Renal dysfunction is associated with a variety of abnormalities in the results of routine laboratory tests. Laboratory measurements may be spuriously increased or decreased in association with uremia. Interference with colorimetric tests may occur due to the presence of unidentified substances that accumulate with renal failure. Several medications interfere with tests that measure renal function. This article reviews the effect of renal failure on a variety of common laboratory tests and also discusses those conditions that alter the tests used to evaluate renal function.

Evaluating Renal Function

The serum urea nitrogen and serum creatinine values are the two most common parameters used to assess renal function. When renal function declines, the filtered load of urea increases, leading to increased urea reabsorption and decreased urea secretion. The net result is an increase in serum urea nitrogen. In most clinical laboratories in this country, serum or plasma is separated from whole blood for these laboratory determinations. Although it is common to refer to the “BUN,” this designation is imprecise and a better abbreviation would be “SUN” or “PUN” depending on which fluid is used for the test. For the remainder of this discussion, “SUN” will be used to denote the measurement of urea nitrogen in serum.

A variety of non-renal conditions may elevate the SUN (Table I). These conditions result in pre-renal azotemia. Any condition that reduces renal perfusion will cause an increase in the renal tubular reabsorption of urea. Intravascular volume depletion, congestive heart failure, severe liver disease with ascites, and renal artery stenosis all may result in an increase in the SUN. Other causes of pre-renal azotemia include increased protein intake, gastrointestinal bleeding, and drugs such as corticosteroids and tetracycline, which induce tissue breakdown, or a catabolic state.

The SUN may be reduced in states of reduced urea production such as low protein intake and severe hepatic failure, which is associated with the liver’s inability to metabolize ammonia to urea. Dilution of the serum with body water, as in states of excess water intake or increased antidiuretic hormone secretion, will also result in a reduced SUN level independent of renal function.

The serum creatinine value is probably a more reliable indicator of renal function than is the SUN. Creatinine is derived from muscle metabolism, filtered by the glomerulus, and both reabsorbed and secreted by the renal tubule to some degree. In subjects with normal renal function, the net effect of renal creatinine handling directly reflects the degree of glomerular filtration. Thus, serum creatinine correlates to some degree with the glomerular filtration rate. Yet as renal function declines the creatinine value becomes less reflective of renal function.

A variety of non-renal events may also alter the serum creatinine level (Table II). Several drugs that compete with creatinine for tubular secretion sites may cause a spurious elevation in the serum creatinine. These include trimethoprim-sulfa, cimetidine, and cefitoxin. The beta-blocker propranolol may decrease cardiac output and renal perfusion, but the creatinine level is usually unchanged because propranolol also increases creatinine secretion.

Diabetic ketoacidosis is also associated with increased serum creatinine. This is artifactual and due to the interference in the measurement of creatinine by acetocacetate when some alkaline picrate techniques are used. The serum creatinine value may also be increased by the excessive ingestion of cooked meat, which causes an increased filtered load of creatinine.

Patients with a markedly increased serum bilirubin concentration may have a spuriously decreased serum creatinine concentration.

Thus, while the SUN and serum creatinine concentrations are generally good monitors of renal function, a variety of drugs and other non-renal conditions may alter these measurements. These factors should always be considered when evaluating renal function.

Tests Altered in Uremia

Hematology

Anemia is common in advanced renal failure, caused by a variety of abnormalities associated with renal...
failure. Erythropoietin production by the kidney is reduced in renal failure. In addition, complications of uremia such as gastrointestinal bleeding, malabsorption, malnutrition, and blood loss from the dialyzer all result in chronic anemia.7

The WBC count is usually normal in patients with renal disease. Yet the WBC count markedly decreases during the first hour of the dialysis procedure. The reason for this early leukopenia is unknown, but believed to be due to an interaction between the white cells and the dialyzer membrane, leading to sequestration of these cells in the dialyzer or in the lungs. Later in the dialysis procedure, the white cells return to the circulation and the WBC count returns to its predialysis values.8,10

Eosinophilia is also noted in some patients with renal failure who are treated with hemodialysis. The frequency of this is reported to be between 5% and 38%. The cause of this phenomenon is believed to be hypersensitivity to several of the components of the dialysis procedure.11

Blood coagulation is usually prolonged in advanced uremia, especially in those patients not treated with dialysis. The most striking abnormalities involve platelet function. Platelet adhesiveness is reduced as is platelet aggregation by ADP and thrombin.7,12,13 Platelet counts are also decreased in about 25% of non-dialyzed uremic patients.13 Most of these abnormalities are transiently corrected, at least partially, by hemodialysis.13

Biochemical Evaluation

Serum electrolytes, serum enzymes, and a variety of hormones may be altered by uremia or its treatment. The serum electrolyte balance is critical in the management of patients with renal failure. The electrolyte composition of the blood is influenced by the diet and by the composition of the dialysate, as well as by the poorly functioning kidney. Certain types of renal disease may be associated with the inability of the kidney to excrete solute-free water, resulting in dilutional hyponatremia.14

Dilutional hyponatremia may also be seen in states of excessive secretion of antidiuretic hormone or excessive water intake.15 Hyponatremia may also be seen in patients with severe hyperglycemia, because glucose is osmotically active and draws water from cells into the extracellular space.16 Hypernatremia may result from severe dehydration, as in patients with adrenal insufficiency. Yet in patients with renal failure who are treated with dialysis, hypernatremia may result from a technical failure of the dialysis machine to correctly dilute the concentrated dialysate with water or from the use of peritoneal dialysate with high glucose or sodium concentrations.17

Hyperkalemia, hyperphosphatemia, and hypocalcemia are the result of renal failure and vitamin D and parathyroid hormone abnormalities. Once the patient is treated with dialysis, dietary potassium and phosphate restriction, and calcium and vitamin D supplementation, these abnormalities usually reverse themselves.

The early period of the hemodialysis procedure is also associated with a marked hypoxemia and hypocarbia, despite correction of the metabolic acidosis. The cause of these findings is currently under intensive investigation. Margination of white cells in the pulmonary microvasculature with impairment of pulmonary gas exchange, and diffusion of these gases into dialysate are two proposed causal mechanisms.18,19

Enzyme Measurements

Hyperamylasemia is frequently observed in patients with end-stage renal failure, caused by the failing kidneys' reduced ability to clear endogenous amylase. It is useful to obtain baseline serum amylase levels in stable dialysis patients in order to evaluate abdominal pain in patients with renal failure, because an increased incidence of pancreatitis also exists in these patients. Since urinary amylase excretion is markedly increased in the presence of acute pancreatitis in patients with normal renal function, it has been suggested20 that the ratio between urinary amylase and urinary creatinine be used to differentiate an elevated amylase value due to acute pancreatitis from an elevated value due to macroamylasemia, a condition in which serum amylase exists in the form of a high molecular weight complex.

Another enzyme that is increased in renal failure is the muscle enzyme creatine phosphokinase (CK). This enzyme is cleared from the blood by the reticuloendothelial system and this clearance may be deranged in renal failure. Several investigators have suggested21,22 that CK elevations in renal failure may be caused by increased muscle wasting or myopathy in chronic uremia. Difficulty in interpreting an elevation of the MB fraction of this enzyme may arise because a subset of uremic patients demonstrates persistent CPK-MB elevations in the absence of signs or symptoms of acute cardiac disease.21

Liver disease is common in patients with chronic renal failure and the usual tests of liver function can be used to detect liver function abnormalities. The alkaline phosphatase value, when elevated, is most likely increased due to the presence of renal osteodystrophy rather than liver disease. Aspartate amino transferase (AST) is sometimes reduced in patients with advanced uremia. This may be due to the presence of a uremic toxin interfering with the method of assay, or it may be related to the finding that uremic patients have biochemical evidence of pyridoxine deficiency. AST depends on a coenzyme, pyridoxal-5-phosphate, for its activity and the activity is low in the presence of pyridoxine deficiency.23,24

Serum albumin levels may reflect the patient’s state of hydration inde-
Uremia may also be associated with abnormal albumin turnover, which also produces low serum albumin levels in the low-normal or low range. Chronically uremic patients, as a group, appear to be malnourished and in general demonstrate serum albumin levels in the low-normal or low range. Uremia may also be associated with abnormal albumin turnover, which also produces low serum albumin levels. Patients with the nephrotic syndrome have markedly reduced serum albumin levels due to increased urinary albumin losses and increased serum cholesterol levels due to increased hepatic activity as the liver attempts to manufacture more albumin in response to these losses.

Uremic patients display an abnormal lipid profile. Serum cholesterol is usually at low or normal levels, but the total triglyceride level is elevated. High-density lipoproteins are decreased; low-density lipoproteins are markedly increased; low-density lipoproteins are increased; low-density lipoproteins are increased.

A large body of research has demonstrated that the usual patient with renal failure is clinically euthyroid, but subtle abnormalities in thyroid function do exist. These abnormalities may be difficult to evaluate because of the recognized deviations in the measurement of thyroid function which are secondary to the presence of renal failure. Total T₄ and T₃ levels decrease with decreasing renal function and are low in patients treated with dialysis. Serum reverse T₃ concentration is normal, but free reverse T₃ is elevated. Both thyroxine-binding globulin and thyroid-stimulating hormone (TSH) are usually normal in these patients. These findings are similar to the abnormalities in thyroid function noted in non-uremic patients who are undergoing catabolic stress. Although the abnormalities in thyroid function tests resemble hypothyroidism, patients are clinically euthyroid. Serum TSH levels may be the most appropriate measure of thyroid function in patients with renal failure.

Adrenal function may also be altered by renal insufficiency. Patients treated with hemodialysis demonstrate elevated basal plasma cortisol levels and either normal or increased ACTH values. One study has shown that standard pituitary-adrenal axis evaluation in hemodialysis patients yields results suggesting Cushing's syndrome.

The kidney is an important site for the inactivation and clearance of peptide hormones and the gastrointestinal hormone profile is indeed abnormal in patients with renal failure. Gastrin, cholecystokinin, gastric inhibitory polypeptide, and glucagon levels are all elevated in patients with renal disease. The serum levels correlate directly with the degree of renal insufficiency. Since gastrointestinal symptoms and peptic ulcer disease are common in patients with renal disease, these findings may have important clinical consequences.

The normal kidney is important in the metabolic degradation of insulin. To avoid hypoglycemia, diabetic patients who take exogenous insulin must often reduce the dose as renal function deteriorates.

### Drug Levels in Renal Failure

A large number of common therapeutic agents are used to treat a variety of non-renal conditions in patients with renal failure. The kidney is a crucial organ for the metabolism and excretion of many of these drugs. Thus, drugs may accumulate in patients with renal failure, resulting in increased serum levels. In addition, protein binding and distribution of drugs may be altered in the patient with renal disease, resulting in spurious decreases or increases in the serum levels of certain drugs. An inclusive discussion of drug interactions in renal failure is beyond the scope of this article and readers should consult a recent review on this subject. Nevertheless, a few important drugs are worthy of mention.

Many patients with renal failure are treated with digoxin for concomitant heart disease. A recent report indicates that an endogenous digoxin-like substance is found in the blood of uremic persons. Thus, detectable levels of digoxin may exist in patients who are not treated with digoxin and the digoxin levels of those treated with the drug may be spuriously increased. This is important in the management of digoxin therapy, which depends on the kidney for its removal from the body and thus also accumulates in patients with renal failure.

Uremic patients experience an increased incidence of seizures and many such patients require diphenylhydantoin.
toin for the management of this disorder. Monitoring diphenylhydantoin blood levels is important to control seizures and avoid drug toxicity. Diphenylhydantoin levels are reduced in uremic subjects, while the major metabolite of diphenylhydantoin, 5-phenyl-5-parahydroxytoin, accumulates. This metabolite is much less active than diphenylhydantoin. Monitoring blood levels of diphenylhydantoin may not be accurate in uremic subjects if the method also measures the metabolites.

Certain drugs may also interfere with the measurement of other substances in the blood of uremic patients. For example, mild hyperbilirubinemia is noted in dialyzed patients who take large doses of propranolol. This occurs in the absence of liver disease. Propranolol metabolites accumulate in the presence of renal failure and interfere with the automated measurement of serum bilirubin.

Summary

Renal failure results in the alteration of a great many laboratory tests. Some of these alterations are caused by the presence of metabolites that accumulate in renal failure and interfere with the measurement of other substances in body fluids. Other laboratory tests may be altered by the failing kidney itself, which is no longer able to maintain fluid, electrolyte and hormonal homeostasis. Finally, renal function tests themselves may be altered by drugs and other compounds that compete for renal tubular binding sites. Many other abnormalities may exist, but these are poorly understood because of the complex nature of chronic renal failure. Further research is needed to more completely understand the interactions between disease states and laboratory evaluations.

References