients should consist of high-quality protein. The degree of dietary protein restriction in dialysis patients depends on the dialysis regimen. When dialysis frequency or duration is increased, the maximum safe protein intake is increased, and the minimum protein needs rise due to increased losses of free amino acids. When uremic patients are undergoing hemodialysis three times a week for four to five hours per treatment, a dietary protein intake of 1 to 1.2 g/kg of body weight/day is usually nutritionally adequate and well tolerated. Half of the dietary protein should be of high biological value. Higher protein intake with this dialysis regimen may increase the SUN level and uremic symptoms. In poorly nourished patients, dialysis frequency may be increased to allow the patient to eat more protein and stay free of uremic symptoms.

2.2. Dietary protein intake for patients treated with peritoneal dialysis

Dietary protein requirement for patients undergoing maintenance peritoneal dialysis are increased because of the greater amino acid and protein losses during the treatment. High protein intake of 1.5 g/kg of body weight/day appears to compensate for the protein losses with maintenance of serum protein levels in the normal range and positive nitrogen balance [21]. Peritonitis may increase protein losses to as much as 5 to 10 times normal for a prolonged period of time after peritoneal inflammation is cleared. Albumin should be administered intravenously during episodes of peritonitis. Patients who are unable to maintain high protein intakes while on peritoneal dialysis are prone to develop wasting syndromes and should not continue on this mode of therapy.

2.3. Caloric requirements during maintenance dialysis

The recommended caloric intake for healthy men is 34–45 Kcal/kg/day and for women 31–36 Kcal/kg/day. Caloric requirements in dialysis patients have not been determined. It is known, however, that dietary energy intake influences the relationship between nitrogen intake and balance in uremic patients as it does in normals. Given the same nitrogen intake, an increase in energy intake improves nitrogen balance, especially when there is depletion of body protein or muscle mass [12]. In addition, uremia, infection and loss of nutrients during dialysis may all increase caloric requirements. Kopple [16] has recommended a mini-

mal caloric intake of 35 Kcal/kg/day, and this should be increased in patients who are malnourished or subjected to any stress that might increase energy requirements.

2.4. Vitamin requirements during maintenance dialysis

The decreased blood levels of folic and ascorbic acids in patients undergoing maintenance dialysis [20, 24] indicate a need for dietary supplements of these vitamins. Vitamin C deficiency probably results from a combination of losses during dialysis and avoidance of foods that are high in Vitamin C, since many of these are also high in potassium. A daily supplement of 1 mg of folic acid and 100 mg of ascorbic acid should prevent or correct deficiencies of these vitamins. In addition, because of losses during dialysis of other water-soluble vitamins and the frequency of poor dietary intake in dialysis patients, a supplement providing the daily recommended allowance of niacin, riboflavin, thiamin, biotin, pantothenic acid and B_{12} is recommended. These can be simply given as multiple vitamins. Vitamin B_6 (pyridoxine) deficiency frequently occurs in patients with uremia, particularly those on dialysis [18]. The minimum dietary supplement of pyridoxine hydrochloride necessary to correct or prevent B_6 deficiency in dialysis patients is about 10 mg/day. This dose is above the recommended daily allowance of pyridoxine in normals and exceeds the pyridoxine content of most multiple vitamin supplements. There is no need for supplements of Vitamin A, E or K in dialysis patients. In summary, daily vitamin supplements should include 1 mg of folic acid, one multiple vitamin that contains at least 100 mg of ascorbic acid and 10 mg of pyridoxine.

2.5. Anabolic steroids

Androgenic steroids are used in chronically uremic patients to enhance red cell production. The anabolic effect of these agents is transient. It may be useful, however, in situations where a temporary decrease in net protein breakdown may be of value. Thus, anabolic steroids may be used to minimize catabolism in uremic patients with acute intercurrent illnesses and to enhance utilization of dietary protein and calories in uremic patients who are severely malnourished or critically ill. Commonly used anabolic hormones include testosterone enanthatate (Delatestryl) and nandrolone decanoate (Decadurabolin). The latter has less androgenic effects and is used in women.

2.6. Management of inadequate protein and caloric intake

There are several techniques that can be employed to improve dietary intake of dialysis patients ingesting a suboptimal diet. Many patients respond to vigorous, persistent encouragement from the medical staff to increase food intake. A skillful dietitian rearranging meal plans and recipes to satisfy the patient's taste may be of great help. Sometimes, poor food intake may be associated with depression or family and social problems. In this case, a psychiatrist or a social worker may be helpful. Patients may be poorly dialyzed and poor food intake may be caused by uremic symptoms, such as anorexia, nausea and vomiting. In this case, increasing dialysis time or frequency may be helpful. Food intake may also be improved by the use of high-calorie supplements (Table 2). In addition, there are a number of commercial high-calorie, high-protein, and essential amino acid-rich food supplements (Isocal, Amin-Aid). Oral or intravenous supplements with essential amino acids or their keto acid analogues have been used for treatment of dialysis patients [8, 10]. However, there is presently no evidence that these materials have advantages over protein supplements for dialysis patients who can ingest high quantities of protein. It is likely that essential amino acid supplements are of value only when the protein intake is very low.

2.7. Evaluation of adequate dietary intake

Deviation from dietary prescription is not uncommon in dialysis patients. It is, therefore, necessary to evaluate periodically the patient's dietary intake. Frequent dietetic interviews should be performed by doctors and dietitians. The use of dietetic diaries usually provides accurate information concerning the intake of different nutrients. Adequacy of sodium and water intake can be assessed by the state of hydration, interdialysis weight gain and the serum sodium concentrations. Predialysis serum potassium levels should indicate the degree of adherence to potassium restricted diets. Pre-dialysis SUN levels correlate closely with dietary protein intake when factors such as duration and frequency of dialysis are taken into account. The daily increment in SUN levels also reflects the protein intake and is independent of the dialysis regimen. In case of a catabolic stress, the relation between protein intake and both the pre-dialysis level and the daily increment in the SUN is no longer accurate. Adequacy of protein intake can also be assessed by ideal body weight change, serum levels of albumin and transferrin and nitrogen balance studies.

In summary, patients treated with hemodialysis should be prescribed a dietary protein intake of 1–1.2 g/kg/day. For patients treated with peritoneal dialysis, the protein content of the diet should be in the range of 1.5 g/kg/day. Half of the protein intake should be of high biologic value. Dialysis patients should receive at least 35 Kcal/kg/day. In obese patients or in patients with hypertriglyceridemia, caloric intake may need to be reduced. Sodium and potassium intake should be restricted. In general, a diet providing 2 g of sodium and 2.5 g of potassium is adequate. Fluid intake should not exceed 1500 ml/day, especially when the patient is anuric. The diet should always be supplemented with multiple vitamins including folic acid and pyridoxine. Oral iron may be given especially when iron deficiency is present.

3. DIETARY MANAGEMENT FOR PATIENTS WITH ACUTE RENAL FAILURE

Patients with acute renal failure continue to have a high mortality. This is often due to the setting in which acute renal failure occurs, such as trauma, extensive surgery, sepsis, and severe underlying illnesses. In addition, these patients are frequently undernourished, and this may contribute to the high mortality rate. The hypercatabolic state of these patients induces severe tissue breakdown and protein depletion requiring rigorous nutritional management. It is possible that if the nutritional status could be improved and catabolism reduced, host resistance and patient survival may be increased.

Conservative dietary management limited to severe protein and fluid restriction and small quantities of energy supplied by intravenous infusion of 5% dextrose solution is not nutritionally adequate. Protein repletion with high nitrogen intake and the provision of large amounts of calories are necessary to meet the nutritional needs of these acutely ill patients. When the gastrointestinal tract cannot be used, parenteral nutrition should be instituted.

4. PARENTERAL NUTRITION

The amount of protein that is required to reduce catabolism and possibly to induce anabolism (positive nitrogen balance) is in the order of 50 g/day. A mixture of essential and non-essential amino acids is preferable to protein hydrolysate for more efficient utilization. The amount

of calories required to enhance positive nitrogen balance is approximately 3000 Kcal/day [4]. Caloric requirements are supplied in the form of hypertonic dextrose (50–70%) to reduce the amount of fluid infused. The mixture of hypertonic dextrose and amino acid solution is administered through a central vein. High nitrogen requirements and the infusion of a substantial amount of fluid may increase the need for dialysis. Frequent dialysis is an important part in the management of these patients. Dextrose concentrations of 70% may produce glucose intolerance. A continuous insulin infusion of up to 15 units per hour may be necessary to control serum glucose levels. The combination of glucose and insulin may promote anabolism. In addition, the use of anabolic steroids, such as testosterone, to enhance protein retention may be of value in these catabolic patients. Despite renal failure, hypophosphatemia and hypokalemia may occur when the infusion solution contains only a mixture of amino acids and dextrose. Appropriate amounts of potassium and phosphate should be added to the parenteral solution according to the patient's blood levels. Supplementation with multivitamins, folic acid, vitamin K and B_{12} is necessary during parenteral nutrition.

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17. DIALYSIS AND TRANSPLANTATION: PSYCHOLOGICAL MANAGEMENT

MILTON VIEDERMAN and GARY H. RUSK

1. INTRODUCTION

Physicians who care for chronic renal patients have discovered that in order to implement effective medical management, they must inevitably confront the issues of the patient's adaptation to the illness and its treatment, his long-range rehabilitation, and the quality of his life. A useful guide to what is meant by successful adaptation encompasses the following criteria: (1) keeping distress within manageable limits and maintaining adequate sources of pleasure, (2) maintaining self-esteem, (3) maintaining adequate relationships with other people, (4) working out satisfactory personally valued and socially acceptable roles, (5) maintaining some degree of hope for the future, (6) effecting rehabilitation to the patient's maximum physical capacity, and (7) maintaining an effective and reasonably trusting relationship with the treating physician [3].

Inevitably, the advent of end-stage renal disease creates a crisis for the patient. The outcome of this crisis will depend upon many factors, such as the age of the patient and the rapidity of onset of disease, the degree of uremia present when the patient presents himself to the doctor, the patient's personality, intelligence and milieu, and his previous experience with disease. However, not the least important will be his relationship with the physician. This may have an important influence on long-range outcome.

Many patients confronted with physical illness feel extremely alone with their individual anxieties and concerns of which they are often only partially aware. The physician who has learned to listen to his patients with this in mind, and who is able to tactfully communicate his understanding to the patient can diminish the patient's isolation and thereby, perform an important therapeutic task.

However, many compassionate and concerned physicians tend to develop uniform and stereotyped ways of dealing with patients based upon what appears to be natural to them. In many situations this works

reasonably well and often a modus vivendi is established between the doctor and the patient which permits a useful alliance even though the patient may be unable to convey to the doctor some of his most immediate concerns about his disease, his treatment, and its impact upon his life. However, given the special conditions of this very rigorous treatment, a natural alliance may not develop unless particular attention is paid to structuring the relationship in the context of an awareness of the patient's emotional needs.

It is with this problem in mind, that this chapter is written. We will address ourselves to all aspects of the disease and its treatment utilizing illustrative clinical vignettes with the hope that this will guide the physician in patient evaluation and permit the formulation of useful management plans. It is in no way intended to be a comprehensive review of the very rich literature in the field.

2. THE ADVENT OF TERMINAL RENAL FAILURE

Evidence of developing kidney disease usually long precedes the symptoms of terminal renal failure. In many situations, patients are informed that they have kidney disease and that they can expect kidney failure at some time in their lives. There are two general reactions to this information; minimization or denial and hypervigilance.

2.1. Minimization and Denial

The majority of patients who receive the information that they are likely to develop symptomatic kidney disease many years in the future, tend to isolate their feelings of anxiety or worry and deny the potential threat. Under these circumstances, the patient may develop symptoms, or even appear in severe uremia, before consulting a physician. If the denial interferes with proper medical consultation, it is maladaptive and represents a real threat to the patient's life. If it does not lead to avoidance of proper care, this mechanism may usefully protect the patient from distress. It is to be emphasized that the denial has no relationship to intelligence or the inability to intellectually understand the nature of the threat.

Case No. 1 — Mr. G. was a 36 year old married Ph.D. in biochemistry, who worked in a surgical laboratory in a general hospital. His father had died of polycystic kidney disease when the patient was 16. In spite of the fact that he was very knowledgeable and worked in a hospital, the patient was in a state of severe uremia before it was recognized that he needed hemodialysis. Fluid overload was so marked that he experienced severe dyspnea

in walking up a few steps. He consulted an otolaryngologist for this symptom so that, in his words, 'he would be examined only above the neck'. He was properly referred to an internist by this physician, and only after the uremia cleared was he able to realize that he had lived his entire adult life with the specter of an early death and that he had, in essence, totally denied this fear. Although he had not been consciously preoccupied in his own mind with developing his father's disease, he realized in retrospect that the anxiety about an early death had led him to a decision not to have children or to purchase a home.

It is important to keep in mind the fact that patients who present with severe uremia and its associated organic brain syndrome may reveal major disorganizations of their personality which do not necessarily reflect persistent psychopathology. It is not uncommon to observe paranoid and depressive psychotic episodes which are products of the organic brain syndrome of uremia. These behavioral abnormalities may take weeks to clear with dialysis. In the presence of a manifest organic brain syndrome, one cannot adequately evaluate the patient's ultimate adaptive capacity.

2.2. Hypervigilant Behavior

With early diagnosis, patients with approaching renal failure are being seen more and more frequently by physicians before they are symptomatic. Often a decision is made to establish a fistula before hemodialysis becomes necessary. In some instances, this confronts the patient with the inevitability of hemodialysis and offers him time to progressively adapt to what will be an important change in his life. In other situations and particularly in certain personality types, this period of prolonged waiting and anticipation can be very disruptive.

Case No. 2 — Mr. R was a 36 year old married business executive who had one child. This man was highly organized and characteristically had a well-defined life plan which he appeared to be successfully implementing. He had established a schedule for advancement on the corporate ladder and systematically was preparing to compete in the Olympic sailing event. The development of severe leg edema led to consultation and the information that he had chronic renal disease. He became severely depressed, and for nine months, he did little else but work and spend the rest of his time in bed. The symptoms of depression were attributed incorrectly to physical illness. Finally, he was encouraged to seek psychiatric consultation where it was determined that the profound depression had been evoked by the sense of loss of control over his life. This man was much more successful in actively coping with current demands than anxiously anticipating how he would handle future difficulties. The depression lifted when the logic of his depressive response was pointed out, particularly as it pertained to the disruption of control over his life; his fear of dependency in the face of his previous strength and independence and his sense of deterioration of his physical status, greatly exaggerated and augmented by symptoms of emotional origin. The depression in this situation was characteristic of a particular personality type—a person who has a strong sense of his ability to direct his own life and who feels most comfortable when he is actively engaged in proving this.

Although this man received a transplant before having to go on hemodialysis, it is very likely that the anticipation of dialysis was much more difficult for him than the actual experience of it would have been.

3. THE MEANING OF HEMODIALYSIS AND ITS IMPACT UPON ADAPTATION

Any patient confronted with serious illness is forced to relinquish much of his autonomy, independent judgement, and control over his own body. His capacity to establish a trusting relationship with the treating personnel, and to delegate much of his regular authority over himself to others, will influence his emotional reaction to the treatment. This is particularly true in the situation of hemodialysis. The very experience of becoming literally dependent for life upon a machine to which one is connected by tubes visibly carrying blood evokes past images of child-like dependence on the parents and particularly on the mother. This is compounded by the rigorous fluid and food restrictions placed upon the patient. Inevitably, this experience is viewed as reminiscent of the early mother-child relationship; though the patient may be quite unaware of this. The imagery of this relationship often appears in dreams and fantasies and the adaptation to dialysis will often be a function of the patient's early relationship with the mother.

Patients who have had fundamentally healthy mother-child relationships in infancy tolerate relatively easily the partial regression which is demanded by the treatment and effectively establish trusting relationships with both the treating physician and the machine itself.

For other patients, treatment with hemodialysis may involve a terrifying and global regression. This is particularly true of adolescents who, of all age groups, have the most difficulty with hemodialysis. This phase of development by its very nature requires that the adolescent begin to separate himself from his parents and to move toward greater independence. The regressive dependency demands of treatment cause great difficulty for many adolescents.

Case No. 3 — E.J. was a 17 year old girl who has been ill since early childhood and whose anxiety about separation had evoked emotional resonances in both parents who felt guilty about her condition and also had difficulty in separating from her. While this patient was on dialysis, there was a total breakdown in her social functioning (she exposed herself and masturbated openly), in her awareness of reality (she was unable to distinguish nightmares from hallucinatory perceptions of body decomposition), and in her bodily care (she made no attempt to keep herself clean). There were frequent temper tantrums. Her psychological functioning had the quality of that of a small child. Small doses of tranquilizing medication helped to alleviate the intensity of her reaction, but a serious problem continued until successful transplantation was accomplished.

Case No. 4 — Mr. W was a 46 year old man who was one of many children in a poor, lower-class family. A vivid memory was that of his angry mother turning from the wash to slap him across the face with a hand wet with soap suds. The patient's first response to the dialysis machine, which always remained terrifying to him, was that it was like a huge enveloping washing machine. The association between the machine and a punitive mother was clear. This patient had great difficulty in adapting to dialysis at any point.

A third group of patients experienced this new treatment situation as offering a license for dependency gratification, and they make open demands for care and attention.

Case No. 5 — Mrs. D was an articulate, pleasant, attractive woman who was intelligent and relatively knowledgeable about her disease. On the self care unit, however, she seemed forgetful of instructions and unable to master the self care technique. She unabashedly spoke of the need to be 'mothered' by the staff. It was suggested after several months without progress to self care that she switch to a regular dialysis unit. She reluctantly accepted this move until she found that the staff was accepting of and responsive to her need to be passive and cared for. She then experienced the greatest sense of well-being since she had begun dialysis.

A fourth type of patient often presents serious problems in management. They experience the demand for regression as a terrible threat to their masculinity, autonomy, and control.

Case No. 6 — Mr. F was a 46 year old man with an aristocratic manner who had successfully created his own business and struggled to maintain a profound sense of control over his life. This patient was very difficult to manage. He would refuse procedures, snarl at the nurses, treat the physicians with angry disdain, and periodically sign out of the hospital. Any gentleness or sympathy would evoke a hostile reaction. It was clear that the best approach to this patient was to talk to him in a 'man to man', somewhat teasing and unsolicitous way. He experienced the dependent position as an extreme threat and would react explosively in any situation in which he felt babied.

4. THE PROCESS OF ADAPTATION

Adaptation to hemodialysis demands a total change in one's perception of oneself in relation to the world. It is, indeed, a crisis situation. This implies that previous modes of coping are no longer adequate and that one is confronted with an inexorable demand to develop new patterns to deal with a changed reality. The success or failure of this process will determine to a great extent the patient's degree of comfort and freedom from anxiety and depression. Levy and Riechsman [4] have described three phases of adaptation to hemodialysis. (1) The honeymoon phase is a phase of adaptation which occurs in the early weeks and months after dialysis as the patient feels relieved of the very unpleasant symptoms of uremia. (It presumes that the patient was sick with uremic symptoms before the dialysis began.) (2) This is followed by a depressive phase as

the patient comes to realize that improved though he is, he must face a potentially painful and constricting reality. (3) Finally, there is a phase of ultimate adaptation as the patient either successfully adapts or continues to experience great anxiety and depression. This schema is not to be viewed as an indelible pattern of response. Patients who are dialyzed before they become ill obviously never experience the relief which hemodialysis can offer. Moreover, as has been pointed out in Case No. 2, the prolonged wait for dialysis may create difficulties in its own right.

It is important to emphasize that one aspect of this process is closely related to mourning because it involves coming to terms with loss. What the patient experiences as lost will vary from person to person, and it may involve a sense of strength, attractiveness, health, sexual function, freedom to travel, or the ability to work. In the context of this sense of loss, particular attention must be paid to the sources of self-esteem in individual patients. The rudiments of self-esteem are developed early in life. The initial development is contingent upon the sense of being loved by the parents and subsequently is related to the feeling of being able to care for oneself (to acquire control over bodily functions, such as defecation and urination) and to accomplish things in the world. It is easy to see that a significant disturbance in functioning, for example, in work activity or sexual function, may lead to a loss of self-esteem. The approbation which comes from the external world for things accomplished may no longer be available to the patient, and other sources of self-worth must be sought. The loss of physical attractiveness (particularly for women) may be so damaging that the patient may begin to imagine that her spouse is no longer interested in her or seeks other women. In this context, we have seen patients who have literally driven their spouses away because of the sense of unattractiveness even though there is little evidence that the spouse was inclined to leave. These people fear being the passive objects of abandonment.

5. TRANSPLANTATION

Every patient who has undergone hemodialysis and decided to accept transplantation views it on some level as offering a magical resolution of their problems. With some patients, the physicians may present the statistics of transplant rejection, underline the frequency of complications of immunosuppressive therapy, point out the likelihood of an ultimate return to dialysis—all to no avail. The wish for magical relief is

so strong, that, although the patient may be able to repeat word for word what he has been told, his emotional reaction to failure of the transplant and to the complications of treatment belie his presumed acceptance of the knowledge of the complications. Hence, depression and anger are frequent accompaniments of transplant rejection. On the other hand, it is important to recognize that it may come as a relief to a patient to have a transplant nephrectomy if the transplanted kidney had been borderline in function over a period of time and created toxic symptoms. Under these circumstances, the patient feels considerably improved after the nephrectomy in spite of the return to hemodialysis. One must also keep in mind that there are certain personalities who are highly intolerant of uncertainty, and that after a prolonged period of tenuous kidney function, they may be relieved that the outcome is decided even though the kidney is lost.

Another issue of great importance in successful transplants is the change in body image which results from the prednisone treatment. Individuals who lean heavily on their physical appearance as a source of self-esteem, may experience the changes in their bodies as extremely damaging to their view of themselves. In some cases, patients with successfully functioning transplants for many years, discontinue their medication with the hope that their bodies will return to normal without a change in kidney function. It is incumbent upon the physician to make some estimation of the impact which a change in the body image will have on a particular patient so that he can be particularly supportive with vulnerable patients in such a way as to minimize the likelihood of discontinuing treatment.

To emphasize only the negative responses to transplantation would be to present an excessively pessimistic and inaccurate picture of the general response to successful transplantation. For the most part, the patients are extremely pleased, grateful, and experience many pleasures and freedoms which were previously denied them. It is interesting to note that what is particularly valued about the transplantation may vary from patient to patient. Some patients particularly enjoy the dietary freedom, while others find escape from the routine of regular dialysis most important. Another group, particularly men, find the return of urinary function with its associated sense of power the most valuable gain. In spite of the exhilaration which may be generated by a successful transplantation (keeping in mind that prednisone itself may cause elation), the patient is required to readapt to a more normal life once again. Many special hopes have been attached to the idea of successful transplant, but this hardly solves all of life's problems. Patients with an

early history of deprivation are more likely to remain psychological invalids even after return to a state of relative good health.

An important aspect of the response to transplantation pertains to the special meanings this event has for the patient. Inevitably, patients develop fantasies about the meaning of the experience, and on some level, the kidney itself is personified. This is particularly true in patients who receive kidneys from related donors, but it also occurs in cadaver transplants.

Case No. 7 — A young black man received a cadaver transplant and was found six days later to be extremely anxious about rejection in spite of the fact that the kidney was doing quite well. He repeatedly expressed the feeling that the 'kidney will reject me'. On exploration, it became apparent that his fear of rejection originated from a fantasy that the kidney had come from a white woman. He was relieved when he was informed that the donor had been a black woman. This man also expressed considerable bitterness about having to remain the 'slave of the doctors' after the transplant by virtue of this need for continued medical treatment. It is clear that this man's life experience had strongly influenced his perception of the entire procedure. He had the magical expectation that the transplant would release him from the bondage of his previous experience as a black.

This patient illustrates not only the personification of the kidney (his view that it was like a person inside him) but also illustrates what is extremely common—namely, the fantasy that the transplantation is like a rebirth, filled with the expectations of a change in one's personality and a change in one's life. In this context, it is important to emphasize that any crisis situation—transplantation is such a crisis—offers the possibility for personal maturation and growth as well as disorganization and difficulty.

Case No. 8 — A woman in her late 30's experienced a cadaver transplant as a gift from God. Her religiosity appeared to compensate for her feeling of early maternal deprivation which had left her with a damaged self-esteem and a feeling that she was unworthy of dependency gratification. The transplant, interpreted as a gift from God, gave her the sense that she had in some way been favored by God, and she was subsequently able to pleasurably accept things from others and feel comfortable with herself whereas before she had been unable to do so.

Not all patients experience the gift of transplant in such a felicitous way. A common accompaniment of transplant is a sense of guilt related to the feeling that the patient has stolen something from someone. This may be revealed in dreams.

Case No. 9 — Mr. A was a 24 year old man who received a cadaver transplant. His elation and hyperactivity post-transplant covered a certain anxiety. Shortly after the transplant, he dreamed that he was riding with others in a stolen car which was worn and damaged. They came to a halt. The car was reconstructed and made into an excellent vehicle with parts that had been stolen from another car. This patient revealed that guilt had been a very important part of his life, and that he was aware of vague feelings that he had somehow stolen the kidney from someone. The old and worn car reflected his perception of himself as a physically ill and damaged person.

Case No. 10 — A 50 year old woman who had escaped from the Nazi holocaust revealed mild manifestations of what has been called 'survivor guilt'. She received a cadaver transplant and did quite well until the time her 'surgical twin' (a woman whom she knew had received the other kidney from the same cadaver) began a rejection episode. At this time, the patient made a serious medication error which was potentially quite self-destructive. Fortunately, it was noted by one of the staff and corrected. It was clear that her guilt about maintaining a kidney when this other woman had lost hers had evoked guilt and self-destructive behavior.

The utilization of a kidney from a related donor creates very special conditions in view of the complex and special relationship which exists between donor and recipient. Occasionally, the recipient experiences a particular sense of obligation and bondage to the donor who may exploit the situation for his own purposes. The recipient may feel obligated to adopt the value system of the donor and may feel guilty and anxious when he feels that he has failed to live up to the values which have been espoused by the donor. Issues such as previous identifications in the family also play an important role. Patients who are strongly identified with the donor, and thus see themselves as like the donor, in general tend to have less anxiety about rejection than those patients who view themselves as markedly different than the donor. This latter situation is particularly striking where a hostile relationship between donor and recipient preceded the transplant. Under these circumstances, there is often a high degree of depression and anxiety about loss of the transplanted kidney.

Case No. 11 — The patient was a woman in her early 20's who received a kidney transplant from her mother. They had had a long-standing hostile relationship, and the patient had expressed her rebelliousness through promiscuous sexual activity and by taking drugs. The mother was seen as very angry and unaccepting of the patient. This was in striking contrast to the mother's relationship with another daughter who was seen as like the mother and good. After transplantation, with a kidney from the favored sister, the patient had an extremely high level of anxiety about rejection of the kidney even though it was functioning quite well, and repeatedly tried to modify her behavior so she could view herself and be viewed by the mother as a good girl like the favorite sister.

The process of integration of the new kidney into the body schema and the increasing experience of the kidney as part of the self, is a process which occurs over time. The sense of being like the donor facilitates this process. In some situations, the process remains incomplete, and the patient never truly experiences the kidney as part of himself.

Case No. 12 — Seven years after transplant from her father, with whom she had a hostile and argumentative relationship, a 35 year old woman still experienced the kidney as his and not really part of her. She used the same words to describe the kidney and her father, 'temperamental and unreliable'. There was considerable anxiety about rejection.

In general, most patients progressively integrate the well-functioning kidney into their body schema and are much more troubled by the complications of rejection therapy than by anxiety about loss of the kidney itself. Our initial studies of patients who have maintained kidneys over long periods of time suggest that in the absence of major complications, excellent adaptation is likely.

6. PERSONALITY TYPES AND MEDICAL MANAGEMENT

Having discussed the process of adaptation and special meanings of hemodialysis and transplantation, we would like to show the importance of assessing the patient's personality type and its usefulness in medical management. Although our discussion will not be comprehensive nor involve a standard psychiatric classification, it is our intention to show that the understanding of personality type can lead naturally to a rational and useful management plan.

The issues of dependence-independence, hypervigilance-denial, and control-passivity have been discussed above and are frequently referred to in the literature on the psychological and emotional aspects of hemodialysis and transplantation. The physician can assess each patient in this regard during the first few meetings and modify his assessment as his experience with the patient grows. The patient's response to illness and treatment will usually follow a characteristic pattern. In evaluating these patients, we are less interested in traditional concepts of normality or abnormality than in whether an adaptive or maladaptive resolution is reached. The physician is often in a position to facilitate successful coping. Conversely, his behavior may make adaptation more difficult. In our clinical descriptions and vignettes, we have emphasized the extremes of response, although it should be recognized that these principles should be applied for the benefit of the relatively well-adjusted patient.

Groves [2] described four typical patient stereotypes which result from insatiable dependency needs. He emphasized that the physician's negative reactions to these so-called 'hateful patients' are important clinical data which can lead to better understanding and management. We have modified his labels and descriptions somewhat to emphasize the major management tasks which confront the physician.

Three typical patient types will be described: The Non-Compliant Denying Patient, the Dependent Clinging Patient, and the Entitled Demanding Patient. It should be remembered that these descriptions

represent stereotypes for the purpose of exposition and do not do justice to the complexity of human behavior. It is important to recognize and encourage the potentially positive, adaptive value of the behavior and the strengths and assets of even the most difficult patient. The characteristics of these typical hypothetical patient types may overlap and require more complex and varying management strategy.

6.1. The Non-Compliant Denying Patient and the Need to Accept Limitations

Denial as a self-protective maneuver to minimize or avoid the psychological impact of chronic illness is found in virtually all chronically ill patients. The physician can recognize denial in its most adaptive form in those likeable, at times admirable, patients who value their independence and relegate their illness and treatment to a minor role in their lives.

At the other end of the spectrum is maladaptive denial which is self-destructive to the patient and antagonistic to the physician's aims. Patients of this sort seem intent upon their own destruction and frustrate the physician by missing dialysis treatments, not taking medication, and abusing dietary and fluid restrictions. A threatening authoritarian approach is doomed to failure because the patient easily dismisses the frightening, potential consequences of his behavior.

Case No. 13 — A 19 year old Puerto Rican boy was admitted for cadaver transplant after nine months of dialysis in another center. His reputation as a difficult patient had preceded him. He was described as unreliable, overindulgent in fluid intake, inclined to miss dialyses, and to engage periodically in aggressive outbursts. A few days after the transplant, his kidney was working well. He related well and presented no problems in management. A brief discussion with him revealed that his mother had died when he was three and that he had experienced considerable early deprivation. There had been problems in school, and though he occasionally experimented with drugs, he was not an addict. During the interview, he revealed that he was very sensitive to insult and would respond to any implied slight with an outburst of rage and defiant behavior. It was apparent that his self-esteem was tenuous. The previous treating physician had developed a contemptuous attitude to the patient who was unreliable in following medical instructions and a power struggle between them had ensued.

A minor incident which occurred a few days later exemplified the difficulties in working with this patient. A physician examining another patient in the room rather impatiently told him to turn down the television. The patient felt insulted and angrily left the ward. Too much attention had been paid to this other patient, and he felt demeaned. He returned shortly thereafter to apologize for his behavior and effective collaboration with the staff was reinstituted.

Understanding this patient's sensitivity tempered the reaction of the staff. Inevitable breakdowns in the relationship, which develop in moments of stress, have to be tactfully handled and a proper alliance

restored without overreaction to the patient's periodic abuse of the treatment plan. The physician, by recognizing the limitations which the patient's personality imposes, paradoxically experiences less helplessness. It is the sense of helplessness in such a situation which evokes anger with accompanying guilt and leads the physician into a fruitless power struggle with a patient who is always able to maintain the upper hand. Only by changing his expectations can the physician take a more neutral stance and avoid the otherwise inevitable combat. This is likely to ameliorate, if not solve, the problem.

6.2. The Dependent Clinging Patient and the Need to Set Limits

When well-adjusted, the dependent patient may hardly be noticed. These patients are often quiet, compliant, unobtrusive, and are content to leave any initiative or responsibility for their medical management to the physician and family members. They are often overt about their need to be taken care of and easily engage the staff in doing just that. They may make appropriate requests for reassurance and support and express their genuine gratitude for the physician's care.

However, in times of stress, the need for support increases. These patients develop magical expectations of their physicians and are insatiable in their demands for attention and affection. The relationship to the physician, particularly if he is of the opposite sex, may take on a romantic quality akin to infatuation. The physician who is seen as omnipotent and inexhaustible begins to experience the patient as a burden.

Case No. 14 — M was an 18 year old, foreign born boy on hemodialysis who developed severe bone disease with its attendant pain. He worshipped his physician who was an obvious substitute for the father who had abandoned him when he and his mother came to this country. Mother and son established a pattern of calling the physician to report every new symptom and every response to the various medications which were tried. As the number of visits and phone calls escalated, the physician began to experience irritation in spite of his compassion for the patient. He realized that he had to set limits on his availability without feeling guilty or conveying a sense of rejection to the patient. When this was done, not only did the physician feel a great sense of relief, but the patient experienced less pain and made fewer requests for special attention.

Recognizing such patients early in the course of treatment permits the physician to firmly but nonaggressively set limits and define what can realistically be expected of the doctor's time, effort, and knowledge. Regular appointments at reasonable intervals assure the patient that he will not be abandoned. The physician must convey his awareness of how important he is to the patient, and at the same time, establish the

ground rules for appointments and contacts so that the patient can obtain the best medical care. A statement to this effect communicates understanding, tolerance, and dedication and provides a realistic framework for the treatment.

6.3. The Entitled Demanding Patient and the Need to Allow the Patient Some Control

Certain patients respond to illness with the conviction that it entitles them to special consideration. They become demanding, insatiable in their expectations, and use coercion in an attempt to obtain what they inevitably feel is being withheld from them. Often they are suspicious and mistrustful, and accuse the physician of negligence and malpractice. The doctor responds by feeling intimidated, enraged, devalued and is impelled to 'put the patient in his place'. The entitled demanding patient will often manipulate the medical staff in an attempt to have his demands met. One staff member is idealized as a savior while another is vilified and described as a persecutor. These patients are, at moments, very appealing and expect 'intimate', 'special' relationships with the staff which exceed the proper boundaries of such relationships. Any disappointment leads to a sudden outburst of rage toward the offending person who is left feeling bewildered and often guilty. These patients are often so intimidating that their pleasant behavior is experienced as such a relief that they are given special favors. This feeds into their manipulative inclinations.

Case No. 15 — Miss S is a single, 30 year old woman who lives alone and is unemployed. She has been on chronic hemodialysis for two and a half years, and has presented major problems in management because of her antagonistic and coercive behavior with the dialysis staff. She would provoke the staff by refusing to be dialyzed after arriving for treatment or demanding to be taken off dialysis once begun. When her demands were not immediately met, she would threaten to kill herself by not coming for dialysis or by pulling out her needles. She created confusion and friction among the staff by contending that a doctor (not present at the time) had agreed to special favors. Her inclination to regress was marked, and it placed major demands on all members of the staff. On one occasion, the patient threatened suicide when she experienced envy toward the unborn baby of her pregnant physician. Suicidal threats accompanied the departure of members of the staff who were important to her. After many weeks of frustration and confusion, a rational management plan was formulated. A major element of the plan consisted of clarifying what the patient could reasonably expect from the staff and what would not be possible. She was told that she was free to miss dialysis if she so chose, but that the staff would not respond by immediately arranging dialysis at another time. She would not be called at home or entreated to appear for treatment. If she requested discontinuance of dialysis for the day, the staff would comply with her request, but she would be required to wait for her next regularly scheduled dialysis. The plan defined the areas which she could control as well as the limits of the staff's response to this control and thereby, diminished

conflict. They were encouraged not to be seduced by her pleasant behavior, nor disheartened by her sudden changes in mood. Management was greatly facilitated by this plan although continued support was required to maintain a consistent attitude toward the patient.

The patient described above has what is called a borderline personality disorder. Such patients present major problems when they require treatment for chronic disease. A proper plan requires the definition of areas of control for the patient as well as the staff. These boundaries must be made clear to the patient and the staff must consistently adhere to them. Moreover, the staff must maintain a proper distance from the patient, becoming neither excessively involved nor distant. They must be prepared for dramatic shifts from extreme affection to hostile rejection and not allow themselves to be intimidated by coercive threats including threats of suicide. The risk of suicide is real, but is minimized by a consistent approach.

One does not usefully challenge the patient's sense of entitlement which is often experienced as infantile and provocative. The patient may attempt to engage the physician in arguments about the quality of care or the wisdom of the treatment plan. In this situation, the doctor should emphasize that after considering what the patient has to say, he must make his own decisions based on his own judgement.

In summary, we have described certain types of patients who act in ways which run counter to the best efforts at treatment and rehabilitation. In some of these situations, the physician's very wish and inclination to help becomes the weapon which the patient most frequently uses in his attempt to frustrate. Unfortunately, psychotropic drugs offer little help in the management of these patients and often become the focus of further complaints, lack of compliance, and struggle for control. Although some diminution of anxiety, insomnia, or depression may be obtained with these agents, more improvement can be obtained through management based upon a careful evaluation of the personality characteristics of the patient.

7. SPECIFIC CLINICAL SYNDROMES AND THEIR MANAGEMENT

7.1. Painful Feeling States

We will now consider the management of certain painful feeling states such as anxiety and depression, so-called 'target symptoms'. These symptoms must be considered from the point of view of the patient's

current predicament (his physical illness) with all the special meanings attached to it, combined with an understanding of his personality and previous life experience. The common assumption in medicine that the emotional distress of a physically-ill patient is a direct response to the physical illness is imprecise and ignores the fact that inevitably the patient's current predicament had special and personal meanings to him. Often the special meaning of the painful feeling state is quite easily elicited and may have very little to do with what the physician, himself, sees as a realistic threat to the patient. Moreover, the determination of the exact source of discomfort may make it possible to reassure the patient about a source of anxiety or depression which is quite unrealistic. Case No. 7 is an excellent illustration of this point. The patient's anxiety was significantly reduced through understanding and appropriate reassurance *without* the use of psychotropic drugs.

There is another group of phenomena which involves psychological processes known to be useful in ultimate coping and adaptation to threats and painful losses. Grief is the process during which a person gradually comes to terms with and painfully accepts the loss of something which is important to him. This process of grief or mourning was discussed earlier in the section on the process of adaptation. This painful feeling state often merges and is confused with depression, but psychotropic drugs are not indicated for use in this group of experiences.

There are situations in which a particular painful feeling state is so intense as to feed into a vicious cycle of psychological distress and physiological arousal which may adversely affect a patient's physical illness. Psychotropic drugs should be considered under these circumstances; although they are no substitute for an understanding relationship with the physician which will enhance the therapeutic effect of these drugs.

The minor tranquilizers and sedatives are the group of psychotropic drugs with which the physicians are most familiar. There are many drugs in this category. Diazepam (Valium®) and chlordiazepoxide hydrochloride (Librium®) are the most frequently used and have considerable effectiveness for mild or moderate anxiety and mild depression. The minor tranquilizers act rapidly, have a relatively long duration of action, and after stabilization on divided doses has been achieved, can be given as infrequently as once or twice daily. These agents are equally effective and produce less drowsiness and dermatitis than barbiturates. Their effectiveness may wane after several weeks, leading to tolerance and potential abuse. Although they are probably less addicting than the

barbiturates, they produce a similar withdrawal syndrome. Muscle relaxant and anticonvulsive properties are additional benefits. Although caution should be used with patients who have renal failure, these compounds are generally quite safe within a wide therapeutic margin. Diazepam (Valium®), which is available in parenteral form, has been used in selected patients on hemodialysis in doses of 2.5 to 10 mg injected into the arterial line of the artificial kidney as often as every two hours without significant hypotension or other autonomic side effects.

The barbiturates are generally effective for short term use but have the increased risk of suicide, tolerance, and dependence. Their tendency to induce microsomal enzyme systems in the liver which interfere with other drug effects (anticoagulants, anticonvulsants) make them less than ideal for use in patients with renal disease. A short-acting barbiturate like sodium amobarbital is preferable to phenobarbital which is excreted by the kidney in active form.

Anxious patients often have difficulty falling asleep, and insomnia is a serious problem in patients with renal disease who often have reversal of their sleep-wakefulness cycle. Flurazepam (Dalmane®) in hypnotic doses of 15–60 mg at bedtime is safe and effective for at least thirty days. Diphenhydramine (Benadryl®) 25–100 mg at bedtime or chloral hydrate 500–1,000 mg at bedtime may also be useful.

Depressive syndromes vary from neurotic to psychotic with distinct treatment and prognostic implications. The antidepressant drugs are generally most useful in patients who have depressions with accompanying 'vegetative signs'. These patients generally appear severely depressed, and experience apathy, muscular weakness, fatigue, and slowed thought and action. In addition, difficulty in concentration, constipation, anorexia, and insomnia, and loss of sexual desire or capacity are frequent complaints. The patients may describe the vegetative signs without being aware of the subjective experience of depression. They are said to have 'masked depression', and because these symptoms so much resemble those of uremia, the depression may be overlooked. Imipramine (Tofranil®) and amitriptyline (Elavil®) are two frequently used antidepressants. The initial dosage in patients on maintenance hemodialysis should be low, 25 mg twice daily, and raised gradually over a month's period of time until either a therapeutic effect is achieved or significant side effects appear. The maximum dosage is 300 mg. There is a marked individual variation in the metabolism of these drugs and a 7–30 day lag period is common for an antidepressant effect. The patient should be told that these drugs will not create a euphoric state and that the results will not appear immediately. Imi-

pramine is the drug of choice for the depressed patient who is retarded in his behavior (slowed or dull), and amitriptyline is indicated for the depressed patient who is more agitated. If insomnia is a problem, as is often the case, amitriptyline may be used by giving a single daily dose before bedtime. After remission with a stable dose has been achieved for one month, a maintenance dose of one third to one half the maximum dose can be continued for six months. The maintenance dose can then be gradually tapered to zero if no depressive symptoms reappear. The appearance of significant side effects calls for a reduction in dosage to eliminate the symptoms. Common side effects include: fine tremor, orthostatic hypotension, anticholinergic side effects and reversal of the antihypertensive effect of guanethidine (Ismelin®).

7.2. Organic Brain Syndrome and Functional Psychosis

This category includes the major functional psychoses, such as schizophrenia and the severely agitated, disorganized or psychotic brain syndromes. The differential diagnosis between functional and organic psychosis is not always easily made. A careful search for possible causes of disrupted brain function should be made even in the patient who initially presents with what appears to be functional disturbance.

A simple classification of the organic brain syndromes include those clinical entities known as delirium and dementia. The predominant manifestations of these syndromes are the impairment of orientation, recent memory, intellectual functioning, judgement, and emotional response.

Delirium has been called the 'syndrome of cerebral insufficiency' [1] because it implies a relatively acute, potentially reversible disruption of brain function, often precipitated by metabolic or toxic factors. The organic etiology of the underlying disorder must be established so that, if possible, it may be corrected before irreversible brain damage occurs. A frequent cause in renal patients is dialysis disequilibrium syndrome, though secondary hyperparathyroidism occasionally may be responsible. A toxic encephalopathy presenting as delirium may also occur in renal failure due to the accumulation of normeperidine, a metabolite of meperidine (Demerol®). Demerol should not be used with these patients. In deliria, marked anxiety, agitation, hyperactivity, combativeness, hallucinations or delusions, and other disruptive behavior may interfere with diagnostic and therapeutic measures and may eventuate in exhaustion, injury, or even death. Although one must be cautious with medications in the management of such seriously ill patients, disordered

behavior often make their use mandatory. Tranquilizers can usually be avoided in the delirious patient who is apathetic, calm, and cooperative.

Dementia is a category of organic brain syndrome which usually implies chronicity, irreversibility, and often anatomic change in the brain, as well as progression. Virtually all pathologic agents which affect the central nervous system may cause dementia. Frequent causes in chronic hemodialysis are chronic subdural hematoma, uremic encephalopathy, and so-called 'dialysis dementia' with its characteristic prodromata of dysarthria, dysphasia, and dyspraxias of speech. The degree of distress, will be, in part, a function of the rapidity of onset of the syndrome, the severity, and the previous personality of the patient. Environmental management is of great importance in providing a pleasant, supportive setting with a variety of orienting clues, namely, leaving the light on in the room, having a clock at the bedside, providing sensory input like music or television, repeated orienting contacts with a nurse, members of the family, etc.

Although low doses of minor tranquilizers or sedatives may occasionally be helpful in a mild nonpsychotic organic brain syndrome to control anxiety or depression, these drugs, particularly the barbiturates, may precipitate a paradoxical reaction by increasing the confusion and causing agitation. In general, they should be avoided. Antidepressants should be used only with very obvious indications and with caution. Similarly, the major tranquilizers may complicate rather than improve delirium or dementia. However, patients with organic brain syndromes who have such severe behavioral disturbances should be treated with initially small, then increasing doses of one of the major tranquilizers. Haloperidol in small doses is the drug of choice. The presence of an organic psychosis with severe agitation and disruptive behavior is an indication for the use of an antipsychotic agent.

Certain organic brain syndromes can mimic functional psychiatric illness by presenting manic, depressive, or schizophrenic symptomology with a relatively intact sensorium, that is, without impairment of orientation, memory, or intellectual functioning. Examples are the psychosis associated with the administration of exogenous steroids and in hyperparathyroidism. A high index of suspicion is necessary to accurately diagnose these disorders and the principles of management are the same as with other organic brain syndromes. The consistent use of substantial doses of prednisone in post-transplant patients and its frequent use in other patients being treated with hemodialysis (for example, patients suffering from lupus erythematosis) make cortisone psychosis a not

infrequent phenomenon in renal units. The predominant manifestations are increasing states of euphoria, paranoia, less frequently, depression, and depersonalization and derealization. These latter symptoms involve an alteration in the sense of the reality or proportions of the patient's body or a feeling that the world about him is not real. Often the patient is able to describe these feeling states as abnormal. In steroid psychosis, the patient generally remains oriented with intact cognitive functioning.

Table 1. Common psychotropic drugs.

Drug	Standard oral daily dose	Side effects, precautions
Minor Tranquilizers		
Meprobamate (Miltown, Equanil)	800–3200 mg	sedation, dependence
Diazepam (Valium)	5– 60 mg	sedation, dependence
Chlordiazepoxide (Librium)	15– 100 mg	sedation, dependence
Sedative-hypnotics		
Sodium amobarbital (Na Amytal)	50– 400 mg	rapid tolerance drug interference
Flurazepam (Dalmane)	15– 60 mg	dependence
Diphenhydramine (Benedryl)	25– 100 mg	antihistaminic action
Antidepressants		
Imipramine (Tofranil)	75– 300 mg	fine tremor, orthostatic hypotension, anticholinergic action, interference with guanethidine, agitation, mania, tachycardia, arrhythmias
Amitriptyline (Elavil, Endep)	75– 300 mg	sedation (same as imipramine)
Major Tranquilizers		
Chlorpromazine (Thorazine)	30– 800 mg	sedation, orthostatic hypotension, cholestatic jaundice, photodermatitis, decreased seizure threshold, extrapyramidal reactions
Thioridazine (Mellaril)	30– 800 mg	arrhythmias, electrocardiographic changes, sedation
Trifluoperazine (Stelazine)	2– 40 mg	extrapyramidal reactions, sedation
Haloperidol (Haldol)	1– 20 mg	extrapyramidal reactions
Antiparkinson agents		
Trihexyphenidyl (Artane)	4– 16 mg	anticholinergic action
Benztropine mesylate (Cogentin)	2– 8 mg	anticholinergic action

Reprinted from: Viederman, M. and Rusk, G.: 'Appropriate use of psychotropic drugs in physical illness,' *Primary Care,* 4 (4): 601–616, 1977.

The recommended treatment, if possible, is decreasing the dose of prednisone. Major tranquilizers and antidepressants can be of help.

Although none of the major tranquilizers is absolutely contraindicated in physical illness, certain considerations should be kept in mind. All of the drugs have similar efficacy, and there are no established differences in absolute potency. They differ predominantly in the frequency of certain side effects, and it is this fact which should determine the choice of drug. The preferred drug would be the one with the least likelihood of a side effect involving the system in which the pathology already exists. (Notes: Please refer to the table for doses and predominant side effects.)

The reactions to Terminal Renal Failure and its treatment are as varied and complex as the variety of human experience. We have attempted in this article to sketch an outline of these responses with the expectation that this understanding can guide the physician in the management of his patients. Though the demands on these patients are great, we remain impressed by the remarkable capacity of the human being to adapt to the extraordinary demands imposed upon him by illness and its treatment.

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18. DIALYSIS AND TRANSPLANTATION: SURGICAL MANAGEMENT

WILLIAM T. STUBENBORD

1. INTRODUCTION

Surgical considerations are of fundamental importance in the success or failure in both dialysis and transplantation. Dialysis patients' lives often depend on the adequacy of their shunts or fistulas. Creation of an arteriovenous fistula is the most important surgery they undergo: it is their lifeline to the dialysis machine.

Many kinds of surgical procedures, including renal transplantation, are now common and relatively safe in patients with chronic renal failure. Surgery can be done with minimal risk because of advances in the understanding of preoperative, intraoperative, and postoperative management of these patients.

This chapter reviews the basic principles involved in operating upon patients with renal disease, and specifically the surgical aspects of dialysis and transplantation.

2. GENERAL PRINCIPLES

2.1. Timing of surgery

The majority of patients with end stage renal disease are treated with chronic hemodialysis performed on a regular basis two or three times a week for four to six hours. Elective surgical procedures are best performed the morning following dialysis. The heparin effect is fully reversed by then, and the patient is as free as possible from excess body water and potassium. Dialysis therapy is essential to adequate preoperative preparation of patients for elective surgery. Availability of organ preservation systems has allowed sufficient time for dialysis to be done before transplantation. Low dose or regional heparinization may be used if emergency surgery is required, and protamine may be given prior to surgery if the clotting time is elevated. Hyperkalemia can be controlled

by dialysis and ion-exchange resins. Glucose and insulin may be needed to rapidly control significant hyperkalemia.

2.2. Anemia

Anemia is common in renal failure and is most severe in anephric patients. It is remarkable, however, how well these patients adapt to a chroncially low hemoglobin and oxygen carrying capacity. Chronic dialysis patients often have hematocrits in the 15–20% range but if lower than that they should be transfused prior to surgery. We continue to use leukocyte-poor or leukocyte-free red cell transfusions to avoid the possibility of immunization with transplant antigens. However, there is now evidence to suggest a beneficial effect of pre-transplant transfusions on the eventual outcome of transplantation.

2.3. Hypertension

About one-third of dialysis patients are hypertensive and require antihypertensive therapy. Most antihypertensive drugs should be withheld after midnight prior to surgery. During this period and also post-operatively, if the diastolic blood pressure rises above 110 mm Hg, the patient should be treated with short acting parenteral antihypertensive drugs, such as hydralazine (5–20 mg, IM or IV) or diazoxide (3–5 mg/kg or 150–300 mg, IV). However, sudden cessation of some antihypertensive drugs may precipitate a rebound phenomena of hypertension (clonidine-exacerbation of hypertension) or cardiac complications (propranolol-tachycardia and angina). Thus, these drugs should be tapered in advance of elective surgery. If there is not sufficient time to taper these drugs, then clonidine should be withheld, but propranolol should be maintained at lower doses (80–120 mg/day) to avoid serious cardiac arrhythmias or myocardial infarction. A patient who has received propranolol within a few days prior to surgery should not be exposed to anesthetics possessing cardio-depressive properties.

2.4. Corticosteroids

Many renal failure patients receive adrenocorticosteroids because of transplantation, nephrotic syndrome or collagen-vascular disease. Patients who have received a prolonged course of steroid treatment within the previous 6 month period, should be given an increased dose of steroid preparation for surgical stress when having general anesthesia.

Since most of these patients do have intact catecholamine and aldosterone systems, they require smaller doses and shorter courses of steroid supplementation than patients with Addison's disease.

2.5. Operative and postoperative fluid management

Careful and accurate recording and monitoring of all fluids including losses and close supervision of daily weights is mandatory. Even the small amounts used for irrigating catheters must be recorded. Fluid balance must be maintained and all losses, including 600 ml/day for insensible loss, replaced. Insensible losses may be modified, depending upon body weight and temperature variations. Special flow sheets are especially helpful when there are significant losses from catheters and drains. Many recipients of living related donor transplants, and some recipients of cadaveric organ grafts, have massive post-transplant diuresis. In these instances, fluid losses and replacement must be balanced every half hour. Accurate blood pressure determinations must be obtained and often the use of an indwelling central venous pressure line is necessary to frequently evaluate the course of these patients.

2.6. Hemostasis

Intraoperative management includes careful hemostasis. Clotting abnormalities common in patients with uremia lead to an increased incidence of hematomas, unless even minor bleeding is controlled. Bleeding can be exacerbated by postoperative dialysis and consequent heparinization that is often required 24–36 hours after surgery.

2.7. Postoperative dialysis

Postoperative dialysis with low dose or regional heparinization is usually done 24–36 hours after surgery. Wound hematomas occasionally develop, but careful surgical hemostasis and low doses of heparin help obviate this complication. Frequent measurements of serum potassium levels continue to be necessary during this period.

2.8. Wound healing

Many patients with chronic renal failure have delayed wound healing. Sutures are usually left in place longer than in non-uremic patients to allow sufficient time for adequate healing to occur. Patients with renal

failure associated with diabetes, or with connective tissue diseases treated with corticosteroids, are especially subject to poor wound healing.

3. ANESTHETIC MANAGEMENT

3.1. General evaluation

Preoperative evaluation of patients for anesthesia includes consideration of the acute and chronic fluid and electrolyte status, cardiac status, pulmonary reserve, central nervous system function, and bone marrow function. Central nervous system function is variable in uremic patients, and some degree of metabolic encephalopathy may be present. Hemoglobin and hematocrit levels are low, but as noted above, these patients have usually compensated for this during the long course of their illness. In most instances anesthesia can be safely administered to these patients, even in the presence of severe anemia. It is sometimes difficult to find blood with a negative cross-match for chronic renal disease patients, since they may have received many prior transfusions. The patient must be observed closely for evidence of a transfusion reaction when blood is administered during anesthesia.

Fluid overload is another hazard in these patients. Frequent measurement of central venous pressure and frequent auscultation of the lungs should be done to avoid the development of heart failure. Pulmonary congestion may rapidly lead to pulmonary edema.

3.2. Choice of agents

Preoperative sedation should be limited to the amount sufficient to decrease apprehension without producing depression of vital functions. The choice of anesthetic agents and anesthetic technique should be made after considering all the physiologic problems outlined above. We have been very satisfied using a cyclopropane and oxygen mixture for maintenance anesthesia after induction with thiopental. Cyclopropane provides a high concentration of oxygen in the inspired mixture, a rapid induction and emergence, and it has minimal effects on the liver, kidney, and bone marrow. After repeated exposure, there is no known sensitization. Other agents and techniques can be used as long as they are selected with regard to the specific needs of the individual patient.

4. SURGICAL ASPECTS OF DIALYSIS

4.1. Peritoneal dialysis

4.1.1. Acute renal failure

Open or surgical insertion of a peritoneal dialysis catheter is indicated in the presence of ileus or previous abdominal surgery. The catheter should be inserted with sterile technique and in a location so as to avoid previous adhesions.

4.1.2. Chronic renal failure

Surgical placement of a chronic peritoneal dialysis catheter must be under strict aseptic technique since infection and adhesions are the two most frequently encountered problems in this type of dialysis.

4.1.3. Complications of peritoneal dialysis

Peritonitis is the major complication of peritoneal dialysis. If it does not respond to both parenteral and intraperitoneal antibiotics, then removal of the catheter may be necessary. In addition, unsatisfactory dialysis may result from adhesions, or incorrect placement of the catheter. An attempt at relocation of the catheter should be made but does not always correct the problem.

4.2. Hemodialysis

Access to the circulatory system for chronic hemodialysis is often technically difficult and is the source of many frustrations for the surgeon. The discovery of ways to gain repeated access to the circulatory system opened a new era in the treatment of chronic renal disease. It allowed patients with end stage renal disease to be dialyzed on a regular basis, several times a week.

4.2.1. A-V shunts

In 1960, Scribner and his associates described a percutaneous device, made from silastic rubber tubing and teflon cannulas, that shunted blood from the arterial to the venous system [8]. There have been a variety of modifications in the use of shunts since the original description. Many of the shunts used now are all silastic with an integral tip. These are more pliable than the older teflon cannulas. Numerous configurations and designs of the molded silastic rubber are available. They are used in various locations on the extremities and with different sizes

of cannulas to accomodate variations in vessel size. Several problems, however, have been associated with external shunt devices: clotting is the major one. Clotting occurs periodically within the tubing, often requiring surgical revision of one or both limbs of the shunt. The presence of a foreign body, with its exit site from the skin, predisposes to erosion and infection around the tubing. This frequently necessitates removing the shunt and in putting a new one in another extremity. Our experience with external shunt devices includes numerous episodes of clotting, erosion, bleeding and infection. The infection can sometimes be associated with bacterial endocarditis. Some of our patients were maintained on anticoagulants in an effort to avoid clotting, but, unfortunately, without much success. Nevertheless, shunts have been satisfactory for some individuals. They require no needle punctures and the patients may be able to be connected to the dialysis machine with less difficulty than with a fistula. Shunts also provide enough pressure to flow blood through Kiil and hollow-fiber artificial kidneys without a blood pump. This could be important in the future if wearable artificial kidneys ever become a reality. Our overall experience, however, is that, while shunts are a very satisfactory means of access for acute hemodialysis, they lead to difficulties when used chronically. Internal fistulas provide much more satisfactory access for chronic dialysis.

4.2.2. A-V fistulas

In 1966, Brescia and Cimino described the creation of an internal side-to-side fistula between the radial artery and the cephalic vein at the wrist [4]. The superficial veins became arterialized and could be repeatedly cannulated by percutaneous needles. This allowed adequate blood flow for dialysis up to 500 ml/min, using a blood pump. The advantages of fistulas are several. There is no foreign body present, nor is there an exit site except during dialysis. Cosmetically they are satisfactory, do not require the continuous use of a bandage, and allow free use of the arm. Clotting seldom occurs, but when it does operative revision is required. The veins of the forearm become dilated, prominent, and, at times, even aneurysmal. Occasionally fibrosis and scarring occur along the veins from repeated venipunctures and extravasation of blood. Fistulas can usually be used within several weeks following construction. Occasionally they require several months to become adequate for the repeated cannulation necessary in chronic dialysis.

There have been various modifications of the original Brescia fistula. Our experience has been primarily with end-to-end fistulas at the wrist with distal portions of the vessels ligated [10]. Ligating these vessels

prevents distal venous runoff of arterial blood and minimizes swelling of the dorsum of the hand. Ligation of the artery reduces the incidence of steal syndrome from the ulnar side of the hand. The procedure is usually done in the nondominant arm through a short transverse incision with local anesthesia. The ends of the vessels are progressively dilated and thoroughly irrigated with heparin-saline solution prior to making the vascular anastomosis with fine vascular sutures. The vessels are triangulated and tapered to ensure a wide, patent lumen. A thrill should be apparent immediately when the vascular clamps are released. Patients are encouraged to use their arms normally and to report loss of the thrill immediately. Loss of the thrill is usually an indication of thrombosis and requires prompt operative correction. The proper interval for arterialization depends on the size and thickness of the vessels. If interim dialysis is required, peritoneal dialysis may be done, an external shunt may be placed in the other arm, or catheters may be inserted in the femoral vessels. It is best to anticipate the need for chronic dialysis and to construct a fistula electively before it is actually needed.

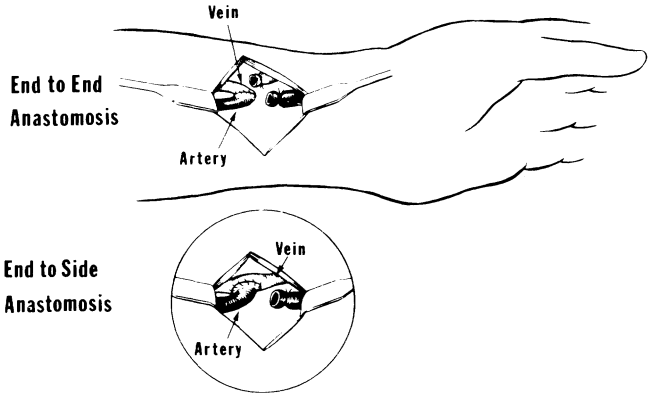

Figure 1. Arteriovenous Fistula. This demonstrates the preferred technique of vascular access — end-to-end anastomosis of the radial artery to the cephalic vein. If the vessels are small, an end-of-artery to side-of-vein (inset) may enable a larger anastomosis to be constructed.

Numerous prior shunt procedures in some patients have damaged the vessels so extensively that peripheral arteriovenous fistulas cannot be constructed. Several alternative approaches are available for these patients. Brachial-cephalic fistulas may be constructed in patients whose forearm vessels are not usable. An end-of-vein to side-of-artery anasto-

mosis is done. Although this type of fistula is more central and usually has a high blood flow, only very rarely does a patient develop heart failure directly related to the fistula.

4.2.3. Graft A-V fistulas

Some patients, especially diabetics, have poor arteries and veins to begin with and satisfactory conventional fistulas are seldom possible. Straight or looped grafts of several types can be interposed between the brachial artery and one of the veins of the arm or axillary area. The arterial anastomosis is end-to-side, while the venous one may be end-to-end or end-to-side. Materials used for these grafts include autologous and homologous saphenous veins, bovine carotid arteries, and synthetic materials such as dacron or expanded polytetrafluoroethylene [5]. All of these materials have advantages and disadvantages and their use will depend upon personal preference and experience of the idividual surgeon. Usually a waiting period of 10–20 days is required before attempting dialysis through one of these grafts after surgical implantation. Interposed grafts may also be placed in the groin or thigh, if the arms are unsatisfactory, between the femoral artery and vein.

4.2.4. Clotted fistulas

Hypovolemia and hypotension can lead to thrombosis of a fistula. Once thrombosis has occurred, the fistula must be revised to make it usable again. The anastomotic area is the usual site of thrombosis and the clot often propagates a short way up the vein. An incision proximal to the previous anastomosis and construction of a new fistula is the most satisfactory way of correcting thrombosis in a peripheral fistula. This is preferable to using the old fistula with its roughened intima and organizing thrombus. Prompt operative intervention is necessary when a fistula clots to prevent the thrombus from propagating further up the arm. Fogarty embolectomy catheters are especially useful for declotting graft fistulas. A new graft will often be required, however, if the primary reason for thrombosis is poor venous runoff.

4.2.5. Thomas A-V shunts

A large external (Thomas) shunt between the femoral artery and vein has been used in some patients who have had repeated shunt and fistula failures [11]. In this device a dacron cuff is attached to the silastic rubber tubing and is sutured as a patch graft directly onto the femoral artery and vein. Dacron velour is wrapped around the tubing to its exit site from the skin. This becomes firmly attached to the surrounding

connective tissue and provides a barrier to infection. High flows are obtained through this type of shunt, and problems with clotting are minimal. Infection, however, is a serious risk. The shunt is directly attached to the side of a major vessel. If it becomes infected, loss of the limb may result. Several of our patients developed significant infections around this type of shunt. The shunt had to be removed and a bypass procedure done to maintain viability of the extremity. With more frequent use of the grafts, Thomas shunts (and their associated danger of infection) have been avoided.

4.2.6. Complications of fistulas

Other than occasional clotting episodes requiring operative correction, there have been few complications of fistulas. Infection is unusual, even with grafts. Large femoral and brachial fistulas, with high flow, are usually well tolerated, and heart failure is surprisingly rare. Whether or not long-term effects will occur remains to be determined. Ischemic symptoms, due to a steal syndrome, have been reported but are unusual. As mentioned above, avoiding side-to-side fistulas in the distal forearm helps to prevent ulnar steal syndromes. Most patients with brachial artery fistulas are also free from ischemic symptoms in the hand. Nevertheless, this is a complication that should be looked for and corrected if present, since loss of digits as a result of ischemia has been noted.

5. SURGICAL CONSIDERATIONS OF TRANSPLANT CANDIDATES

All patients with chronic renal failure are potential candidates for a renal graft. There are few contraindications to transplantation. An active infection is the main reason for deferring transplantation. Transplantation can subsequently be done when the infection has subsided. Infected wounds or shunts are common causes for delaying transplantation.

The lower urinary tract of the potential recipient requires accurate evaluation to determine the possible need for corrective surgery prior to transplantation. Patients with end-stage renal disease on chronic dialysis programs are occasionally found to have previously undetected gross abnormalities of the lower urinary tract. The recipient's urologic system must always be evaluated. It must be physiologically satisfactory to accomodate the new kidney before transplantation is done. A voiding cystourethrogram is the most important study in the evaluation. This

delineates the size, shape, and contour of the bladder and detects obstruction in the urethra or presence of residual urine after voiding. Presence or absence of reflux, at either high or low pressures, and anatomical distortion of the ureters and collecting system can also be identified. Cystoscopy and retrograde studies are sometimes necessary if abnormalities are present, but usually the cystogram is sufficient. Approximately 80 percent of potential recipients have normal studies and need no further evaluation or surgery prior to transplantation.

5.1. Indications for pre-transplant nephrectomy and ureterectomy

Surgery on the upper urinary tracts may be needed for several reasons: infection, excessively large polycystic kidneys, hypertension refractory to drug therapy, or an active immunologic process in the kidney. Malignancy may occasionally necessitate removal of a solitary kidney or bilateral nephrectomy.

Chronic pyelonephritis is usually associated with ureteral reflux and lower tract disease, but may be due to obstruction of the ureteropelvic junction or persistent renal calculi. Infected kidneys must always be removed prior to transplantation and immunosuppression. Although polycystic kidneys may shrink after transplantation, they are sometimes excessively large and occupy too much space. One or both may have to be removed to facilitate transplantation. Less frequently, polycystic kidneys have to be removed for chronic infection, persistent hematuria, or rupture of cysts with abscess formation. Where active renal destruction is present from an immunologically active disease, such as Goodpasture's syndrome, the kidneys should be removed and the patient maintained on dialysis until the process is quiescent.

Pretransplant nephrectomy is sometimes necessary when renal disease has resulted in severe, drug-resistant hypertension. This should prevent morbidity and mortality while the patient is on maintenance dialysis and prevent hypertensive damage to a transplanted kidney.

Rarely, malignancy in a solitary kidney or bilateral tumors necessitate nephrectomies. Considerations in transplanting a patient with malignancy are complex. The problem can only be solved on an individual basis. We have proceeded with transplantation and immunosuppression on several occasions under these circumstances. There is a higher incidence of *de novo* tumors in immunosuppressed patients, but tumors adequately treated prior to immunosuppression do not appear to be influenced adversely.

Almost all types of ureteral dysfunction lead to urinary stasis and

subsequently to chronic pyelonephritis. These patients all require nephroureterectomy. Ureteral valves and ureterovesical junction obstruction with reflux and hydroureter both fall into this category. A dilated ureter, secondary to reflux, provides a perfect focus for chronic urinary tract infection, and should be eliminated. If unilateral reflux exists, the normal ureter should be preserved. Nephrectomy is not indicated when there is minimal reflux in a ureter that appears normal and is not infected. Every effort should be made to preserve kidneys when there is no definite indication for nephrectomy. Patients generally fare better on dialysis with fewer complications and maintain higher hematocrits if they have their own kidneys. If nephrectomy is required, the ureter should only be removed for specific indications. The patient's own ureter might be needed in the future for possible reconstructive use after transplantation.

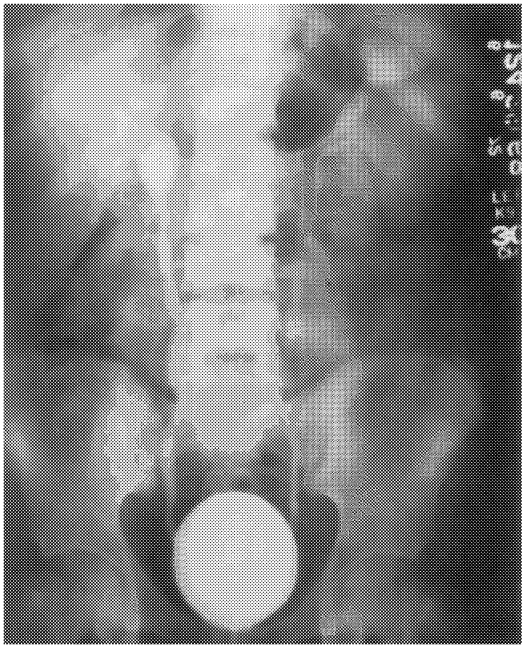

Figure 2. Hydronephrosis and Vesicoureteral Reflux. This cystogram reveals a normal-sized bladder but significant reflux and hydronephrosis. A double ureter is noted also on the left. Bilateral nephroureterectomy is indicated prior to transplantation.

Patients with cutaneous ureterostomies require nephroureterectomy to remove sources of infection, even though their bladder may be functional and usable. The ureteral stumps should also be removed if the cystogram shows significant reflux.

Usually at least 6 weeks should pass following nephrectomy and ureterectomy before the actual transplant is performed.

5.2. Indications for pre-transplant lower urinary tract corrective surgery

The condition of the bladder is one of the most important considerations in preparation for transplantation. Renal transplantation requires a functional bladder or a good substitute. Bladder neck obstruction should be corrected, as a separate procedure, prior to transplantation. Prior corrective surgery may not be necessary in older males with evidence of benign prostatic hypertrophy. Transurethral resection of the prostate is usually not justified and may lead to significant bleeding. Should a cadaveric organ become available, transplantation and cystostomy drainage, followed by a subsequent transurethral resection of the prostate is preferable.

If cystoscopy and cystometrics reveal that the bladder is not satisfactory, an alternative drainage system must be constructed electively prior

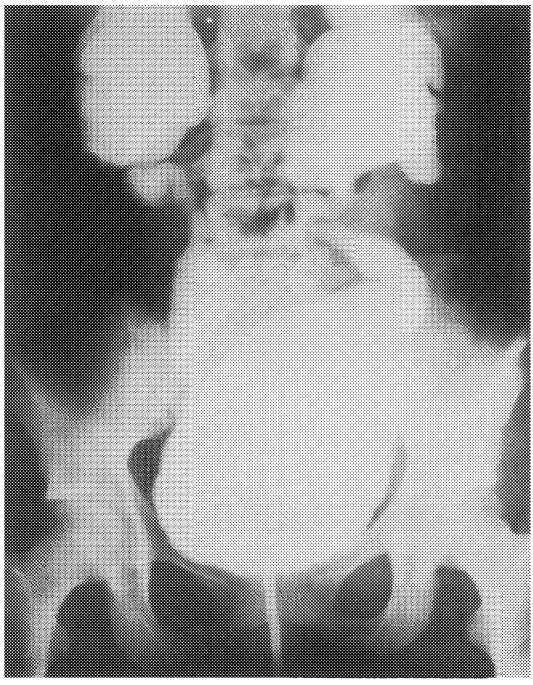

Figure 3. Neurogenic Bladder and Hydronephrosis. This cystogram reveals a large neurogenic bladder with marked hydronephrosis. Bilateral nephroureterectomy and creation of an ileal conduit should be performed prior to the patient's receiving a kidney transplant.

to transplantation. An abnormal bladder is usually associated with infected or distorted kidneys and ureters. Bilateral nephroureterectomy and construction of an ileal loop is done at one operation in these patients. Our experience with conduits has been most satisfactory [9]. Continued reevaluation of the drainage system in patients after transplantation is essential. Retrograde conduitograms and intravenous pyelograms must be done periodically, especially if there is any change in renal function or if recurrent urinary tract infections occur. Contrast media normally refluxes freely into the ureter when a conduitogram is done. The absence of reflux indicates possible obstruction to the urinary outflow tract.

6. CADAVERIC KIDNEYS

The majority of kidneys presently transplanted are obtained from cadaveric donors. These donors meet certain strict criteria which are reviewed below, and then following nephrectomy the kidneys are either kept in cold storage or perfused on a preservation unit prior to actual implantation into the recipient.

6.1. Cadaveric donors

The following are the generally accepted criteria for cadaveric donors:

1. Age: 5–50 although in certain instances infant kidneys are acceptable especially for use in children.
2. No history of hypertension, kidney disease or diabetes.
3. No evidence or history of malignancy except for tumors of the central nervous system or spinal cord and confined to those areas.
4. No evidence of transmittable infectious disease.
5. Meets the criteria of brain death with absence of cortical and brain stem function.
6. Has adequate circulatory system while maintained on a respirator although medications may be required to support this system.
7. Good renal function with satisfaction urinary output and creatinine less than 3.0 mg%.

Most cadaveric donors have had either massive head trauma with few or no associated injuries or a massive cerebro-vascular accident. In this setting they are evaluated as potential donors, a good history obtained and certain basic laboratory determinations made. The donors are maintained on a respirator with careful monitoring of blood pressure and-

urinary output until a determination of cerebral death can be made, and permission for organ donation obtained. This permission should also include the removal of blood, lymph nodes and spleen which are all used for tissue typing and cross matching purposes in an effort to pick the best available recipients. In certain instances the Medical Examiner's Office must also give permission for the donation. An effort should also be made to identify other organs that may be needed for transplantation purposes.

6.2. Cadaveric nephrectomy

Once all the criteria of brain death have been met and the proper forms and consents have been completed, the donor is brought to the operating room and there, blood pressure and respiratory rate maintained as before, while the actual nephrectomy takes place. Some groups now prefer to use donor pretreatment with cytotoxic drugs some hours prior to actual removal of the organs and in this instance blood and lymph nodes are needed beforehand for tissue typing purposes. The use of one of several drugs such as dibenzyline, regitine, or high dose steroids has been shown to be beneficial in protecting the kidney and are to be recommended. Furthermore, heparin should be administered prior to the actual removal of the kidneys.

Various surgical techniques are used in removal of the kidneys some of which include en bloc removal of the organs so as to have the blood supply to the kidneys intact from the aorta and vena cava. This is important if the organs are small or if there are multiple vessels involved. Good aseptic technique is necessary and cultures should be taken from blood and kidneys. The gastrointestinal tract should not be entered in performing the nephrectomy. Under ideal circumstances then, the kidneys are removed with an intact circulatory system and therefore suffer little or no ischemic damage. Immediately following removal, the kidneys are flushed with a cold electrolyte solution to wash out the blood and reduce the core temperature. An accurate description of their anatomy should be made so that any variation may be communicated to the possible user of these organs.

6.3. Cadaveric kidney storage

Two basic techniques of kidney storage are available and each has its advantages and disadvantages.

6.3.1. Cold storage

This technique involves maintaining the kidneys in a simple iced electrolyte solution usually an intracellular type (high K and low Na) at about 4 °C. Kidneys kept this way have remained viable and functional for periods of up to 36 hours, but most surgeons prefer to use them in less than 24 hours following removal. This method is inexpensive, allows easy transport, and is simple. However, the time is limited and no assessment of the kidney is made except for the way it flushed when originally removed.

6.3.2. Perfusion

The use of continuous pulsatile perfusion was first popularized by Belzer and continues to be the means of preservation used today for longer periods than that afforded by cold storage [1]. The basic technique involves the use of a perfusate (plasma-like solution), pulsatile flow, hypothermia (6–8 °C), and some form of oxygenation. The perfusate is monitored for pH and other biochemical levels and the flow, pressure, and temperature observed regularly. This affords some means, although not absolute, of following the kidney and detecting any irreversible damage. Portable battery powered units are available so that kidneys on perfusion may be transported even in commercial aircraft for long distances. Kidneys have been found to function satisfactorily with up to 72 hours of perfusion. It is also possible to use some combination of cold storage and perfusion up to the 72 hour limit previously noted. The cost for perfusion is obviously greater but the extra time it allows has enabled kidneys to be shared over a wide area. In addition, tissue typing and the actual transplant operation may be performed without the haste it would otherwise entail. Some reports of possible mechanical and immunologic damage to perfused kidneys (perfusion nephropathy) have been noted but most investigators consider the advantages to outweigh the possible risks involved.

7. SURGICAL ASPECTS OF RENAL TRANSPLANTATION

7.1. Transplant procedure

The surgical techniques for renal transplantation have been well standardized. The renal graft is usually placed extraperitoneally, in the groin, on the opposite side from whence it came. This location has been found most suitable because of ready access to the blood vessels for the

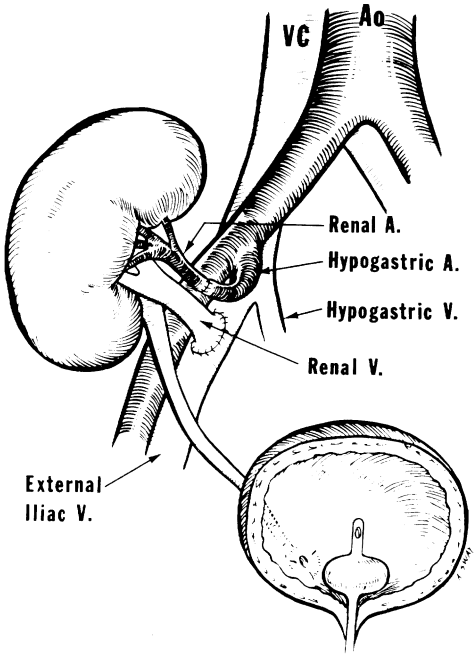

Figure 4. Retroperitoneal Kidney Transplant. This diagram shows the usual anatomical placement of the renal transplant in the false pelvis and the vascular and urologic anastomoses. Note only the urethral drainage catheter.

vascular anastomoses. Grafts in small children, because of the marked difference in size, may have to be placed intra-abdominally. The extra-peritoneal position is preferable, however, and complications are less likely to develop. Our usual procedure is, after induction of anesthesia, to insert a Foley catheter (#18–5 ml bag) into the bladder and instill about 100 ml of 1 gm/dl neomycin solution for better identification and sterilization. An incision is then made in the groin, carried down through the muscle and fascial layers and the peritoneum is reflected superiorly. The inferior epigastric vessels are divided, as is the round ligament in the female. An effort is made to preserve the spermatic cord in males, but occasionally this is not feasible. The external iliac vein is mobilized and prepared for an end-to-side anastomosis to the donor renal vein. All lymphatic vessels along the vein are ligated to prevent accumulation of lymph and formation of a lymphocele. The hypogastric artery is also mobilized throughout its length, then ligated and divided in the area of its bifurcation. An end-to-end arterial anastomosis is then done, using the triangulation technique. Intravenous furosemide is usually given (100 mg for a living donor and 200 mg for a cadaveric

organ). The ischemic time should be no more than 20 to 30 minutes, unless unusual difficulty in the vascular anastomoses is encountered. Significant accessory arteries may be placed end-to-side into the external iliac artery and this second anastomosis, if needed, can usually be done following revascularization of the main portion of the kidney. Other methods of dealing with accessory vessels include anastomosis to one of the following arteries: (1) the main renal artery itself; (2) the inferior epigastric artery, or (3) the bifurcated hypogastric artery. Care must be taken to maintain the blood pressure at a satisfactory level throughout the procedure, especially after revascularization of the kidney.

The bladder is mobilized after completion of the vascular anastomoses. A cystostomy is performed and ureterovesical continuity is established by the Paquin tunnel technique [7]. Care must be taken not to twist the ureter and to ensure its patency at the conclusion of reimplantation. A catheter is usually passed upward into the renal pelvis, unless there already is a free flow of urine. Only a urethral catheter is left in place. Urologic complications are minimal with urethral drainage alone after careful ureteral implantation. The bladder is closed in two layers and should be irrigated free of clots before closure to prevent urinary obstruction. The entire transplant wound is then thoroughly irrigated with saline, followed by an antibiotic solution [3]. Clips are placed on the four borders of the kidney for radiographic visualization and comparison views in the future. Drains are only rarely left in place since they may lead to subsequent infection. Accurate hemostasis usually obviates the need for drainage.

A normal adult kidney is too large to be placed in the groin of infants and children under 20 kg, and the size of the vessels is disproportionate. An intra-abdominal location must be used in these instances. The cecum is mobilized and the kidney placed behind the colon, using the aorta or right common iliac artery for the arterial anastomosis and the inferior vena cava for the venous return. A long midline incision is best for this approach and for the ureterovesical anastomosis. Often bilateral nephrectomy can be done at the same time with no added morbidity. With the intra-abdominal approach, however, the irrigation with antibiotic solution is avoided.

An ileal loop is used if the bladder is unsatisfactory. As noted above, it should be constructed electively, prior to transplantation. The loop is irrigated with neomycin before surgery and the ureteral anastomosis to the loop is made over a splinting catheter. The conduit should be extraperitoneal or readily accessible through a small peritoneal opening. The splint, just as the Foley catheter, is left in place for 7 days.

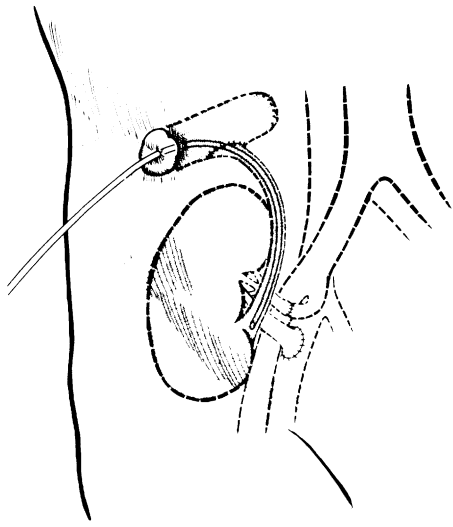

Figure 5. Kidney Transplant with an Ileal Conduit. This illustrates the use of an ileal conduit when the bladder is unsatisfactory. The ureter is anastomosed to the isolated ileal loop over a splinting catheter.

7.2. Surgical problems following transplantation

7.2.1. Vascular complications

Acute vascular problems, either thrombosis or disruption, are unusual following renal transplantation. When they do occur, they are often the result of an acute transplant rejection episode. ^{99}Technitium and ^{131}Hippuran scans should be done the day following transplantation to evaluate blood flow through the kidney. ^{99}Technitium scanning is particularly helpful in demonstrating patency of the arterial anastomosis. Scans are repeated as needed during the postoperative period and are helpful in differentiating rejection from other causes of acute renal failure. If no blood flow can be seen with this noninvasive technique, immediate exploration is indicated. The use of ^{99}Technitium scanning has obviated much of the need for arteriography.

Disruption of an anastomosis is usually the result of an infectious process. This castrophe requires immediate exploration and usually requires removal of the graft.

Chronic vascular problems are unusual. Stenosis of the arterial anastomosis is a recognized post-transplant entity and it may produce hypertension following transplantation. Stenosis of the transplanted ren-

al artery usually appears months following transplantation. It is correctable, if the area of stenosis is well localized to the anastomosis or just beyond it. The use of balloon dilatation to correct transplant renal artery stenosis may well be a significant advance in dealing with this problem. Venous thrombosis can also occur following transplantation and is often accompanied by significant proteinuria. Venography may be helpful in establishing this diagnosis. Although the catheter may not pass easily into the renal vein, the washout from the renal vein should be seen on the venous return through the external iliac vein.

7.2.2. Urologic complications

A urethral catheter is normally the only drainage used following reimplantation of the ureter into the bladder. Decreasing urinary output in the post-transplant period may therefore indicate obstruction. Obstruction of urine flow may occur either from outside the ureter, due to pressure from a hematoma or lymphocele; from within the ureter, due to a blood clot; or from edema of the ureter. Acute cessation of urine output in the early post-transplant period is usually a sign of mechanical obstruction and it requires immediate exploration of the kidney. This type of obstruction can usually be relieved either by correction of an extrinsic pressure source, or by nephrostomy drainage, if intrarenal bleeding or edema is at fault. Undetected acute obstruction generally results in loss of the kidney, but, if treated promptly the kidney can often be saved. Slowly decreasing output is more likely due to rejection or acute tubular necrosis. Immediate exploration in these patients is ordinarily of no value.

Slough of the ureter with fistula formation can also occur in the postoperative period. This is usually the result of compromised ureteral blood supply. Care must be taken to preserve the blood supply to the ureter when removing kidneys from either living related or cadaveric donors. Post-transplantation urinary leaks have been significantly reduced by careful implantation of the ureter into the bladder and by avoiding the use of splints and cystostomy drainage [2, 12]. The recipient's own ureter may be used with ureteropyelostomy and nephrostomy drainage if ureteral slough should occur early in the postoperative period. This procedure can save kidneys that otherwise might be lost. It requires removal of the recipient's own kidney and preservation of the ureter which must, of course, have a satisfactory ureterovesical junction.

Urethral drainage catheters are maintained for 7 days. A cystogram is done prior to removal of the catheter to make certain that there is no

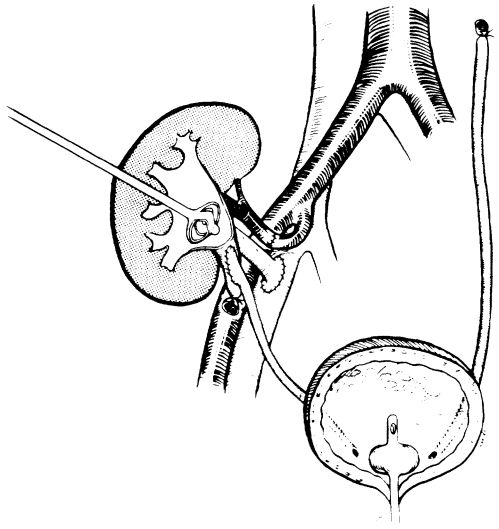

Figure 6. Kidney Transplant with Ureteropyelostomy. This shows the technique for ureteropyelostomy with nephrostomy drainage. This type of urologic continuity is useful when a ureteral slough or fistula has developed and the recipient's own ureter is satisfactory and the kidney has been removed.

bladder leak. Removal of the catheter prior to this time may give rise to disruption of the bladder closure. Should a leak occur in the bladder closure, simple Foley catheter drainage is usually sufficiently to allow the fistula to close. Sometimes, however, a cystostomy tube must be placed for adequate decompression.

Chronic urinary fistulas are distinctly uncommon, but stenosis of the ureter, either at its entrance into the bladder wall or at the ureterovesical anastomosis, can occur and result in hydronephrisis. Ureteropyelostomy with the recipient's own ureter or reimplantation is required to preserve the kidney. Repeated attacks of urinary tract infections should alert the physician to this possibility of ureteral obstruction. Periodic pyelography of the transplanted kidney is necessary to make sure obstruction is not developing. Before discharge from the hospital following transplantation, intravenous pyelography should be done. A repeat pyelogram is indicated when there is any change in renal function in the post-transplant period. Ureteral stenosis is more common in patients with intestinal conduits and in these cases, stenosis usually develops in the region of the anastomosis or at the ureteropelvic junction. Retro-

grade study of the conduit is helpful in outlining the anatomy and showing any stenosis that may be present.

7.2.3. Wound complications

Wound infections are more common after transplant surgery than after other procedures because of immunosuppression. An antibiotic solution is used routinely at the time of transplantation to irrigate the wound, and this procedure decreases the infection rate. The antibiotic solution is also used at the time of any re-exploration of a transplant wound. Perinephric fluid collections can easily occur in the large area dissected around the kidney and in the retroperitoneal space. Bleeding may also occur in these areas and provide a rich medium for infectious agents. Several units of blood are easily accomodated in the perinephric and retroperitoneal space and can extend up to the recipient's renal fossa. Unexplained fever in the post-transplant period must always be considered as possibly septic in origin. Frequent blood cultures must be obtained and the wound examined repeatedly to rule out the possibility of a deep infection. Such infections can be subtle in their appearance, and take weeks to become obvious. Sonography has been of great value in defining some of these problems.

Fracture of the kidney surface from intracapsular swelling and edema as a result of rejection may occur [6]. This is usually associated with extensive bleeding. The patient frequently complains of severe pain in the transplant wound site radiating up the back. A fall in hematocrit often occurs and, with severe bleeding, may be associated with decreased blood pressure. Although most of these kidneys cannot be salvaged, an effort should be made to explore the wound, evacuate the hematoma, and, if possible, oversew the disrupted area. The underlying rejection is usually so severe, however, that nephrectomy is required.

7.2.4. Transplant nephrectomy

Removal of a rejected renal allograft can be a most difficult operation. The kidney becomes extensively surrounded by adherent scar tissue, or it becomes swollen and difficult to remove because of severe rejection. Scarring and swelling obscure the anatomy of the area. Injury to the major vessels is much more likely to occur at the time of transplant nephrectomy than at the time of the transplant. Bleeding often occurs during transplant nephrectomy because the rejected kidney may be very vascular, the capsule of the kidney may become adherent to the adjacent tissues, and there may be a large denuded area in the retroperitoneal space where bleeding is difficult to control. Hematomas often occur

in the transplant nephrectomy wound, and may require either placing drains or a Hemovac. Most of these patients have been heavily immunosuppressed, and infected wounds are much more frequent than at the time of the original transplant. The antibiotic solution described previously is used routinely and significantly reduces infection rates. Significant perinephric infections present at the time of transplant nephrectomy require that drains be left in place. Occasionally, the wound must be left widely open because the infection is so extensive. A hernia sometimes develops in such wounds. Some wounds require several months to heal because of massive infection. A wound infection is a contraindication to further transplantation until it has completely resolved. The arterial suture line should be removed, if possible, and the hypogastric artery ligated proximately. A small patch of grafted vessel must be left on the venous side and also where an end-to-side arterial anastomosis has been done.

Not all rejected kidneys need to be removed. A small contracted kidney as a result of chronic rejection, may be left in place but any infection or symptoms of pain or bleeding from a rejected kidney are indications for its removal.

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19. DRUG METABOLISM AND DOSE ADJUSTMENT IN PATIENTS WITH RENAL FAILURE

JHOONG S. CHEIGH and MARCUS M. REIDENBERG

1. DRUG METABOLISM IN UREMIA

The elimination of drugs and other foreign chemical compounds taken into the body can be either by excretion or by metabolic biotransformation to other chemical compounds which are then excreted. The excretion pathway can be urinary or biliary, the pathway often being dependent on the molecular weight of the compound. High molecular weight water-soluble compounds often have substantial biliary excretion, while low molecular weight compounds are excreted almost entirely in the urine. Both excretion pathways require that the excreted substance be water-soluble. Lipid-solubles tend to be protein-bound, which also retards their excretion. In addition, lipid-soluble compounds filtered at the glomerulus are rapidly reabsorbed as the urine is concentrated during its passage down the nephron. Thus, lipid-soluble drugs tend to remain in the body.

1.1. Biotransformation

Most biologically active drugs are more soluble in lipid than in water. This lipid solubility is probably one of the characteristics for a chemical to be able to diffuse into a cell to exert its biological effect. The various pathways of drug metabolism tend to convert lipid-soluble drugs into water-soluble metabolites. These water-soluble metabolites tend to diffuse slightly, if at all, out of the urine and hence are readily excreted. Thus, the body would tend to excrete water-soluble metabolites and reabsorb rather than excrete the lipid-soluble drugs.

1.1.1. Pathways

The chemical reactions of drug metabolism can be classified into four broad groups: oxidations, reduction, hydrolyses, and syntheses. Drugs are usually metabolized in two stages. The first stage includes the reactions in the oxidation, reduction and hydrolysis groups. During this

stage, the drug molecule tends to be given reactive groups such as hydroxyl or carboxyl (–OH or COOH) groups. The metabolite is now more polar or water-soluble than the parent drug. The second stage, the stage of synthesis, involves the linking of the drug or metabolite with a very polar molecule such as glucuronic acid or sulfate. This new product is now much more polar than its parent drug. It would be readily excreted in the urine.

1.1.2. Prototype Drug Pathway

A typical metabolic pathway for many drugs is the oxidation of the drug by adding an –OH group to a benzene ring in the structure. The second stage, synthesis, then adds a glucuronic acid molecule to the –OH group. Whereas the parent drug may have been water-soluble, the glucuronide is an acid with a pK of 3 to 4 and would be ionized and therefore highly water-soluble at the pH of blood or urine. Normal individuals would then rapidly excrete this metabolite.

1.2. Effect of Renal Failure

Renal failure can modify this normal pathway of drug disposition in two ways. The rate of a particular pathway of drug biotransformation can be altered. The excretion of the ultimate metabolite in the urine will be slowed. The effects of uremia on the elimination rate of some drugs in man are summarized in Table 1.

Some recent studies have led to the unexpected observation that certain drug oxidations occurring in the liver endoplasmic reticulum (which on cell fractionation in vitro becomes the liver microsomes) are accelerated in uremia. The first observation of drug metabolism being more rapid than normal in uremia was by Letteri, et al. in a study of diphenylhydantoin elimination. This has since been confirmed by Odar-Cederlöf and Borga, and would mean that uremic patients require larger than average doses of diphenylhydantoin to maintain therapeutic concentrations in the body. Because of impaired plasma protein binding of diphenylhydantoin in uremia, the plasma levels of this drug will be low even when therapeutic levels in the brain are achieved. One can correct for this decreased binding and interpret serum phenytoin levels in patients with renal failure as shown in Figure 1.

Table 1. Apparent elimination rate of drugs in patients with renal failure.

Drug	Effect	Reference
A. *Oxidations*		
Antipyrine	Normal or rapid	Lichter et al.
Antipyrine	Normal or rapid	Maddocks et al.
Histamine	Normal	Beall, VanArsdel
Lidocaine	Normal	Thompson et al.
Lidocaine	Normal	Collinsworth et al.
Meperidine	Normal	Szeto et al.
Pentobarbital	Normal	Reidenberg et al.
Phenacetin	Normal	Prescott
Phenacetin	Normal	Dubach
Phenobarbital	Normal	Fabre et al.
Phenytoin	Rapid	Letteri et al.
Phenytoin	Rapid	Odar-Cederlöf, Borgå
Propranolol	Normal	Thompson et al.
Propranolol	Normal	Lowenthal et al.
Propranolol	Rapid	Bianchetti et al.
Quinidine	Normal	Kessler et al.
Tolbutamide	Normal	Glogner et al.
Tolbutamide	Normal	Reidenberg
Vitamin D	Slow	Avioli et al.
B. *Reduction*		
Cortisol	Slow	Englert et al.
C. *Syntheses*		
Glucuronide conjugation		
Chloramphenicol	Normal	Kunin et al.
Acetaminophen	Normal	Lowenthal et al.
Sulfate conjugation		
Acetaminophen	Normal	Lowenthal et al.
Acetylation		
p-Aminosalicylate	Slowed	Ogg et al.
Isoniazid	Normal	Bowersox et al.
Isoniazid	Normal	Reidenberg et al.
Isoniazid	Slowed	Dettli, Spring
Sulfisoxazole	Slowed	Reidenberg et al.
Glycine conjugation		
Salicylate	Normal	Lowenthal et al.
D. *Hydrolyses*		
Peptides		
Insulin	Slowed	O'Brien, Sharp
Insulin	Slowed	Horton et al.
Insulin	Slowed	Rabkin et al.
Esters		
Procaine	Slowed	Reidenberg et al.
Cephalothin	Slowed	Kirby et al.

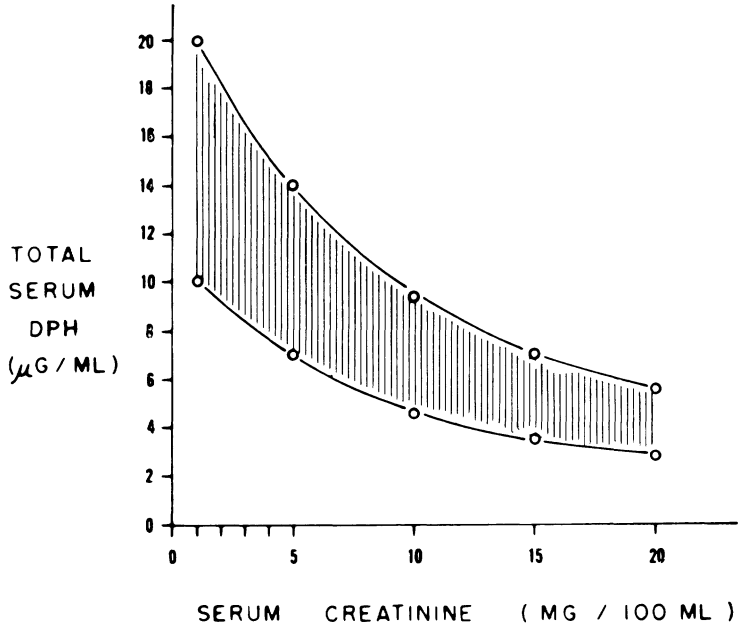

Figure 1. Concentration of phenytoin (DPH) in serum of patients with varying degrees of azotemia that will produce concentrations of drug in plasma water equal to that in otherwise normal epileptic subjects when their phenytoin levels are in the therapeutic range. Figure reproduced from Ann NY Acad Sci (226:115, 1973), with permission.

1.3. Retention of Active Drug Metabolites

The retention of drug metabolites in uremic patients can lead to several difficulties. If these metabolites are pharmacologically active, then the duration of effects of a drug will be prolonged even if the drug itself is normally metabolized. The sulfonylurea drug, acetohexamide, for example, is normally oxidized to hydroxyhexamide, a potent hypoglycemic compound, which is then excreted unchanged or further metabolized. Conditions that impair the excretion of hydroxyhexamide lead to prolonged hypoglycemia after acetohexamide administration even though the rate of biotransformation of the drug is normal. Another example of this problem is the acetylation of procainamide to N-acetylprocainamide in uremic patients. N-acetylprocainamide apparently has pharmacologic activity similar to procainamide and is present in high concentration in the plasma of patients taking procainamide. This active metabolite is not measured by the usual methods of measuring blood levels of procainamide and its pathway of elimination from the body is primarily by

urinary excretion. We have observed high and sustained levels of this metabolite in plasma from uremic patients who had taken procainamide and suspect that it, rather than the parent drug, is the cause of the very prolonged effect of procainamide seen in some uremic patients.

1.4. Retention of Inactive Metabolites

If the retained drug metabolites in uremia are pharmacologically inactive, a different sort of problem occurs. If the analytical method for measuring the drugs is non-specific and measures the metabolite as well as the drug, patients will appear to be resistant (fail to have the effect) to a drug when plasma levels are 'adequate'. There are several examples of this. The usual way of measuring sulfonylureas determines the inactive metabolites of tolbutamide as well as the parent drug. Several studies claimed slowed metabolism of tolbutamide in uremia before Glogner, Lange and Pfab did the correct study showing normal metabolism of tolbutamide with failure to excrete inactive metabolites. A similar story exists for quinidine with the older analytical method measuring both active drug and inactive metabolites. Uremic patients had normal plasma half-life values for quinidine but showed marked retention of inactive (but fluorescent) quinidine metabolites that were measured as 'quinidine' by the standard method of measuring quinidine by the fluorescence of a protein-free filtrate of plasma.

2. DOSE ADJUSTMENT IN RENAL FAILURE

Before any drug is prescribed to patients with kidney disease, physicians must consider many factors that are unique to these patients. These are: is the drug nephrotoxic and will it aggravate existing renal disease; will it be excreted poorly or metabolized abnormally and induce cumulative effects; will it be removed during dialysis and render reduced doses usually given to patients with renal failure ineffective; will it interfere with the internal environment of the body and aggravate uremic symptoms; if the indication for the drug is infection in kidneys or urinary tract, will the drug concentration in the diseased kidney tissue or in the urine be sufficient to maintain therapeutic levels at the site of the infection? Only after considering all these factors, can physicians arrive at a choice of drug and dose that is the most effective but least dangerous for the patient. In practice, the drug chosen may not be either the most effective for the indication or the least dangerous for the

patient, but rather the best balanced drug one can choose from the many alternatives.

In general, patients with mild renal insufficiency eliminate drugs as do normal people. However, they may not be able to eliminate drugs normally when kidney function is less than 1/2 to 1/3 of normal. The most obvious reason for limiting use of certain drugs in patients with renal failure is their accumulation in the body if they are normally excreted by the kidney. The consequences of accumulation are of course more serious, the more toxic the substance.

The consequences of renal insufficiency do not depend only on the type of renal excretion of the substance, whether tubular, as for some drugs like penicillin, or glomerular as for other drugs like gentamicin; they also depend on drug-protein binding, distribution, biotransformation and possibly, retention of active metabolites. On the other hand, agents may be lost during dialysis and therapeutic blood levels may not be maintained. This is especially true if the molecular weight of the drug is less than 200 and it is not bound to tissue or plasma protein. Because our current dialysis membrane pore size permits passage only of substances with low molecular weights, drugs that are tightly bound to tissue or protein are nondialyzable.

Adjustment of dosage schedules can be made either by keeping the dosage constant and varying the interval between doses, by keeping the interval constant and varying the dosage, or by some combination of these two methods. Equilibration time, the time required to reach a steady-state drug concentration, is independent of dosage or frequency of administration; it depends only on the biologic half-life of the particular drug. All drugs require about five half-lives to reach a steady state. The time required for drugs removed primarily by the kidneys to reach a steady-state concentration is significantly delayed in renal failure because of their prolonged half-lives. Therefore, a simple reduction in dosage or modification of the interval of drug administration, could result in serious delays in establishing therapeutic concentrations of drugs, and could lead to wide fluctuations in drug levels. Similarly, dialysis patients require special dosage modification for many drugs to prevent excessively high and toxic levels during the non-dialysis periods, or excessively low and ineffective levels at the end of dialysis treatment.

Available information about the use of drugs in patients with kidney diseases is limited. The guidelines presented in this manual are not absolute, but are intended to be practical and reasonable, based on the best current information for an adult patient of average size with kidney

disease. However, the final dose of any drug depends on the nature and severity of the disease being treated, as well as on the degree of renal failure. The dose of antibiotics, for instance, is different for cellulitis than for bacterial endocarditis. In some instances, special laboratory tests are often used to monitor drug levels in the plasma.

2.1. Antimicrobial Drugs

Patients with uremia have a high incidence of infection. The increased infection rate is probably the result of both increased risk factors and impaired host defense mechanisms. The infection is usually caused by common pathogenic organisms, but there is also a high incidence of nosocomial infections. Diagnosis and localization of infection, and procedures for identification of infectious organisms are no different in these patients than in non-uremic patients. Selection of antimicrobial drugs depends on the nature of infection, causative organisms and their sensitivities to antimicrobial drugs.

Some antimicrobials require minor or no dose modification in patients with renal failure. These drugs are either eliminated predominantly by extrarenal mechanisms or their margin of safety is sufficiently wide that moderate drug accumulation does not produce adverse effects. Antimicrobials in this category are listed in Table 2. Their availability for

Table 2. Antimicrobials requiring minor or no dose adjustment for patients with renal failure.

Drugs	Dialyzability	Comments
Ampicillin	yes (HD)	Lower range of therapeutic dose generally used; extra dose (500 mg) after PD or HD
Chloramphenicol	yes (HD)	Extra dose (250–500 mg) after Hd
Clindamycin	no	—
Cloxacillin	no	—
Dicloxacillin	poorly	Lower range of therapeutic dose generally used
Oxacillin	no	—
Doxycycline	no	—
Erythromycin	no	—
Methicillin*	poorly	Lower range of therapeutic dose generally used; nephrotoxic – tubulo-interstitial nephritis
Nafcillin	poorly	Lower range of therapeutic dose generally used
Penicillin G	yes (HD)	Lower range of therapeutic dose generally used; rarely nephrotoxic – tubulo-interstitial nephritis. 1,000,000 units of potassium penicillin contains 1.7 mEq of potassium

Note: PD = peritoneal dialysis; HD = hemodialysis.

* Although any penicillin derivatives can induce acute tubulo-interstitial nephritis, it has been seen more often in patients treated with methicillin.

Table 3. Antimicrobials that require dose modification in renal failure

Drugs:	Amikacin (IM, IV)	Carbenicillin (IV)	Cefazolin (IM,IV)	Cephalexin (oral) ⇒	Cephalothin (IV) ⇒	Gentamicin (IM, IV)	Kanamycin (IM)	Streptomycin (IM)	Tetracycline (oral)	Tobramycin (IM, IV)	Vancomycin (IV)
Therapeutic serum levels:	15-30 μq/ml	25–100 μg/ml	...	...	...	4–8 μg/ml	10 μg/ml	...	...	6–12 μg/ml	5–10 μg/ml
Loading dose:	5–7.5 mg/kg	4–6 g	0.5 g	0.5 g	1–3 g	1–2 mg/kg	7 mg/kg	1.0 g	0.5–1.0 g	1.0 mg/kg	1.0 g
Ccr			Usual dose			1–1.5 mg/kg/ 8hr	7 mg/kg/every third $T^1/_2$				
80					1–2 g/ 4–6 hr						
70	6 mg/kg/12 hr										
60		4–5 g/4 hr		500 mg/ 4–6 hr			($T^1/_2$ = Cr × 3)				
50						0.5 mg/kg/(Cr × 4) hr				Kg/Cr = mg of tobramycin/8 hr or 1.0–1.5 mg/ kg/(Cr × 6) hr	
40	5 mg/kg/12 hr										
30			250 mg/6 hr	500 mg/ 8–12 hr		0.5–0.8/kg/ 8hr		0.5–1.0 g/ 2-3 days			
20	2 mg/kg/12 hr	2–4 g/ 6–12 hr	250 mg/ 6-12 hr		1–2 g/ 6–8 hr	0.5 mg/kg/ 12 hr	0.25 g/24 hr		0.5 g/day		1.0 g/ 10–14 days
10				250 mg/ 12 hr			0.25 g/48 hr	0.5 g/ 3–4 days			
5	1 mg/kg/12 hr	2 g/12 hr	250 mg/ 48 hr	250 mg/ 12–24 hr	1–2 g/ 8–12 hr	0.3 mg/kg/ 12 hr	7 mg/kg/ 5–7 days		0.25 g/day	0.1 mg/kg/ 8 hr	
0											
Hemodialysis		2 g/12–24 hr and 2 g/ PHD	250 mg/ 48 hr and 250 mg PHD	250 mg/ 12–24 hr and 500 mg PHD	1–2 g/ 8–12 hr and 1–2 g PHD	0.25 mg/kg/ 12 hr or 1.0–1.5 mg/kg PHD	7 mg/kg/every other HD	0.5 g/3–4 days and 250 mg PHD	0.25 g/day and 0.25 g PHD	1 mg/kg PHD	1.0 g/7–10 days
Peritoneal dialysis		2 g/6–12 hr	...	...		1 mg/kg/ 12 hr	3.5 mg/kg 24 hr or 0.25 g/24 hr	...	...	...	...
Cautions	Nephrotoxic dose related (ARF)	1 g contains 4.7 mEq Na^+ Hypokalemia alkalosis	...	...	Nephrotoxic probably dose related (ARF)	Nephrotoxic dose related (ARF, rarely tubular dysfunction)	Nephrotoxic dose related (ARF, rarely tubular dysfunction)	Nephrotoxic dose related (ARF)	Nephrotoxic dose related (ARF), increases catabolism	Nephrotoxic dose related (ARF)	Nephrotoxic dose related (ARF)

NOTE: hr = hours, ARF = Acute renal failure, Cr = Serum creatinine (mg/100 ml), Ccr = creatinine clearance (ml/min). $T^1/_2$ = half-life (hr), P = post, HD = hemodialysis. IV = intravenously; IM = intramuscularly, Na^+ = sodium ion, kg = body weight in kg.

dialysis, however, should be noted to determine the need for supplementary doses during or after dialysis treatment.

Those antimicrobials eliminated predominantly by the kidney accumulate in the presence of renal failure and require modified dosages. Antimicrobials in this category are listed in Table 3 with guidelines for dose modification for patients with renal failure. Antimicrobial assay techniques should be utilized to evaluate the adequacy of the drug levels in the plasma whenever questions arise, particularly when those antimicrobials having dose-dependent toxicities are used.

Generally, the standard doses of antimicrobials are effective for kidney and urinary tract infection until the creatinine clearance falls to 10 ml/min. When the creatinine clearance is below this level, efficacy of

Table 4. Antimicrobials absorbed from the peritoneal cavity

Ampicillin	Crystalline chloramphenicol
Aqueous penicillin	Gentamicin
Carbenicillin	Kanamycin
Cephaloridine	Methicillin
Cephalexin	Oxacillin
Cephalothin	Polymyxin B
Cloxacillin	Streptomycin
Colistimethate	Tetracycline
	Tobramycin

Table 5. Antimicrobials and dosages for intraperitoneal administration

Antimicrobials*	Dose per exchange (mg/2,000 ml dialysate)
Amphotericin B	4–8
Ampicillin	50–100
Carbenicillin	100–200
Cephalothin	50–100
Clindamycin	10–20
Gentamycin**	10–15
Kanamycin**	20–40
Methicillin	200
Oxacillin	20
Penicillin G	10,000–100,000 U
Tobramycin**	20
Vancomycin**	30

* Tetracyclin, erythromycin and chloramphenicol are not recommended to use intraperitoneally.

** One parenteral loading dose recommended.

antimicrobials for urinary tract infections diminishes because of decreased drug penetration into the diseased kidney tissue and decreased drug concentration in the urine. Plasma antimicrobial levels must be maintained at higher concentrations to achieve adequate tissue and urinary levels.

The absorption rate of antimicrobials from the peritoneal cavity is unpredictable. Intraperitoneal instillation without systemic administration of antimicrobials should not be used to treat patients with extraperitoneal or systemic infections. Those antimicrobials listed in Table 4 can be absorbed through the peritoneal membrane in a significant amount and can produce systemic toxicities by intraperitoneal instillation.

Usually it is not necessary to add antimicrobials to peritoneal dialysate prophylactically. This method can be used effectively to treat bacterial peritonitis during peritoneal dialysis. Antimicrobials, commonly used for this indication are listed in Table 5.

2.2. Urinary Antiseptics

Effectiveness of most bacteriostatic drugs (methenamine mandelate and hippurate, nalidixic acid, nitrofurantoin, and sulfonamides and trimethoprime-sulfamethoxazole) for urinary tract infections depends on high renal excretion rates and high medullary and urinary concentrations. In general, these drugs are not recommended for the treatment of patients with urinary tract infections if their creatinine clearance is less than 20 ml/min. Clinical efficacy of such agents in advanced renal failure is markedly decreased and the progressive accumulation of drugs increases systemic toxicity. Usual doses of trimethoprime-sulfamethoxazole, however, can be used for the treatment of patients with urinary tract infection, even when their renal function is severely impaired.

2.3. Antimycotic Drugs

2.3.1. Amphotericin B

Although amphotericin is eliminated by predominantly non-renal mechanisms, its half-life does increase in patients with renal failure and the dose should be reduced in patients with impaired renal function to avoid its dose-dependent nephrotoxicity (acute and chronic renal failure, tubular dysfunction, renal tubular acidosis, hypokalemia). However, since the daily and total dose of amphotericin and the duration of therapy vary so widely depending on offending mycotic agents and locations of infection, no specific formula for dose adjustment can be

made. Because of it's high protein binding property (90%), amphotericin is not dialyzable.

Although simultaneous infusion of mannitol (12.5–25 gm) with amphotericin B has been advocated to mitigate nephrotoxicity, its clinical efficacy has not been proved. This combination would be hazardous in renal insufficiency (see mannitol).

2.3.2. 5-Fluorocytosine

5-fluorocytosine, an oral synthetic antimycotic agent for cryptococcosis, candidiasis and aspergillosis, is predominantly excreted by the kidneys and a substantial amount is dialyzable. Therapeutic serum levels of the drug are 10–90 μg/ml and a blood specimen should be taken 2 hours after drug administration or at the end of hemodialysis. Recommended doses of the drug are summarized in Table 6.

Table 6. Recommended doses for 5-fluorocytosine

Ccr (ml/min)	Oral Dose (mg/kg)	Interval (hour)
>40	25–50	6
40–20	25–50	12
20–10	25–50	24
<10	25	24
Hemodialysis	25–50	24

2.4. Antituberculosis Drugs

2.4.1. Isoniazid

Usual doses (300–400 mg/day) can be given to patients with mild to moderate renal failure or to dialysis patients. However, patients with severe renal failure, not undergoing dialysis and who are slow acetylators, should receive smaller doses (200 to 300 mg/day). Pyridoxin (50 mg/day) should be given along with isoniazid to prevent drug induced neuropathy superimposed on uremic neuropathy.

2.4.2. Rifampin

No dose modification is needed for the treatment either of patients with renal failure or those undergoing dialysis.

2.4.3. Ethambutol

Approximately 80% of ingested ethambutol is removed by the kidney within 24 hours and a substantial amount of ethambutol is dialyzable.

Recommended daily doses of ethambutol are: 25 to 15 mg/kg for those with creatinine clerance of 50 to 25 mg/min, 15 to 7.5 mg/kg for those with creatinine clearance of 25 to 10 ml/min and 5 mg/kg for those with creatinine clearance less than 10 ml/min and those undergoing dialysis. The therapeutic serum levels of ethambutol range from 2 to 5 μg/ml.

2.5. Antimalarial Drugs

2.5.1. Chloroquine

No dose adjustment is required for short-term daily therapy (*e.g.*, malaria) or for intermittent therapy (*e.g.*, malaria prophylaxis). However, prolonged therapy for other indications (*e.g.*, amebic liver abscess) does require reduced dosages; 150 mg/day for those who have creatinine clearance between 60 and 30 ml/min and 100 mg/day when clearance is less than 30 ml/min. These dosages should be halved after two weeks of therapy.

2.5.2. Quinine

Usual doses can be used for intermittent therapy (*e.g.*, nocturnal cramps), but the dose should be reduced for prolonged therapy (*e.g.*, malaria) in patients with severe renal failure to approximately 600 mg/day.

2.6. Diuretics

Diuretics for the treatment of fluid retention and congestive heart failure are indicated only in those patients who still retain some kidney function. Response to diuretics decreases with decreasing kidney function, and higher doses or more potent agents are required. Control of fluid overload and congestive heart failure in dialysis patients must be accomplished by fluid restriction and dialysis.

Excessive use of diuretics in patients with impaired kidney function may produce dehydration, electrolyte imbalance, alkalosis and other metabolic disturbances, and exacerbate existing renal failure and uremic symptoms, or may produce systemic toxic effects of the drug due to progressive accumulations (*e.g.*, ototoxicity).

2.6.1. Furosemide and ethacrynic acid

These drugs are two of the most potent diuretics available and are often effective in patients with creatinine clearance as low as 5 ml/min.

The dose of these diuretics varies widely. Usually, the lower the kidney function, the larger the dose (up to 1,000 mg of furosemide/day) required. Excessive use of these diuretics can produce hypovolemia, hyperuricemia, acid-base and electrolyte imbalance and further deterioration of renal function. Administration of a large dose of ethacrynic acid is not recommended for patients with renal failure. It is not more potent than furosemide, but it is more ototoxic, a complication that is not always reversible.

2.6.2. Mannitol

Mannitol is an osmotic diuretic, and it is less effective and more hazardous in the treatment of established acute or chronic renal failure than the loop diuretics. Since mannitol is not metabolized but is eliminated exclusively by the kidney, it may remain in the intravascular space in patients with renal failure for a long time. Repeated doses can precipitate acute pulmonary edema or produce hyponatremia, acidosis and diffuse degenerative brain disorder.

In instances of impending acute renal failure, an initial dose of 100 ml (25 gm) can be given. Unless the urine volume increases with this dose, larger doses will probably be unsuccessful. For those patients who have fluid overload and oligo-anuria secondary to established organic kdieny disease, mannitol is contraindicated.

2.6.3. Mercurial Diuretics

Usual doses of mercurial diuretics can be used if the creatinine clearance is greater than 30 ml/min. However, it is nephrotoxic (acute renal failure, membraneous nephropathy with nephrotic syndrome) and should not be used in patients with fluid overload secondary to organic kidney disease.

2.6.4. Thiazide Diuretics

Efficacy of thiazide diuretics is diminished when creatinine clearance is less than 20 ml/min and adverse effects are more common (dehydration, hyponatremia, alkalosis, hyperglycemia, hyperuricemia, hypercalcemia, pre-renal azotemia and further deterioration of renal function).

Thiazide diuretics rarely are associated with acute tubulo-interstitial nephritis and may potentiate nephrotoxic effects of other drugs.

2.6.5. Spironolactone and Triamterene

Usual doses of these diuretics can be given to patients with mild to moderate renal failure. However, these drugs should not be used in

patients with moderate to advanced renal failure. Not only are they ineffective, but they may cause hyperkalemia. Potassium supplements should not be used with these diuretics, regardless of the degree of renal function, since this combination can rapidly result in fatal hyperkalemia.

2.7. Antihypertensive Drugs

The kidney is important in controlling normal blood pressure, and disturbances in the regulation of sodium and extracellular fluid volume or secretion of vaso-regulatory hormones can lead to hypertension. Renal hypertension not only increases cardiovascular complications but also accelerates deterioration of renal function.

The goals of antihypertensive therapy are to reduce blood pressure and to maintain diastolic pressure below 100 mm Hg without adverse side effects or postural hypotension. Renal function may deteriorate after aggressive antihypertensive therapy, but as the blood pressure stabilizes at a lower level, renal function may eventually improve.

Some antihypertensive drugs (*e.g.*, guanethidine) may decrease renal blood flow and glomerular filtration rate and should be avoided. Still, other drugs (*e.g.*, clonidine, diazoxide, minoxidil, prazocin) tend to increase renal sodium and water reabsorption and should be used with diuretics which will prevent fluid retention and potentiate antihypertensive effects of the other drugs.

Most antihypertensive drugs are eliminated by non-renal mechanisms and proper doses of the drugs are determined by titration of dose against blood pressure response. Thus, in general, the total daily doses and interval between doses are affected little by either renal failure or dialysis. However, short-acting antihypertensive drugs are usually withheld 4 to 6 hours before dialysis to avoid a hypotensive response during hemodialysis.

2.7.1. Diazoxide

The usual dose is 3 to 5 mg/kg (150 to 300 mg bolus), intravenously, regardless of the degree of renal function or dialysis treatment.

It can be given several times a day and can be repeated intermittently over several days if needed to maintain adequate blood pressure control. Since uremic subjects and patients receiving other potent antihypertensive drugs tend to be more sensitive to diazoxide, it would be safer to start with smaller doses (100 to 200 mg). Simultaneous use of furosemide will prevent sodium and fluid retention.

2.7.2. Guanethidine

No dose modification is required in the presence of renal failure or dialysis treatment.

The administration of guanethidine may reduce cardiac output, renal blood flow and glomerular filtration rate. It is recommended to withhold the drug one to two weeks prior to elective surgery to avoid the possibility of hypotension and cardiac arrhythmia during general anesthesia.

2.7.3. Hydralazine

Therapeutic doses vary greatly but no dose adjustment is required for patients with renal failure or those undergoing dialysis.

Prolonged use of a large amount (over 300 mg/day) of hydralazine may produce a systemic lupus erythematosus-like syndrome in some patients. The syndrome rarely involves the central nervous system and kidney, and is usually reversible by withholding the drug. The administration of hydralazine in patients with systemic lupus erythematosus, however, does not seem to adversely affect the natural course of the disease.

2.7.4. Clonidine, Methyldopa and Prazocin

None of these antihypertensive agents requires dose modification for either treatment of patients with renal failure or those undergoing dialysis.

The dose of clonidine should be slowly tapered prior to elective surgery. In cases of emergency operation, clonidine should be resumed as soon as possible after the operation to avoid rebound hypertension.

2.7.5. Propranolol

Therapeutic doses of propranolol vary widely depending on the indication for the drug (from 40 to 300 mg/day for angina pectoris, ventricular arrythmia, or hypertrophic subaortic stenosis, and from 80 to 1,000 mg/day for hypertension) regardless of the degree of renal function.

It is generally recommended that the dose of propranolol be tapered and discontinued by 48 hours before elective surgery to avoid cardiocirculatory complications during general anesthesia. However, in cases of emergency operation, maintenance of a smaller dose (from 80 to 120 mg/day) is safer than abrupt withdrawl.

2.7.6. Sodium Nitroprusside

The dose of sodium nitroprusside depends on the patient's blood pressure response to the drug, or the achievement of blood pressure levels

necessary to reduce afterload in treating cardiogenic shock. The usual rates of infusion vary from 0.5 to 8 mcg/kg/min (average is 3 mcg/kg/min). Nitroprusside is metabolized to cyanide which is then metabolized to thiocyanate. Thiocyanate is eliminated exclusively by the kidneys, with a half-life of one week, when renal function is normal. This drug should be used with caution in patients with renal failure, and blood levels of thiocyanate should be monitored when it is used longer than a week. Toxic symptoms of thiocyanate or cyanide (nausea, vomiting, fatigue, disorientation, myoclonus, convulsions, psychosis) begin to appear at plasma levels above 10 or 15 mg/dl. Plasma levels of thiocyanate can be reduced rapidly by hemodialysis.

2.7.7. Minoxidil

Minoxidil's no longer investigated antihypertensive effect depends primarily on its direct arteriolar vasodilatory action. Since minoxidil reflexly accelerates the heart rate and increases renal sodium reabsorption, use of the drug usually requires simultaneous administration of propranolol and diuretics to overcome these adverse effects. Although total body clearance of the drug is independent of renal function, patients undergoing dialysis treatment tend to require lower maintenance doses (5 to 10 mg, every 8 to 12 hours).

2.8. Drugs Acting on the Heart

Congestive heart failure and pulmonary edema are among the most common causes of death in patients with advanced acute and chronic renal failure. There may be multiple causes for circulatory failure in these patients such as hypertension, arteriosclerosis, anemia, A-V fistula and uremic pericarditis and cardiomyopathy; but the final catalytic event is often sodium and fluid overload rather than primary myocardial failure.

Treatment of congestive heart failure in these patients should be directed toward decreasing extracellular fluid volume as rapidly as possible. This can be done by a variety of methods depending on the degree of renal function (diuretics, dialysis, hemodiafiltration). Inotropic agents and drugs that reduce pre and/or afterload should be considered if there is intrinsic myocardial disease or if heart failure is refractory to fluid control alone.

2.8.1. Digoxin and Digitoxin

Digoxin is predominantly (80 to 90 percent) and digitoxin is partially (10 to 15 percent) eliminated in the urine. The half-life of digoxin in normal

volunteers is 1.5 days and this increases to 4.5 days in the anephric patient. In contrast to digoxin, digitoxin's half-life and serum concentration are not greatly affected by impaired renal function. Thus, the maintenance doses of the digoxin should be modified as renal function deteriorates. The size of the initial loading dose does not depend upon renal function but slightly lower digitalizing doses (0.8 to 1.2 mg digoxin) are usually required for patients with advanced renal failure, including those undergoing dialysis.

When these drugs are indicated for the control of supraventricular tachy-arrhythmia, proper doses of the drugs can be determined by titration of the dose against cardiac rate and its response to therapy. When the drugs are indicated for their positive inotropic effects, however, there is no clear and safe end-point that can be used for dose adjustment. To guide estimation of maintenance doses of digitalis glycosides in relation to the degree of renal function, several formulas and nomograms have been proposed. However, few of these are practical or adequate for general use (Table 7). As a simplified schedule for patients with severe renal failure, a maintenance dose of 0.125 mg of digoxin or 0.1 mg of digitoxin, five times per week, is usually adequate. Periodic monitoring of serum drug levels will aid in making further dose adjustments. Therapeutic serum levels of digoxin range from 1.0 to 2.0 ng/ml (over 3.3 ng/ml is potentially toxic) and that of digitoxin range from 15 to 30 ng/ml (over 40 ng/ml is potentially toxic).

Table 7. Recommended doses for digoxin

C Cr (ml/min)	Daily Dose (mg)
0	0.125
25	0.20
50	0.25
75	0.30
100	0.35

Since digitalis glycosides are highly bound to tissue, less than 3% of the body store is lost during a course of either hemodialysis or peritoneal dialysis, and no extra dose of digitalis is required after dialysis. However, a rapid decrease in the plasma potassium level during dialysis increases the effects of digitalis on the heart and may lead to serious cardiac arrhythmia. To avoid this complication, the addition of 3.0 to 3.5 mEq/l of potassium in the dialysate is recommended.

2.8.2. Lidocaine

The half-life and duration of action of lidocaine in uremic patients is not different from normal subjects. When lidocaine is indicated for the treatment of cardiac arrhythmia, the usual doses of lidocaine can be given to patients with renal failure, including those undergoing dialysis, either as an intravenous drip or as an intermittent bolus. Therapeutic serum concentrations range from 1.5 to 5 μg/ml.

Intravenous infusion of lidocaine (2.0 mg/kg in 100–200 ml of saline) can sometimes relieve uremic pruritus. Its effect may be dramatic, and its antipruritic effect may last for many hours.

2.8.3. Procainamide

Both procainamide and its active metabolite, N-acetyl procainamide, accumulate in patients with renal failure. Recommended doses of procainamide at varying degrees of renal function are shown in Table 8. Therapeutic serum levels of procainamide range from 4 to 6 μg/ml assuming a normal procainamide-acetylprocainamide ratio. In uremia, the ratio is abnormal and acetylprocainamide should be measured as well.

Table 8. Recommended doses for procainamide

Ccr (ml/min)	Oral Dose (250–500 mg)
100–50	3–4 hr
50–25	4–6 hr
25–10	6–8 hr
<10	8–12 hr
After hemodialysis	250–500 mg extra dose

2.8.4. Quinidine

Dose modification is not required either for the treatment of patients with renal failure or for those undergoing dialysis (200 to 300 mg, every 6 hours, orally).

Therapeutic serum levels of quinidine range from 2.0 to 8.0 μg/ml.

2.9. Antiarthritic Drugs

2.9.1. Phenylbutazone

The metabolite of phenylbutazone, oxyphenylbutazone, tends to accumulate in both uremic and nonuremic patients when given over long

periods of time. There is a high incidence of adverse reactions to accumulated metabolites in uremic patients.

It is best to avoid this drug except in patients with mild renal failure who can receive the usual doses of phenylbutazone. If phenylbutazone is absolutely indicated, a schedule of gradually decreasing amounts can be given as follows: the first five days, 100 mg given orally every 6 hours; the second five days, 100 mg given orally every 12 hours; and maintenance doses, 100 to 200 mg/day.

Phenylbutazone is nephrotoxic, causing such conditions as acute renal failure, acute cortical necrosis, and acute tubulo-interstitial nephritis.

2.9.2. Indomethacin

No dose modification is required, although its effects on the gastrointestinal tract may aggravate uremic symptoms (nausea and vomiting) and gastric bleeding.

2.9.3. Colchicine

Symptomatic gout is rare in patients with hyperuricemia secondary to renal failure. It can occur, however, as a primary disease or as an adverse effect of drugs in those receiving diuretics (thiazides, furosemide). Usual doses of colchicine can be given to patients with renal failure. However, care must be taken to avoid diarrhea and dehydration, a common side effect of colchicine, which might exacerbate pre-existing renal insufficiency.

2.9.4. Probenecid

Most patients with a creatinine clearance below 30 ml/min respond poorly to uricosuric drugs. If they do respond, the risk of nephrolithiasis and urolithiasis may be increased. This drug should not be used in patients with renal failure.

2.9.5. Allopurinol

Allopurinol is an ideal drug for lowering serum uric acid in patients with impaired renal function. It is metabolized to oxypurinol, which is also active and slowly removed by the kidney. Allopurinol interferes with the metabolic degradation of azathioprine and the combined use of these two drugs at usual dosage levels, can cause severe myelosuppression. Patients with a creatinine clearance less than 10 ml/min or undergoing dialysis, should receive slightly reduced doses of allopurinol (100 mg every 12 hours). Patients receiving allopurinol should receive substantially reduced doses of azathioprine or 6-mercaptopurine if these two latter drugs are to be administered.

2.10. Analgesic Drugs

2.10.1. Salicylates and Phenacetin

Salicylates at ordinary doses and phenacetin are predominantly eliminated by non-renal mechanisms. They should not be used in high doses in patients with impaired renal function. Both drugs can impair renal function in short-term use and produce analgesic nephropathy in very long-term use. Salicylates may aggravate gastric symptoms, platelet dysfunction and bleeding tendencies in uremic patients.

2.10.2. Phenazopyridine

Phenazopyridine (Pyridium®) is excreted in the urine where it exerts a topical analgesic effect of the mucosa of the urinary tract and relieves pain, burning, urgency and frequency. Since its effects depend upon urinary excretion, the drug is not effective in the presence of impaired renal function. Excessive doses of phenazopyridine can produce acute renal failure with yellowish discoloration of the skin.

2.10.3. Other Analgesic Drugs

The following drugs are metabolized primarily by the liver and can generally be used without dose modification in patients with impaired renal function and in those undergoing dialysis; acetaminophen, codeine, meperidine, methadone, morphine, pentazocine and propoxyphene. A metabolite of meperidine, normeperidine, however, is primarily excreted by the kidney and it has an excitatory effect on the central nervous system. Thus, it is not recommended to be used at high doses or for prolonged periods in uremic patients.

2.11. Anticonvulsant Drugs

A seizure disorder is a common complication of uremia. Clinical manifestations range from mild twitching or asterexis to grand-mal seizures, with post-ictal phenomena. There are multiple causes for uremic seizures, most of which are related to combined metabolic derangements such as hyponatremia, hypocalcemia, or hypertension. Despite the frequent occurrence of hypocalcemia, hypocalcemic tetany is uncommon in uremia.

During hemodialysis, rapid changes in blood pressure, fluid volume, electrolytes and other chemical components of uremic patients may cause convulsions (disequilibrium syndrome).

2.11.1. Phenytoin (diphenylhydantoin)

Patients with uremia have a lower plasma concentration (but disproportionately high free drug concentrations), decreased protein binding and a shorter half-life of phenytoin than that of normal subjects. Uremic patients do respond to phenytoin at relatively low plasma concentrations. In general, uremic patients require the usual loading dose, followed by the usual or higher maintenance doses of the drug (300 to 500 mg/day) than others. No dose modification is required for dialysis treatment.

Therapeutic serum levels are from 7 to 15 μg/ml. More than 20 μg/ml is associated with toxic symptoms such as nystagmus (20 to 30 μg/ml), ataxia (30 to 40 μg/ml) and changes in higher integrative brain function (over 40 μg/ml). Lower levels are associated with these changes in uremia.

2.11.2. Amobarbital, Diazepam and Phenobarbital

No dose modification is required for either patients with renal failure or those undergoing hemodialysis for short-term use of these drugs.

2.12. Immunosuppressive Drugs

Uremic patients' immune function is defective in both cellular and humoral mechanisms. However, many patients with primary or secondary renal diseases receive immunosuppressive drugs for nephrotic syndrome, vasculitis, kidney transplant, or other pathologic immune processes. The metabolism and excretion of most of these drugs in uremic patients is not substantially different from that of nonuremic patients. Thus, in general, doses are determined by the specific indication and the activity of the diseases, rather than by the degree of renal function.

2.12.1. Adrenocorticosteroids

For preparations of both natural and synthetic adrenocorticosteroids, doses depend on the indication for the drug, regardless of the degree of renal function or dialysis.

2.12.2. Azathioprine

Azathioprine is primarily removed from the body by metabolic degradation, but small amounts of the drug and its active metabolite, mercaptopurine, do appear unchanged in the urine. Furthermore, uremic patients tend to have a higher incidence of leucopenia from azathio-

prine. However, the dose need not be adjusted for patients with impaired renal function or those undergoing dialysis.

Since allopurinol interferes with normal degradation of azathioprine, patients requiring both drugs should receive approximately one third of the usual maintenance doses of azathioprine.

2.12.3. Cyclophosphamide

Although cyclophosphamide is predominantly removed by nonrenal mechanisms, the excretion rate of active alkylating metabolites may depend upon renal function. When a large dose of cyclophosphamide is required as a cytotoxic drug, the dose should be reduced for patients with impaired renal function. When a relatively small dose (1 to 5 mg/kg) of cyclophosphamide is needed as an immunosuppressive drug, reduction of the dose is unnecessary.

Although cyclophosphamide has no direct nephrotoxic effect, prolonged use of this drug may produce oligospermia, sterility, hemorrhagic cystitis and transitional cell carcinoma in the urinary bladder.

2.13. Hypoglycemic Drugs

Many uremic patients exhibit glucose intolerance to exogenous carbohydrate loads that results from multiple defects in carbohydrate metabolism, including abnormal sensitivity of pancreatic beta-cells to plasma glucose and impaired tissue utilization of glucose. On the other hand, exogenous insulin may produce a prolonged hypoglycemic effect due to decreased degradation of insulin by the diseased kidney, and low carbohydrate intake and storage. Mild glycosuria, without hyperglycemia, may occur in patients with impaired renal function because of defective tubular reabsorption (renal glucosuria). As renal failure progresses, however, the renal threshold for plasma glucose also increases and little or no glucose may appear in the urine even when blood glucose levels are substantially elevated. Thus, for the treatment of diabetic patients with renal failure, doses of any hypoglycemic drugs should be guided by blood sugar levels.

2.13.1. Insulin

About 30 to 40 percent of the insulin that reaches systemic circulation is normally degraded by the kidney. The half-life of insulin increases and the insulin requirement gradually decreases as renal failure progresses in diabetic patients. Therapy should be started in these patients

with small doses of short-acting insulin given at 8 to 24 hour intervals, and a long-acting insulin gradually introduced.

When glucose and insulin are given for hyperkalemia in uremic patients, whether diabetic or not, the ratio of insulin to dextrose should be 1 unit of regular insulin to 5 to 10 gm of dextrose in order to avoid delayed hypoglycemic responses.

2.13.2. Oral Hypoglycemic Drugs

Oral hypoglycemic drugs (chlorpropramide, tolbutamide) should be avoided in diabetic patients with renal failure because their use is associated with a high incidence of adverse reactions and insulin is a more effective treatment of the diabetes.

2.14. Anticoagulants

Both heparin and warfarin are eliminated by nonrenal mechanisms and uremic patients have the same sensitivity to these drugs as do normal persons. Anticoagulant effects of these drugs are, however, superimposed on the uremic bleeding diathesis. However, the usual doses of these drugs can be used under close supervision, with the appropriate coagulation studies. Heparin is neither dialyzable nor absorbable through the peritoneal membrane.

3. DIALYSIS OF DRUGS AND POISONS

Dialysis treatment is an effective procedure for treatment of acute and chronic intoxication with various drugs and chemicals. For dialysis to be effective, the suspected chemical must be distributed in plasma or other body fluid compartments that are in equilibrium with plasma and it should have a time-dose-toxic relationship.

Schreiner et al. suggest the following guidelines for deciding whether a patient poisoned with a dialyzable drug should undergo dialysis:

1) Severe clinical intoxication with abnormal vital signs (hypotension, hypothermia, apnea) or progressive clinical deterioration or prolonged coma with secondary complications (aspiration pneumonia, sepsis).

2) Ingestion and probable absorption of a potentially lethal dose, or a blood level that is in the potentially lethal range.

3) The presence of a significant quantity of a circulating chemical which is metabolized to a more toxic substance (methanol to formaldehyde and ethylene glycol to oxalic acid).

Table 9. Dialyzable drugs, poisons, and chemicals.

Barbiturates (H*, P)
- Amobarbital
- Butabarbital
- Cyclobarbital
- Pentobarbital
- Phenobarbital
- Secobarbital

Anticonvulsants
- Diphenylhydantoin (H*, P)
- Primidone (H)

Hypnotics, sedatives and tranquilizers
- Chloral hydrate (H*, P)
- Ethchlorvynol (H*, P)
- Ethinamate (H)
- Gallamine triethiodide (H*, P)
- Glutethimide (H*)
- Meprobamate (H*, P)
- Methaqualone (H*, P)
- Methypyrlon (H*, P)

Antidepressants
- Amitriptyline (P)
- Amphetamine (H, P*)
- Imipramine HCl (H, P)

Alcohols
- Ethanol (H, P)
- Ethylene glycol (H*, P)
- Isopropranol (H)
- Methanol (H*, P)

Analgesics
- Acetylsalicylate (H*, P*)
- Methylsalicylate (H*, P*)
- Paracetamol (H*)

Antibiotics and chemotherapeutics
- Ampicillin (H)
- Carbenicillin (H)
- Cephalexin (H)
- Cephaloridin (H)
- Cephalothin (H)
- Cycloserine (P)

Antibiotics and chemotherapeutics *(cont.)*
- Ethambutol (H, P)
- Gentamicin (H*, P)
- Isoniazid (H, P)
- Kanamycin (H*)
- Nitrofurantoin (H)
- Neomycin (H*)
- Penicillin (H)
- Streptomycin (H*)
- Sulfonamide (H)
- Tetracycline (H)

Metals
- Aluminum (H)
- Arsenic (H, P)
- Calcium (H*, P)
- Iron (H)
- Lead (P)
- Lithium (H*, P)
- Magnesium (H)
- Potassium (H*, P*)
- Sodium (H*, P*)
- Strontium (H)
- Thallium (H)

Halide
- Bromide (H*, P)

Cytotoxic drugs
- Azathioprine (H)
- Cyclophosphamide (H)
- 5-Fluorouracil (H, P)
- Methotrexate (H)

Miscellaneous
- Boric acid (P)
- Camphor (H)
- Chromates (H)
- Mushrooms (amanita phalloides) (H*)
- Quinine

Endogenous intoxications
- Hyperuricemia (H*, P*)
- Lactic acidosis (H*, P)

* Effectively removable by dialysis.

H: dialyzable by hemodialysis.

P: dialyzable by peritoneal dialysis.

4) The presence of an underlying disease which impairs excretion or degradation of the drug (renal failure or hepatic dysfunction).

In addition to dialysis, patients should receive all available supportive measures such as coma care, air way care, forced diuresis, manipulation of blood or urinary pH to increase urinary excretion rate and prevention of infection.

A summary of dialyzable drugs and poisons is updated periodically and published in the Transactions of the American Society of Artificial Internal Organs. In addition, a Poison Manual is available (Poison Index. Dialysis and haemoperfusion in poisonings. Seyffart G., Bad Homburg, Munich, Fresenius Foundation, 1977). Some of the more common agents incriminated in self-inflicted or iatrogenic overdose are listed in Table 9, along with dialysis information. Local poison control centers can give current information about any toxic chemicals.

BACKGROUND READINGS

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APPENDICES

Appendix 1

Composition of Electrolyte and Colloid Solutions

Solutions	Electrolytes (mEq/l)*							
	Na^+	K^+	Ca^+	Mg^{++}	NH_4^+	Cl^-	lactate	bicarbonate
0.45% Saline	77					77		
0.85% Saline (isotonic)	145					145		
0.9% Saline	154					154		
3.0% Saline	513					513		
5.0% Saline	856					856		
1/6 molar sodium lactate, 1.9% (isotonic)	167						167	
1/6 molar ammonium chloride, 0.9% (isotonic)					168	168		
Ammonium chloride, 2.1% (hypertonic)					400	400		
Sodium bicarbonate, 1.5% (isotonic)	178							178
Ringer's solution	147	4	4			155		
Lactated Ringer's solution (Hartmann's modified)	130	4	3			110		27
Plasma	152	4				100		
Salt poor albumin (concentrated)	64					8		
Dextran in isotonic saline	144					144		

* NaCl:
1 gm = 17 mEq
$NaHCo_3$:
1 gm = 12 mEq
Na lactate:
1 gm = 9 mEq
KCl:
1 gm = 14 mEq
K acetate:
1 gm = 10 mEq
K citrate:
1 gm = 8.3 mEq
$CaCl_2$:
1 gm = 20 mEq (272 mg of elementary Ca)
Ca gluconate:
1 gm = 5 mEq (90 mg of elementary Ca)
$MgSO_4$:
1 gm = 8.3 mEq

Appendix 2

Normal Arterial Blood Pressure*

Age	Systolic				Diastolic				Sources
	Men		Women		Men		Women		
	Mean	*s*	Mean	*s*	Mean	*s*	Mean	*s*	
Newborn	69	6			38				*1*
1 day	70	5							*1*
3 days	72	6							*1*
9 days	73	6							*1*
3 weeks	77	5							*1*
3 months	86	5							*1*
6–12 months	89	14.5	93	9.1	60	10.0	62	9.3	*2*
1 year	96	15.2	95	11.9	66	12.3	65	15.0	*2*
2 years	99	12.4	92	12.2	64	12.3	60	11.7	*2*
3 years	100	12.4	100	11.2	67	11.7	64	8.3	*2*
4 years	99	10.1	99	10.6	65	5.1	66	9.8	*2*
5 years	92	6.0	92	6.5	62	7.5	62	6.5	*3*
6 years	94	6.5	94	7.0	64	7.5	64	7.0	*3*
7 years	97	6.5	97	7.0	65	7.5	66	7.5	*3*
8 years	100	6.5	100	7.0	67	7.0	68	7.0	*3*
9 years	101	6.5	101	7.0	68	6.5	69	7.0	*3*
10 years	103	6.5	103	7.0	69	6.0	70	6.5	*3*
11 years	104	6.5	104	7.0	70	5.5	71	6.5	*3*
12 years	106	6.5	106	7.0	71	5.0	72	7.0	*3*
13 years	108	6.5	108	6.5	72	5.0	73	7.5	*3*
14 years	110	6.5	110	6.5	73	5.0	74	8.5	*3*
15 years	112	7.0	112	7.0	75	5.5	76	9.5	*3*
16 years	118	12.2	116	12.1	73	10.3	72	9.6	*4*
17 years	121	12.9	116	11.5	74	9.4	72	9.2	*4*
18 years	120	12.0	116	11.4	74	10.0	72	8.6	*4*
19 years	122	15.0	115	11.9	75	10.3	71	8.9	*4*
20–24 years	123	13.8	116	11.8	76	9.9	72	9.7	*4*
25–29 years	125	12.6	117	11.4	78	9.0	74	9.1	*4*
30-34 years	126	13.6	120	14.0	79	9.7	75	10.8	*4*
35–39 years	127	14.2	124	13.9	80	10.4	78	10.0	*4*
40–44 years	129	15.1	127	17.1	81	9.5	80	10.6	*4*
45-49 years	130	16.9	131	19.5	82	10.8	82	11.6	*4*
50–54 years	135	19.2	137	21.3	83	11.3	84	12.4	*4*
55–59 years	138	18.8	139	21.4	84	11.4	84	11.7	*4*
60–64 years	142	21.1	144	22.3	85	12.4	85	13.0	*4*
65–69 years	143	26.0	154	29.0	83	9.9	85	13.8	*5*
70–74 years	145	26.3	159	25.8	82	15.3	85	15.3	*5*
75–79 years	146	21.6	158	26.3	81	12.9	84	13.1	*5*
80–84 years	145	25.6	157	28.0	82	9.9	83	13.1	*5*
85–89 years	145	24.2	154	27.9	79	14.9	82	17.3	*5*
90–94 years	145	23.4	150	23.6	78	12.1	79	12.1	*5*
95–106 years	145	27.5	149	23.5	78	12.7	81	12.5	*5*

Appendix 2 key

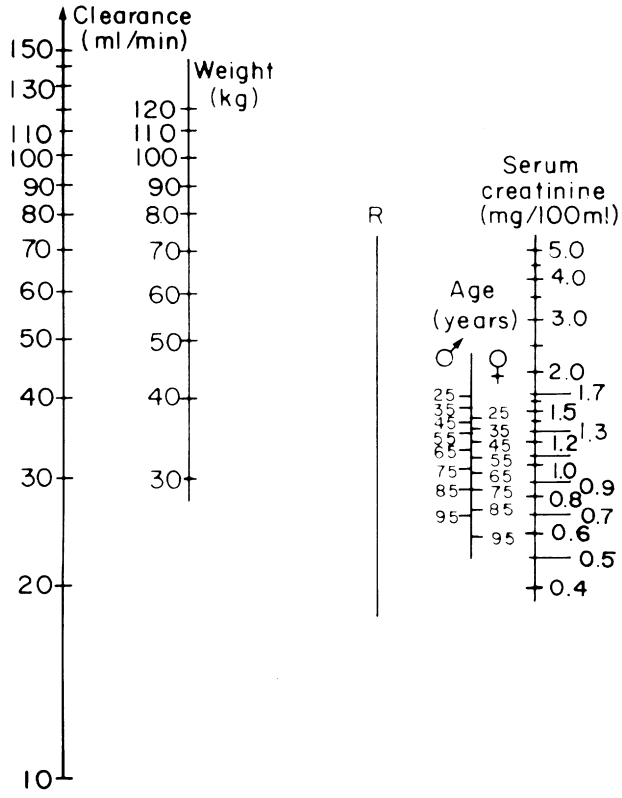
1) (Systolic) Holland and Young, *Brit. med. J.*, 2, 1331 (1956); (diastolic) Dexter et al., *Preeclamptic and Eclamptic Toxemia of Pregnancy,* Boston, 1941, quoted by Smith, C.A., *The Physiology of the Newborn Infant,* Oxford, 1959.
2) Allen-Williams, G.M., *Arch Dis Childb.*, 20, 125 (1945). 3) Faber and James, *Amer. J. Dis. Child.*, 22, 7 (1921). 4) Master et al., *Normal blood Pressure and Hypertension,* Philadelphia, 1952. 5) Master et al., *Ann, intern. Med.*, 48, 284 (1958).

The 'clinical normal range' of systolic and diastolic blood pressure in adults is the mean $\pm 1.282\,s$ mmHg; the lower limit of hypertension is the mean $\pm 2\,s$ mmHg (Master et al., Normal blood Pressure and Hypertension, Philadelphia, 1952).

* Reproduced from Documenta Geigy Scientific Tables (sixth edition), with kind permission of Ciba-Geigy, Basle.

Appendix 3

Nomogram for Estimation of Endogenous Creatinine Clearance *

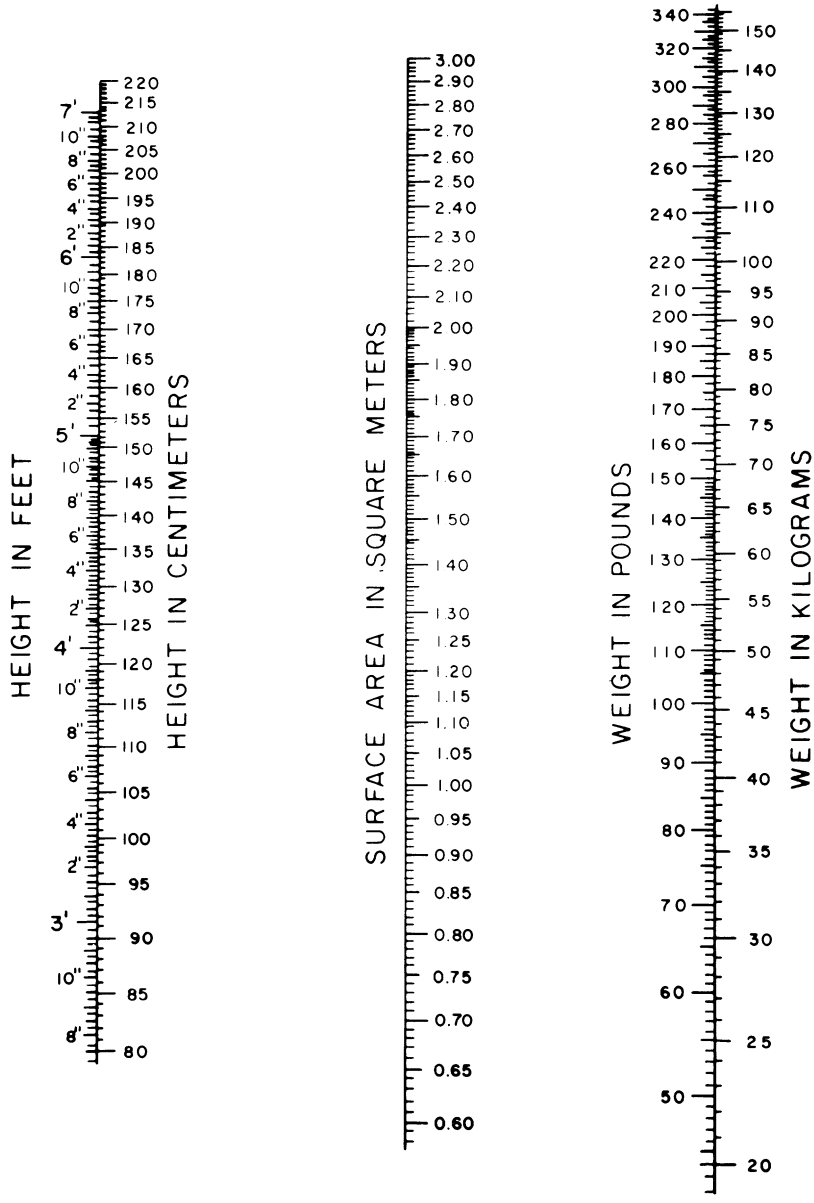


With a ruler, join weight to age. Keep ruler at crossing-point of line marked R. Then move the right-hand side of the ruler to the appropriate serum-creatinine value and read the patient's clearance from the left side of the nomogram.

* Reproduced from Lancet 1:1134, 1971 (K. Siersback-Nielsen, J.M. Hansen, J. Kampmann, M. Kristensen) with kind permission.

Appendix 4

Nomogram for Calculating the Body Surface Area of Adults*



* Reproduced from Eugène F. Dubois, Basal Metabolism in Health and Disease. Philadelphia: Lea & Febiger, 1936.

Appendix 5

Conversion tables: Temperature

Celsius to Fahrenheit (1 °C = 1.8 °F)		Fahrenheit to Celsius (1 °F = 0.54 °C)	
C°	F°	F°	C°
0	32.0	0	−17.78
1.0	33.8	10	−12.22
5.0	41.0	20	− 6.67
10.0	50.0	30	− 1.11
15.0	59.0	40	4.44
20.0	68.0	50	10.0
25.0	77.0	60	15.56
30.0	86.0	70	21.11
35.0	95.0	80	26.67
35.5	95.9	85	29.44
36.0	96.8	90	32.22
36.5	97.7	95	35.0
37.0	98.6	96	35.56
37.5	99.5	97	36.11
38.0	100.4	98	36.67
38.5	101.3	99	37.22
39.0	102.2	100	37.78
39.5	103.1	101	38.33
40.0	104.0	102	38.89
40.5	104.9	103	39.44
41.0	105.8	104	40.0
41.5	106.7	105	40.56
42.0	107.6	106	41.11
45.0	113.0	107	41.67
50.0	122.0	120	48.89
60.0	140.0	140	60.0
70.0	158.0	160	71.11
80.0	176.0	180	82.22
90.0	194.0	200	93.33
100.0	212.0	212	100

Appendix 5 (continued)

Conversion Tables: Weight

Pounds to Kilograms
(1 kg = 2.2 lb.; 1 lb. = 0.4536 kg)

lb.	kilo.	lb.	kilo.
5	2.3	135	61.2
10	4.5	140	63.5
15	6.8	145	65.8
20	9.1	150	68.0
25	11.3	155	70.3
30	13.6	160	72.6
35	15.9	165	74.8
40	18.1	170	77.1
45	20.4	175	79.4
50	22.7	180	81.6
55	25.0	185	83.9
60	27.2	190	86.2
65	29.5	195	88.5
70	31.7	200	90.7
75	34.0	205	93.0
80	36.3	210	95.3
85	38.6	215	97.5
90	40.8	220	99.8
95	43.1		
100	45.4		
105	47.6		
110	49.9		
115	52.2		
120	54.4		
125	56.7		
130	58.9		

Appendix 5 (continued)

Conversion Tables: Height

Feet and Inches to Centimeters
(1 cm = 0.39 in.; 1 in. = 2.54 cm)

ft.	in.	cm	ft.	in.	cm
2	0	61.0	4	2	127.0
2	1	63.5	4	3	129.5
2	2	66.0	4	4	132.0
2	3	68.6	4	5	134.6
2	4	71.1	4	6	137.1
2	5	73.6	4	7	139.6
2	6	76.1	4	8	142.2
2	7	78.7	4	9	144.7
2	8	81.2	4	10	147.3
2	9	83.8	4	11	149.8
2	10	86.3	5	0	152.4
2	11	88.8	5	1	154.9
3	0	91.4	5	2	157.5
3	1	93.9	5	3	160.0
3	2	96.4	5	4	162.6
3	3	99.0	5	5	165.1
3	4	101.6	5	6	167.6
3	5	104.1	5	7	170.2
3	6	106.6	5	8	172.7
3	7	109.2	5	9	175.3
3	8	111.7	5	10	177.8
3	9	114.2	5	11	180.3
3	10	116.8	6	0	182.9
3	11	119.3	6	1	185.4
4	0	121.9	6	2	188.0
4	1	124.4	6	3	190.5

Appendix 6

WHO nomenclature for factors of the HLA system (September 1977)

Locus A	Locus B	Locus C	Locus D	Locus DR
A1	BW4	CW1	DW1	DRW1
A2	B5	CW2	DW2	DRW2
A3	B7	CW3	DW3	DRW3
A9	B8	CW4	DW4	DRW4
A10	B12	CW5	DW5	DRW5
A11	B13	CW6	DW6	DRW6
A25	B14		DW7	DRW7
A26	B15		DW8	
A28	B17		DW9	
A29	B18		DW10	
AW19	B27		DW11	
AW23	B37			
AW24	B40			
AW30	BW16			
AW31	BW21			
AW32	BW22			
AW33	BW35			
AW34	BW38			
AW36	BW39			
AW43	BW41			
	BW42			
	BW44			
	BW45			
	BW46			
	BW47			
	BW48			
	BW49			
	BW50			
	BW51			
	BW52			
	BW53			
	BW54			

The designation 'W' before an Arabic numeral indicates that at a previous workshop, evidence pointed to the existence of such an antigen as a pure entity, but that further studies for confirmation were needed.

Appendix 7

Elements and Atomic Weights

Name	Symbol	Atomic number	Atomic weight	Valence
Aluminum	Al	13	26.97	3
Antimony (stibium)	Sb	51	121.76	3, 5
Arsenic	As	33	74.91	3, 5
Barium	Ba	56	137.36	2
Bismuth	Bi	83	209.00	3, 5
Bromine	Br	35	79.916	1
Calcium	Ca	20	40.08	2
Carbon	C	6	12.01	2, 4
Chlorine	Cl	17	35.457	1
Chromium	Cr	24	52.01	2, 3, 6
Cobalt	Co	27	58.94	2, 3
Copper	Cu	29	63.57	1, 2
Fluorine	F	9	19.00	1
Gold (aurum)	Au	79	197.2	1, 3
Helium (liquid)	He	2	4.003	0
Hydrogen (liquid)	H	1	1.008	1
Iodine	I	53	126.932	1
Iron (ferrum)	Fe	26	55.85	2, 3
Lead (plumbum)	Pb	82	207.21	2, 4
Lithium	Li	3	6.940	1
Magnesium	Mg	12	24.32	2
Manganese	Mn	25	54.93	2, 4, 6, 7
Mercury (hydrargyrum)	Hg	80	200.61	1, 2
Molybdenum	Mo	42	96.95	3, 4, 6
Nickel	Ni	28	58.69	2, 3
Nitrogen (liquid)	N	7	14.008	3, 5
Oxygen (liquid)	O	8	16.0000	2, 3, 4, 8
Palladium	Pd	46	106.7	2, 4
Phosphorus	P	15	31.02	3, 5
Platinum	Pt	78	195.23	2, 4
Potassium (kalium)	K	19	39.10	1
Radium	Rd or Ra	88	226.05	2
Radon (niton)	Rn	86	222.0	0
Selenium	Se	34	78.96	2, 4, 6
Silicon	Si	14	28.06	4
Silver (argentum)	Ag	47	107.880	1
Sodium (natrium)	Na	11	22.997	1
Strontium	Sr	38	87.63	2
Sulfur	S	16	32.06	2, 4, 6
Tin (stannum)	Sn	50	118.70	2, 4
Tungsten (wolframium)	W	74	184.0	6
Uranium	U	92	238.07	4, 6
Vanadium	V	23	50.95	3, 5
Zinc	Zn	40	91.22	4

Appendix 8

Normal Chemical Values of Body Fluids

Constituent	Old Units		S.I. Units**		Conversion factor multiply by	
	Normal range	Units	Normal range	Units	Old to new	New to old
Plasma acid phosphatase	1–3.5	KAU/100 ml	2–6	IU/l 37 °C	1.8	0.56
Plasma acid phosphatase (tartrate-labile)	0–0.8	KAU/100 ml	0–1.4	IU/l 37 °C	1.8	0.56
Plasma alanine transaminase (= GPT)	1–12	IU/l 25 °C	7–45	IU/l 37 °C	*	*
Plasma albumin	3.5–5.3	g/100 ml	35–53	g/l	10	0.1
Plasma alkaline phosphatase	3–14	KAU/100 ml	35–105	IU/l 37 °C	*	*
Plasma amylase	75–200	Somogyi/100 ml	70–300	IU/l 37 °C	*	*
Plasma aspartate transaminase (= GOT)	4–14	IU/l 25 °C	9–41	IU/l 37 °C	*	*
Plasma bicarbonate	20–30	mEq/l	20–30	mmol/l	1	1
Plasma bicarbonate (standard)	21–26	mEq/l	21–26	mmol/l	1	1
Plasma bilirubin (total)	0.2–1.0	mg/100 ml	3–17	μmol/l	17	0.058
Plasma bilirubin (conjugated)	Negative	—	< 6	μmol/l	*	*
Plasma calcium	8.8–10.5	mg/100 ml	2.20–2.62	mmol/l	0.25	4.0
Plasma chloride	99–108	mEq/l	99–108	mmol/l	1	1
Plasma cholesterol	110–380	mg/100 ml	2.9–9.9	mmol/l	0.026	38.7
Plasma cortisol (at 9 a.m.)	6–26	μg/100 ml	170–720	nmol/l	27.6	0.036
Plasma creatine kinase	3–40	IU/l 25 °C	10–120	IU/l 37 °C	*	*
Plasma creatinine	0.6–1.4	mg/100 ml	53–124	μmol/l	88	0.011
Plasma gamma-glutamyl transferase	4–28	IU/l 25 °C	7–50	IU/l 37 °C	*	*
Plasma globulin	1.6–3.3	g/100 ml	16–33	g/l	10	0.1
Blood glucose (fasting)	60–100	mg/100 ml	3.3–5.5	mmol/l	0.056	18

* Direct conversion not possible.
** S.I.: Système International d'Unités.
+ Normal range varies with duration of pregnancy.

continued on next page

Appendix 8 (continued)

Constituent	Old Units		S.I. Units**		Conversion factor multiply by	
	Normal range	Units	Normal range	Units	Old to new	New to old
Serum hydroxybutyrate dehydrogenase	55–140	IU/l 25 °C	55–140	IU/l 25 °C	1	1
Serum immunoglobulin-A	90–450	mg/100 ml	0.9–4.5	g/l	0.01	100
Serum immunoglobulin-G	800–1800	mg/100 ml	8.0–18.0	g/l	0.01	100
Serum immunoglobulin-M	60–280	mg/100 ml	0.6–2.8	g/l	0.01	100
Plasma ions difference	12–20	mEq/l	12–20	mmol/l	1	1
Plasma iron	40–250	μg/100 ml	7–45	μmol/l	0.18	5.6
Plasma iron-binding capacity	250–410	μg/100 ml	45–73	μmol/l	0.18	5.6
Plasma magnesium	1.8–2.4	mg/100 ml	0.7–1.0	mmol/l	0.41	2.43
Plasma osmolality	280–300	mosmol/kg	280–300	mmol/kg	1	1
Blood PCO_2	33–46	mmHg	4.4–6.1	kPa	0.133	7.5
Blood pH	7.36–7.43	—	7.36–7.43	—	1	1
Blood PO_2	80–105	mmHg	10.7–13.9	kPa	0.133	7.5
Plasma phosphate (inorganic as P)	2.0–4.5	mg/100 ml	0.6–1.5	mmol/l	0.32	3.1
Plasma potassium	3.3–4.8	mEq/l	3.3–4.8	mmol/l	1	1
Plasma protein (total)	6.0–8.3	g/100 ml	60–83	g/l	10	0.1
Plasma sodium	137–145	mEq/l	137–145	mmol/l	1	1
Plasma thyroid stimulating hormone	0–4	μU/ml	0–4	mU/l	1	1
Plasma thyroxine	5.4–12.4	μg/100 ml	70–160	nmol/l	12.9	0.078
Plasma triglyceride (fasting)	26–130	mg/100 ml	0.3–1.5	mmol/l	0.011	89
Plasma triiodothyronine	0.8–1.8	ng/ml	1.2–2.8	nmol/l	1.54	0.65
Plasma urate	2.8–8.4	mg/100 ml	170–500	μmol/l	59.5	0.017
Plasma urea	16–50	mg/100 ml	2.7–8.4	mmol/l	0.167	6.0

* Direct conversion not possible.
** S.I.: Système International d'Unités.
\+ Normal range varies with duration of pregnancy.

continued on next page

Appendix 8 (continued)

Constituent	Old Units		S.I. Units **		Conversion factor multiply by	
	Normal range	Units	Normal range	Units	Old to new	New to old
Urine calcium	0.13–0.33	g/24 h	3.2–8.3	mmol/24 h	25	0.04
Urine chloride	120–240	mEq/24 h	120–240	mmol/24 h	1	1
Urine creatinine	1.0–2.0	g/24 h	9–18	mmol/24 h	8.8	0.113
Urine 4-hydroxy 3-methoxy mandelate (= VMA)	1.0–7.6	mg/24 h	5–38	μmol/24 h	5.05	0.2
Urine estriol	+	mg/24 h	+	μmol/24 h	3.47	0.29
Urine osmolality	50–1300	mosmol/kg	50–1300	mmol/kg	1	1
Urine phosphate (inorganic as P)	0.5–1.5	g/24 h	15–50	mmol/24 h	32.3	0.031
Urine potassium	35–80	mEq/24 h	35–80	mmol/24 h	1	1
Urine protein (total)	< 0.05	g/24 h	< 0.05	g/24 h	1	1
Urine sodium	120–220	mEq/24 h	120–220	mmol/24 h	1	1
Urine urate	0.25–0.75	g/24 h	1.5–4.5	mmol/24 h	5.95	0.17
Urine urea	13–36	g/24 h	220–600	mmol/24 h	16.6	0.06
Urine xylose (after 5 g orally)	1.2–2.4	g/5 h	8–16	mmol/5 h	6.66	0.15
C.S.F. glucose	50–75	mg/100 ml	2.7–4.1	mmol/l	0.056	18
C.S.F. protein (total)	15–45	mg/100 ml	0.15–0.45	g/l	0.01	100
Fecal fat	3.0–5.0	g/24 h	11–18	mmol/24 h	3.52	0.28

* Direct conversion not possible.
** S.I.: Système International d'Unités.
\+ Normal range varies with duration of pregnancy.

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