RECENT advances in our understanding of the pathologic and functional disturbances of the heart in renal disease have led to more rational and effective therapy. The purpose of this communication is to review this progress.

The relation between the renal disease and the cardiovascular disorder is variable. In some instances renal disease is primary, and causes secondary hypertension; these renal diseases are glomerulonephritis, pyelonephritis, polycystic disease. On the other hand renal disease may develop secondarily during the course of essential hypertension, simultaneously with rheumatic heart disease, or during the progress of subacute bacterial endocarditis. In diffuse visceral diseases, the kidneys and heart may be commonly affected as in amyloidosis, periarteritis nodosa, and lupus erythematosus. In diabetes mellitus, renal complications and hypertensive and arteriosclerotic heart disease may develop in succession. It is evident that a cardiac disorder may appear and constitute the major problem in management in the course of acute or chronic renal disease.

RECOGNITION OF RENAL DISEASE

It is usually impossible to define precisely when a renal lesion appears in the above-mentioned conditions. Detection of a clinically significant degree of renal damage is usually less difficult. Constant proteinuria is the fundamental diagnostic finding of clinical renal disease in the absence of congestive heart failure.1

Renal Function

In patients with renal disease, the functional status may be determined by urine concentration test, phenolsulfonphthalein excretion 15 minutes after the intravenous injection of 6 mg. of the dye, and the level of the blood nonprotein nitrogen. For clinical purposes one may consider that normal renal function is present when a concentration test yields urine of 1.026 or higher specific gravity; impaired kidney function is present if the maximal specific gravity is 1.018, the excretion of phenolsulfonphthalein is less than 25 per cent, and the blood nonprotein nitrogen is within normal limits (30 to 40 mg. per 100 cc.); renal insufficiency is present if the maximal specific gravity is 1.012, the phenolsulfonphthalein excretion is less than 5 per cent and the blood nonprotein nitrogen is 45 mg. per 100 cc., or higher.

Although clearance methods for the study of discrete renal functions have contributed significantly to our understanding of the physiology of kidney function in renal and cardiac disease, such technics are not readily adaptable for use in the clinic.

Intravenous or retrograde pyelography may be indicated to establish the presence of two kidneys, the functional capacity of each, deviations in gross size and shape, deformities in the calyceal architecture and obstructive phenomena. The diagnosis of unilateral renal disease can be made only by this method of investigation. The possibility of ureteral obstruction is of such paramount importance in patients with anuria that retrograde investigation by a skilled urologist is usually indicated.

HEART IN ACUTE GLOMERULONEPHRITIS

Patients with acute glomerulonephritis whom the physician is usually called upon to treat are
those who present overt phenomena such as gross hematuria, edema, heart failure, pulmonary edema, hypertension, cerebral phenomena, oliguria and anuria, a few days to four weeks after a streptococcal infection. The diagnosis under such conditions is not difficult. On the other hand, signs and symptoms suggestive of heart failure may mask the clinical picture to such an extent that the underlying renal condition may be overlooked.

In the initial stage of acute glomerulonephritis, the danger to the circulation is of primary importance; the commonest cause of death is heart failure.

Friedberg and Derow have recently emphasized the important manifestations of cardiovascular disturbances in acute glomerulonephritis—that is, hypertension, cardiac enlargement, electrocardiographic abnormalities and heart failure.

**Hypertension**. Elevated blood pressure of variable severity is observed in many cases. Its cause remains unexplained. The role of hypertension in the development of cardiac enlargement and heart failure in acute glomerulonephritis is not as evident as its importance in causing encephalopathic phenomena.

**Cardiac Enlargement**. Hypertrophy frequently appears within the first week or two in acute glomerulonephritis. The enlargement is usually slight, but may be considerable when signs of severe heart failure occur. I have repeatedly observed by serial x-ray examinations the return to normal size of the cardiac shadow with the onset of spontaneous diuresis and the subsidence of the renal disease. No evidence of pericardial effusion has been found at autopsy to account for the enlarged cardiac silhouette seen on x-ray study. Dean reported that cardiac enlargement may persist for many years after acute glomerulonephritis in spite of little or no elevation of the blood pressure; however, the possibility that the cardiac enlargement in his three cases antedated the nephritis cannot be excluded.

Although the cardiac enlargement is usually attributed to the hypertension, it has also been observed in the absence of elevation of the blood pressure. Gore and Saphir stated that it is doubtful whether a presumably normal heart could enlarge to a weight of 500 Gm. in 10 days (their case 3) through muscular hypertrophy alone. In their study of 106 cases of acute and subacute glomerulonephritis, 16 patients were found to have cardiac enlargement and 14 of these presented the signs and symptoms of heart failure. The factor common to all the enlarged hearts in their studies was a patchy serous myocarditis. Such increases of interstitial fluid could increase the weight of the heart appreciably and rapidly. They and other observers suggested that increased capillary permeability was the underlying cause of the serous myocarditis. However, Christian stated that “in fatal cases on which postmortem studies had been made no changes have been found in the myocardium of sufficient extent or degree to explain satisfactorily the cardiac condition observed during life.” The finding of an underlying disorder of the myocardium in acute glomerulonephritis has not been sufficiently uniform to explain the cardiac enlargement in all cases.

The role of the expanded blood volume caused by retention of salt and water in acute glomerulonephritis in producing interstitial edema remains to be clarified.

**Electrocardiographic Abnormalities**. These occur more frequently than overt signs of heart failure in acute glomerulonephritis. Low or inverted T waves in lead I and in the precordial leads are the commonest changes. These abnormalities disappear with the subsidence of the renal lesion. Interstitial fluid accumulation resulting in electrolyte and other metabolic disturbances may account for the T-wave changes. Similar electrocardiographic changes may occur in cases of overdosage of desoxytocicosterone acetate.

**Heart Failure**. Failure, or a syndrome resembling it clinically, is the most frequent complication and the commonest cause of death during the initial stage of acute glomerulonephritis. Since a complex combination of factors may exist in such patients, it may be difficult to assess the role of each factor in the pathogenesis of the syndrome. Of the utmost importance is the fact that the clinical features of heart failure may appear in previously healthy individuals without a past history of cardiac
disease, and that with the onset of diuresis the apparent heart failure often disappears very rapidly as the size of the heart returns to normal. It is well known that manifestations of heart failure in acute glomerulonephritis may occur without significant hypertension; elevations of blood pressure may, however, precipitate heart failure.

The possible occurrence of an underlying metabolic disorder of the myocardium that might be of primary importance in the pathogenesis of heart failure in acute glomerulonephritis was discussed above. Davies, however, on the basis of his studies, concluded that the evidence for the view that heart failure in acute nephritis is due to myocardial damage was not convincing.

Disturbances of electrolyte balance may result in altered function and decreased efficiency of heart muscle. Bradley stated that although deficient excretion of sodium and water because of the primary renal disease results in an increased blood volume, it is probable that heart failure is rarely, if ever, induced by increase in blood volume; an underlying disorder of the myocardium must be present.

Recently, Davies and Rosenheim suggested that the phenomena of heart failure—that is, hypervolemia, elevated venous pressure, cardiac enlargement, pulmonary congestion and edema—and hypertension in acute glomerulonephritis are similar to those observed in cases of overdosage of desoxycorticosterone acetate (DOCA) or cortisone. They also stressed the rapid reversibility of the apparent heart failure in these conditions with the onset of diuresis.

The term “heart failure” in acute glomerulonephritis may be misleading since it calls attention to the heart as the cause of the phenomena mentioned above. Actually, the reduction of glomerular filtration owing to the glomerular lesion may result in sodium and water retention, hypervolemia, increased venous pressure, cardiac enlargement, hydrothorax, ascites, edema, dyspnea, orthopnea and attacks of pulmonary edema. In the opinion of Davies the absence of previous history of cardiac damage, the normality of the cardiac output and circulation time, the rapid reversibility of heart failure with spontaneous diuresis, and the usual absence of histologic changes in the myocardium in fatal cases suggest that the heart is not primarily involved and that salt and water retention with resultant expansion of the blood volume may be the cause of the apparent heart failure.

Altschule has suggested the term “natrigenic hypervolemia” to characterize the phenomena that resemble heart failure not only in cases of acute glomerulonephritis but also in patients suffering with overdosage of desoxycorticosterone acetate, corticotropin, or cortisone; the “central” fault is in the kidneys and not the heart. Friedberg’s observations on the occurrence of the clinical syndrome of congestive heart failure as a result of sodium and water retention in cases of carbon tetrachloride nephrosis without evidence of cardiac disease support this concept.

Stead recently made the following statement: “The only way to tell whether a person with acute glomerulonephritis has heart failure is to measure the cardiac output and to relate it to the total oxygen consumption. If the cardiac output and mixed venous-arterial oxygen differences are normal, heart failure is not present, as this disease is not one of those which speeds up the circulation. If the venous-arterial oxygen difference is increased, mechanical heart failure is likely.”

The occurrence of cardiac enlargement and acute pulmonary edema with dyspnea suggests the presence of acute heart failure. This clinical impression has, to date, not been substantiated by the necessary hemodynamic studies; indeed, such studies may not be performed because of the hazards to the patient under the circumstances. The heart failure might be due to metabolic disturbances that interfere with enzyme systems and normal contractility of the myocardium. The renal factor is undoubtedly of great importance and may be the primary cause of the heart failure.

Obviously, the pathogenesis of the apparent heart failure in acute glomerulonephritis is obscure and its clarification must await further study.
Treatment

Treatment is largely symptomatic in a disease such as acute glomerulonephritis in which the etiology is unknown and from which most patients recover. There is no known specific therapy that influences healing of the glomerular lesions and prevents progression from the acute to the chronic form of the disease. However, treatment based on current knowledge of the abnormal physiology of acute glomerulonephritis may be effective in the prevention and management of complications and major symptoms.

Heart Failure. The development of heart failure constitutes an emergency that may result in death in a small number of obviously severe cases of acute glomerulonephritis. Awareness of this serious complication, its prevention if possible and its early recognition and management make the active treatment of acute glomerulonephritis important.

While the mortality in the initial stage is in large measure related to the severity of the heart failure, the patient who survives this complication has as good a chance of complete recovery from acute glomerulonephritis as the one with the milder form of the disease.

Heart failure may be characterized by a sudden onset of dyspnea and orthopnea progressing to severe acute pulmonary edema. It may develop more insidiously and may involve the systemic as well as the pulmonary circulation.

The knowledge that the several pathogenetic factors are present to produce or simulate heart failure should emphasize the importance of the following measures:

Complete bed rest is essential during the initial stage of acute glomerulonephritis as long as heart failure, edema, hypertension, oliguria or anuria persist.

Diet and fluid intake should be carefully regulated in the initial stage. The “hunger and thirst treatment” of Volhard, formerly widely practised, is now being supplanted by a diet containing 100 to 150 Gm. of carbohydrate, no sodium salts, and fluid restriction to the volume excreted by the kidneys, in addition to about 1000 to 1200 cc. lost by insensible perspiration.

Intravenous infusions may precipitate or aggravate heart failure by increasing the blood volume. A more liberal diet and fluid intake are instituted after disappearance of heart failure, edema, hypertension and oliguria.

In the presence of impending or actual pulmonary edema, rapid venesection—500 cc. of blood in adults, and proportional amounts in children—should be done. In addition to venesection, early administration of oxygen by tent or positive pressure mask, and antifoaming agents should be employed in the treatment of severe pulmonary edema; morphine and atropine in adequate doses should also be given. Tourniquets on all four extremities may be employed. Tilting of the patient’s head below the edge of the bed may relieve respiration by providing drainage of the pulmonary edema. At times, the suddenness and rapidity with which pulmonary edema develops preclude the use of any therapeutic measure to prevent death.

The rapid subsidence of the signs and symptoms of severe heart failure without the benefit of digitalis in these cases leaves the impression that the improvement is due to the spontaneous diuresis rather than changes in the contractility of the heart. The possibility also arises that the spontaneous diuresis signifies recovery from capillary and metabolic derangements. Although digitalis in a rapidly excreted form (such as Cedilanid and Digoxin) is recommended by the oral or intravenous route, depending upon the urgency for the treatment of heart failure in acute glomerulonephritis, it is difficult to evaluate its effect.

There is no reliable method of treatment for freeing the obstructed glomeruli to initiate glomerular filtration. Diuretics are of no value and in fact may be harmful.

Hypertension. Frequent, careful determinations of blood pressure should be made in all cases of acute glomerulonephritis. However, not all patients who have an elevated blood pressure exhibit hypertensive complications. Gradual or sudden rise of the blood pressure sometimes provides objective evidence of the imminence of heart failure. In spite of the fact that the pathogenesis of heart failure in acute
glomerulonephritis remains to be clarified, the development of severe hypertension may either precipitate heart failure or aggravate already existing failure.

The reduction of the blood pressure to normal levels will at least serve to eliminate the hypertensive factor in the genesis of the heart failure. Sometimes the return of the blood pressure to normal levels appears to contribute favorably to the patient’s recovery from the heart failure. The dosage and frequency of administration of vasodepressor preparations depend upon the degree and duration of the hypotensive effect, the relief of the cardiac symptoms, and avoidance of toxic manifestations, including severe hypotensive collapse; dosage of vasodepressor medication must be individualized to obtain satisfactory results.

Magnesium sulfate administered orally, rectally, or parenterally is often effective in reducing the blood pressure. Because of the lack of any blood pressure lowering effects of magnesium sulfate in some cases, effective vasodepressor oral preparations of veratum alkaloids and hydrazinophthalazine may be used in mild or moderately severe hypertension; in severer cases these medications may be given parenterally. Although a transient decrease in urinary volume is observed after the injection of veratum alkaloids and hydrazinophthalazine, this decrease is not marked unless a profound hypotensive effect is produced by large doses of these drugs. The oliguria is accompanied by reduction of the glomerular filtration rate and of sodium and water excretion; these phenomena are transient. Even though the oliguria is usually followed by a marked polyuria, the reduction in function may be detrimental if continued for a prolonged period when azotemia is present.

Rapid venesection of 500 cc. of blood in adults and proportional amounts in children is sometimes effective in lowering the blood pressure. This procedure should not be employed in the presence of anemia.

Sedation is of great importance in these patients because of the restlessness, irritability and apprehension usually present. Small doses of phenobarbital are helpful not only in providing relaxation and rest but also in lowering the hypertension. Rectal administration of chloral hydrate or paraldehyde may be beneficial. However, it is sometimes necessary to resort to such drugs as Sodium Amytal in doses of 0.25 Gm. given intramuscularly or intravenously.

**Heart in Acute Renal Failure**

In the past few years, much has been written about acute renal failure, a syndrome characterized by severe oliguria or anuria and renal insufficiency. The varied etiology and pathogenesis of this syndrome, and the pathology and functional derangements of the kidney, have been described by many observers. Therapeutic regimens directed at the alleviation of nitrogen retention and the correction of electrolyte disturbances of the blood until the damaged kidneys recovered spontaneously have included the artificial kidney, peritoneal dialysis, intestinal irrigation and exsanguinotransfusion. The conservative management, without dialyzing procedures, has been improved greatly as a result of more thorough familiarity with the physiology of fluid balance, electrolyte relationships and protein metabolism. The purpose of all types of treatment of acute renal failure is to tide the patient with reversible urinary suppression over the critical anuric phase until spontaneous recovery and diuresis occur.

However, only recently has an appreciation developed of the fact that after the appearance of acute urinary suppression, cardiac failure is the most serious complication and the principal cause of death. Potassium intoxication, with abnormalities of cardiac conduction terminating in ventricular fibrillation or asystole, may also contribute to a fatal outcome.

**Heart Failure**

Friedberg emphasized the fact that the deficient excretion of sodium and water in acute renal failure can produce the complete syndrome of congestive heart failure without cardiac disease. While the danger of fatal pulmonary edema due to massive intravenous infusions and the futility of such measures to overcome urinary suppression have been stressed and recognized, there is still inadequate
recognition of the frequency of edema and other evidences of congestive heart failure induced by the administration of moderate amounts of fluid which have no egress because of the complete or almost complete cessation of renal excretion of sodium and water.

There may be some question about the applicability of the term “congestive heart failure” to cases of acute renal failure in which there is no clinical, electrocardiographic or pathologic evidence of cardiac disease and no previous history suggesting cardiac damage. Nevertheless, at some stage in the clinical course most or all of the cardinal features of congestive heart failure may occur in patients with acute renal failure—dyspnea, orthopnea, attacks of pulmonary edema, engorged neck veins and elevated venous pressure, enlargement of the liver, subcutaneous edema, hydrothorax, ascites and gallop rhythm. In patients with pronounced pulmonary congestion the second pulmonic sound is accentuated. As in cases of congestive heart failure associated with the common cardiac diseases, the symptoms may be precipitated or intensified by sodium-containing fluids and alleviated by sodium and fluid restriction, or, in acute episodes, by phlebotomy.13

Although cardiac failure may be defined physiologically in terms of adequacy of the cardiac output, in practice it is defined as a clinical syndrome and is recognized by the above-mentioned clinical features.13 From the latter viewpoint the criteria for “congestive heart failure” are fulfilled even though there is no evidence of underlying heart disease.

The circulation time in cases of acute renal failure with heart failure is normal or decreased. The circulating blood volume is usually increased and the venous pressure elevated.

*Pathogenesis.* In the usual type of congestive heart failure associated with chronic cardiac disease, the “central fault” lies in the heart.21, 22 Myocardial weakness results in a deficient cardiac output as a consequence of which the blood flow to the kidneys is greatly reduced. Diminished glomerular filtration, increased tubular reabsorption, increased renal venous pressure and possibly other factors are responsible for the impairment of renal excretion of sodium and water. In acute renal failure, however, the “central fault” lies in the kidneys; the severe oliguria or anuria is also associated with reduced renal blood flow and deficient excretion of sodium and fluid.

Because of the impaired excretion of sodium and water in congestive heart failure due to underlying cardiac disease as well as acute renal failure, the administration of sodium-containing fluids may precipitate, and their restriction may alleviate symptoms in both conditions.

In acute renal failure, heart failure is perhaps due to metabolic or hemodynamic disturbances that interfere with enzyme systems and normal contractility of the myocardium. The renal factor is undoubtedly of great importance and may indeed be the primary cause of the heart failure.

*Potassium Intoxication.*

The clinical manifestations, dangers and electrocardiographic changes of hyperkalemia and the methods for controlling it have become familiar in the past few years. Potassium intoxication seems to depend upon many factors beside the absolute serum concentration of potassium. Merrill and his associates23 have shown that hypotension and acidosis aggravate the toxic effects of hyperkalemia. In acute renal failure, serial electrocardiograms and serial determinations of the concentration of serum potassium, sodium and carbon dioxide combining power provide adequate warning of progressing hyperkalemia and potassium intoxication. The clinical manifestations of potassium intoxication seldom appear before the condition is advanced and a fatal outcome is imminent.

Hyperkalemia develops in most cases of acute renal failure if potassium salts, fruit juices and protein are administered or as a result of liberation of potassium by rapid catabolism of tissue protein, hemolysis or injury to muscle. Even though potassium intoxication—an elevation of the concentration of serum potassium above 8.0 mEq per liter and the appearance of characteristic electrocardiographic changes beyond mere “peaking” of T waves—develops less often, it may prove to be fatal when present.
**Electrocardiographic Changes.** The electrocardiographic abnormalities of hyperkalemia may be simulated or modified by hyponatremia and acidosis. With serum potassium levels in excess of 6 mEq. per liter the T waves become tall and pointed, a configuration termed “peaking” or “tenting.” With levels above 8 or 9 mEq. per liter, prolongation of the P-R and QRS intervals and decreased amplitude and disappearance of the P wave occur. With higher levels of potassium, the T wave decreases in amplitude, the QRS complex and T wave merge; paroxysms of abnormal ventricular rhythms and periods of asystole may appear.

**Treatment**

In the management of acute renal failure, treatment should be planned to prevent congestive heart failure and potassium intoxication since these complications are most apt to cause death. The details of such therapy have recently been presented by Friedberg, Stock, and Swan and Merrill. The need for individualizing the management because of the variability of the clinical course of acute renal failure must be emphasized; also, that diuresis and recovery usually occur spontaneously within two weeks provided the patient can be tided over the critical anuric phase of the syndrome.

Since the details of therapy of acute renal failure are available to the reader in the reports of the above mentioned observers, only a summary will be presented here with special emphasis on the prevention and treatment of congestive heart failure and potassium intoxication.

**Heart Failure.** Because of the reduced tolerance for sodium in acute renal failure, the use of sodium-containing fluids to correct hyponatremia, hypocholeteremia and acidosis may precipitate cardiac failure. No sodium should be administered in any form until diuresis is established because these electrolyte disturbances constitute only minimal risks. Stock on the other hand has carefully used small amounts of alkali to correct these abnormalities in part without precipitating congestive failure.

In acute renal failure the body has no satisfactory mechanism for removing fluid administered in excess of the amount of insensible loss, that is, about 1000 cc. Much harm may be done by the administration of large or moderate quantities of fluid, parenterally or orally; increased blood volume with cardiac failure, peripheral edema, pulmonary edema and death may occur. The amount of fluid given should replace only that amount of fluid lost by the body and no more. This requires an estimation of insensible water loss, careful measurement of any urine, all vomitus, diarrheal stools, loss by saliva (in cases of mercurial stomatitis); the total daily fluid deficit, volume for volume, should be replenished.

The correction of anemia by small frequent transfusions may result in pulmonary congestion. The use of infusions of packed cells reduces this hazard.

The rapid subsidence of the signs and symptoms of heart failure without the benefit of digitalis in these cases leaves the impression that the improvement is due to the spontaneous diuresis rather than changes in the contractility of the heart. The possibility also arises that the spontaneous diuresis signifies recovery from metabolic and capillary derangements. In the author's experience the effect of digitalis in the management of “congestive heart failure” in acute renal failure has been difficult to evaluate.

Mercurial diuretics and acidifying salts are to be avoided in view of the presence of the kidney damage, azotemia and acidosis.

If pulmonary edema develops as a result of the excessive or moderate administration of sodium-containing fluids the management of the patient should include the measures described above in the “Heart in Acute Glomerulonephritis.”

**Potassium Intoxication.** The measures that may be employed to reduce threatening levels of plasma potassium concentration are the administration of glucose and insulin to bring about a shift of potassium into the cells of the liver and muscles, the use of cation exchange resins and intestinal irrigation to promote gastrointestinal losses of potassium, and the employment of dialysis with a perfusion fluid low in potassium. Dialyzing technics have recently been so improved that in the event...
that potassium intoxication does not respond to conservative management, the use of the artificial kidney may be indicated.

**Heart in Chronic Renal Disease**

Cardiac involvement in chronic renal disease is usually the result of hypertension and associated coronary arteriosclerosis. However, nonhypertensive heart disease as well as cardiac damage due to amyloidosis, lupus erythematosus and periarteritis nodosa may coexist with chronic renal disease. Only rarely does the heart escape damage in primary chronic renal disease until advanced renal insufficiency develops.

**Renal Function in Chronic Renal Disease**

Normal renal function may persist throughout the course of chronic renal disease, and death may be due to nonrenal causes. In cases of unilateral renal disease of inflammatory, vascular or congenital origin, total renal function may be normal. Impaired renal function may develop during and persist throughout the course of chronic renal disease. However, after a variable period, renal insufficiency may supervene. Uremia is by far the commonest cause of death in primary renal disease, such as glomerulonephritis. In chronic renal insufficiency, anemia, electrolyte disturbances and acidosis occur frequently. Furthermore, chronic renal insufficiency may be complicated by acute renal failure if dehydration with resultant reduction of blood volume is prolonged and untreated.

**Hypertension and Coronary Arteriosclerosis**

The cause of hypertension in chronic renal disease is unknown. The role of hypertension, primary or secondary, in the development of cardiac involvement has been known for many years. As a result of increased work imposed upon the heart, it dilates and hypertrophies as the work either continues or increases. Hypertension and coronary arteriosclerosis are intimately and frequently associated. Heart failure, angina pectoris and other manifestations of coronary insufficiency may develop during the course of the hypertensive-renal disease. Primary hypertension may be present for many years with gradual development of cardiac manifestations; renal insufficiency appears in only a small number of such cases. On the other hand, in cases of chronic renal disease with secondary hypertension, acceleration of the destruction of the renal parenchyma due to the addition of renal arteriosclerosis, may result from the elevated blood pressure, especially if it is severe and continuous. However, the progress of the renal disease may be slower than the development of cardiac involvement, so that heart failure, angina pectoris or other manifestations of coronary insufficiency may develop before renal insufficiency appears. In many cases of chronic renal disease, cardiac manifestations occur during the stage of impairment of renal function and may precipitate acute renal insufficiency as a result of the oliguria of congestive failure, or the peripheral circulatory collapse of myocardial infarction. Furthermore, in chronic renal insufficiency, cardiac failure or myocardial infarction may supervene and aggravate the already existing renal insufficiency.

Patients may die in uremia without congestive heart failure at a time when the heart is enlarged and severe anemia, acidosis and pericarditis are present.

The supervention of the syndrome of malignant hypertension during the course of primary or secondary hypertension usually accelerates the tempo of the hypertensive disease with early development of cardiorenal problems. Hypertension, occasionally of the malignant form, may mask underlying unilateral renal disease and be responsible for a clinical picture that is essentially cardiac.

Cardiorenal problems similar to those described above are also seen in diabetes mellitus because of the frequent association of coronary arteriosclerosis and renal disease and in various forms of nonhypertensive heart disease including amyloid and collagen diseases coexisting with renal disease.

**Treatment of Hypertension.** The treatment of hypertension in chronic renal disease without renal insufficiency may be undertaken to prevent or reduce the strain upon the heart. Curative forms of hypertension should be looked for; nephrectomy for unilateral renal disease
and the surgical removal of a pheochromocytoma in cases of sustained hypertension may lower the elevated blood pressure to normal.

Drugs, diet therapy, and sympathectomy, either singly or in various combinations, have been successful in reducing the elevated blood pressure in many patients with consequent lessening of the strain upon the heart. However, abrupt, severe and prolonged hypotensive collapse is an occasional hazard of this type of therapy; it may lead to impaired circulation to the heart, brain and kidneys. Coronary occlusion or myocardial infarction may result in patients with coronary artery disease. The development of shock may be followed by acute renal failure.

In chronic renal insufficiency, therapy directed to diminish the hypertension is often hazardous because of the delayed excretion of drugs with severe toxic potentialities, and the worsening of existing electrolyte derangements. However, it may be possible to reduce the azotemia and slow the progress of the renal disease by moderate lowering of the severe hypertension in chronic renal insufficiency. Although sympathectomy has afforded symptomatic relief in some of these patients, this procedure is usually contraindicated.

Anemia

A normocytic, normochromic anemia almost always develops in chronic renal insufficiency; there is, however, not always a correlation between the levels of azotemia and the degree of anemia. The cardiac adjustments in chronic anemia and their clinical manifestations have been described by Blumgart and Altschule and others.

Cardiac enlargement occurs more frequently in patients with very low levels of hemoglobin. Electrocardiographic changes of minor degree occur, and may signify anoxia, coexistent coronary arteriosclerosis and degenerative changes in the myocardium. Angina pectoris may develop with severe anemia and is almost always associated with coronary arteriosclerosis. Congestive failure may occur because of the necessity for the maintenance of the cardiac output and cardiac work at an abnormally high level for long periods of time, and the delivery to the myocardium of blood deficient in oxygen. Factors favoring congestive failure in anemic patients are coronary arteriosclerosis and hypertension.

Edema may develop in anemia even in the absence of heart failure. Delayed excretion of sodium, varying in degree with the severity of the anemia occurs and is perhaps a result of the markedly reduced renal blood flow.

Dyspnea is not necessarily a manifestation of heart failure since it may also be consequent to anemia. A variety of mechanisms favors hyperventilation and contributes to dyspnea in anemia. In addition the high cardiac output at rest reduces the cardiac reserve available for exercise and thereby favors exertional dyspnea.

It is clear that the anemia of chronic renal insufficiency may be responsible for some clinical cardiac manifestations. The coexistence of organic cardiac disease and the added strain upon the heart due to anemia and anoxia of the myocardium are especially prone to result in congestive heart failure, angina pectoris, coronary failure, or myocardial infarction.

Electrolyte Disturbances and Acidosis

Changes in the chemical composition of body fluids result from failure of renal regulation in chronic renal insufficiency. Dehydration and disturbances of acid-base adjustment and of maintenance of balance among various ions is evident in the distortions of the chemical structure of the plasma and the extracellular fluid. The ions usually affected are sodium, chloride, bicarbonate, calcium, sulfate and phosphate. Changes in the concentration of potassium may occur but are of minor importance unless oliguria and anuria develop. Dehydration reduces plasma volume and may lead to peripheral circulatory collapse and the clinical picture of acute renal failure. Acidosis in chronic renal insufficiency develops as a result of retention of sulfate, phosphate and probably organic acids and from the cessation of ammonia production and the loss of sodium. The sodium loss is associated with loss of bicarbonate and chloride. These changes may be aggravated and severe acidosis precipitated by the administration of acidifying salts such as ammonium chloride and other substances such
as renal carbonic anhydrase inhibitors and cation exchange resins employed in the treatment of congestive heart failure. Hypocalcemia develops as a result of phosphate retention and a decrease in absorption of calcium from the gastrointestinal tract as well as the obligatory renal excretion of fixed base.

The electrolyte disturbances and acidosis in chronic renal insufficiency may be responsible for cardiac manifestations such as disturbances in rhythm and in electrocardiographic pattern.

Alterations in the concentration gradient across the myocardial cell of sodium, potassium, bicarbonate and hydrogen ions and perhaps other components may result from electrolyte derangements. Since myocardial function is ultimately dependent upon processes by which depolarization and repolarization occur in sequence with systole and diastole, severe alterations in electric potential may result in cardiac failure.  

Hyperpnea or Kussmaul breathing, is one of the most striking manifestations of the acidosis of chronic renal insufficiency; its cause appears to be the lowered pH of the fluid bathing the respiratory center.

The coexistence of organic heart disease in chronic renal insufficiency and the added strain upon the heart consequent to electrolyte derangements, acidosis and anemia may cause congestive failure. Peripheral circulatory collapse with acute renal failure as a result of dehydration or myocardial infarction may further complicate and aggravate the electrolyte disturbances.

Uremic Pericarditis

Uremic pericarditis occurs in the terminal stage of renal insufficiency; its cause is unknown. Pathologic studies reveal pericarditis in more than half the cases of chronic renal insufficiency. Although acute fibrinous or serofibrinous pericarditis is usually found, there may be sterile serofibrinous or hemorrhagic effusions. Organization of the exudate and almost complete obliteration of the pericardial sac may occur. Occasional cases show slight degeneration and mononuclear infiltration of the myocardium beneath the layer of pericardial exudate. Although the pericardial exudate is almost invariably sterile, a terminal bacterial infection may be present in rare instances.

The pericarditis is usually asymptomatic; however, in some patients precordial distress with radiation to the shoulders may be present. In rare cases, the precordial discomfort may be severe and associated with slight fever, leukocytosis, fall in blood pressure, friction rub and electrocardiographic changes; such a picture may closely simulate myocardial infarction. The diagnosis of pericarditis is made on the basis of an audible friction rub varying in character from extremely soft and evanescent to coarse and persistent; the sounds are usually heard in the precordial area and rarely in the left interscapular region. Electrocardiographic changes of pericarditis may be seen in those cases in which the myocardium is involved beneath the pericardial exudate. Pericarditis usually appears shortly before death but survival for months or longer may take place.

Electrocardiographic Abnormalities

Electrocardiographic abnormalities occur frequently in chronic renal disease. In the absence of renal insufficiency, changes consistent with left ventricular hypertrophy and myocardial damage are often seen in those cases associated with hypertension and coronary arteriosclerosis. In patients without an elevated blood pressure, the electrocardiogram is usually normal unless other forms of heart disease coexist.

Electrocardiographic abnormalities arise in chronic renal insufficiency as a result of anemia, electrolyte disturbances—hypocalcemia and hypopotassemia—acidosis and pericarditis. In addition to these changes, those associated with hypertension and coronary arteriosclerosis may be found. Abnormalities consistent with hyperkalemia may develop if acute renal failure supervenes. The electrocardiogram sometimes shows a complex picture that is difficult to interpret. On the other hand, in spite of severe electrolyte derangements, the electrocardiogram may be normal in the absence of hypertension and pericarditis.
“Uremic Edema” of the Lungs

A characteristic roentgenologic picture has been described\textsuperscript{20} in some patients with renal insufficiency: symmetric dense opacities that fan out from both hilar regions like the wings of a butterfly; the apices and the peripheral and basal portions of the lungs are usually clear; the outer borders of the “butterfly” opacities may be poorly or sharply defined. These densities change rapidly or disappear completely within a short time. The curious “butterfly” distribution of the radiologic lesions has not been satisfactorily explained.

Pathologic studies have revealed edema of the lungs associated with a fibrinous or aluminous alveolar exudate; hyalinization of the exudate is seen in the more advanced cases. Although infection rarely appears to be a factor in the development of these findings, left ventricular failure is usually present.

Physical findings are often minimal. These patients may present no symptoms except slight cough; in the more advanced cases, severe dyspnea may develop and contribute to the death of the patient.

Nephrotic Syndrome

The nephrotic syndrome characterized by massive proteinuria, hypoalbuminemia and hypercholesterolemia with or without edema, occurs most often during the course of glomerulonephritis, diabetes mellitus and amyloidosis. The prolonged elevation of the serum cholesterol in the nephrotic syndrome of glomerulonephritis is considered to be one of the factors responsible for the development of coronary arteriosclerosis in a young age group in which arteriosclerosis is relatively rare.\textsuperscript{46} Myocardial infarction in young nephrotics has been observed.

The nephrotic syndrome with edema, especially in elderly patients with diabetes mellitus, may coexist with or simulate congestive heart failure. The differential diagnosis is often difficult.

Angina Pectoris, Coronary Failure, and Myocardial Infarction

Angina pectoris, coronary failure and myocardial infarction occur in chronic renal disease most often as a result of coronary arteriosclerosis. Rarely, in diffuse visceral diseases with cardiorenal involvement—such as, periarteritis nodosa and amyloidosis—these clinical disturbances of the heart may also develop. Excellent expositions of the pathogenesis, diagnosis, prognosis and therapy of angina pectoris, coronary failure and myocardial infarction have recently been presented by Blumgart\textsuperscript{41} and Friedberg.\textsuperscript{2}

Patients with cardiac pain and chronic renal disease with normal kidney function should usually be treated in the same manner as those without renal disease. However, if renal insufficiency coexists with coronary artery disease, anemia, especially when severe, may cause angina pectoris by increasing the work of the heart. In some of these patients, correction of the anemia by carefully administered transfusions of packed red cells may be followed by amelioration or even disappearance of cardiac pain.

The development of acute myocardial infarction in chronic renal insufficiency is catastrophic. In such cases with anemia and shock, the coronary blood flow is reduced because of the lowered blood pressure; the oxygen supply to the myocardium is still further lessened because of the anemia. In addition, shock is also responsible for the deprivation of the blood supply to the kidneys and the consequent supervention of acute renal failure. Not infrequently shock and pulmonary edema may appear simultaneously. The management of such patients is extremely difficult. The treatment of shock by the use of pressor amines, such as norepinephrine should be instituted immediately. It should be remembered, however, that intravenous infusions may aggravate existing pulmonary edema. The volume and rate of flow of the infusion should be carefully watched and held to the smallest quantity necessary to correct the hypotension. Because of the presence of anemia, venesection is contraindicated for the treatment of the pulmonary edema. In general, the principles of therapy described above under “Acute Renal Failure” should be followed. Drug therapy should be undertaken with extreme caution since excretion of all medications may be delayed to such
a degree that toxic blood levels ensue. Electrolyte derangements, acidosis and anemia present difficult therapeutic problems. Anticoagulant therapy is contraindicated because of the danger of hemorrhage as a result of the delayed excretion of the drugs.

In the absence of shock or pulmonary edema, myocardial infarction in cases of chronic renal insufficiency may be managed with the usual forms of therapy except anticoagulants. Such patients require close supervision for the recognition and cautious correction of electrolyte disturbances, acidosis and anemia.

Arterial embolization and renal infarction may develop consequent to myocardial infarction in rare cases; in the presence of chronic renal insufficiency, such an occurrence may be disastrous.

**Congestive Heart Failure**

Congestive heart failure in chronic renal disease is usually the result of hypertension and coronary arteriosclerosis; less commonly it is due to rheumatic heart disease and cardiac involvement associated with amyloidosis and collagen diseases. In chronic renal insufficiency, anemia, electrolyte derangements and acidosis are added strains upon the heart and contribute further to the development or aggravation of congestive heart failure.

The concept that congestive heart failure develops whenever the cardiac output becomes inadequate for the metabolic needs of the body has been widely accepted. Studies of the cardiovascular renal hemodynamics and metabolic interrelationships have shown that congestive heart failure is a consequence of changes in pressure-flow relationships in the circulation and disturbances in fluid and electrolyte metabolism, which lead to retention of sodium and water and the development of edema. The changes in fluid and electrolyte metabolism in congestive heart failure are the result of a number of complex mechanisms such as impaired renal hemodynamics, changes in tubular function, increased adrenocorticotrophic activity, and increased renal venous pressure, which are activated when the cardiac output becomes inadequate.

**Dyspnea.** In chronic renal insufficiency, dyspnea is not always cardiac in origin but may be due to severe anemia, acidosis, and cerebral anoxia; it may be difficult to differentiate the various factors responsible for the dyspnea. Congestive heart failure may be complicated by these phenomena and give rise to more severe dyspnea.

**Edema.** In chronic renal disease edema may be due to congestive heart failure, the nephrotic syndrome and severe anemia in renal insufficiency. Often, congestive heart failure may be superimposed upon the nephrotic syndrome and renal insufficiency.

**Renal Function.** Oliguria, proteinuria and azotemia commonly occur in congestive heart failure. If the urinary specific gravity is high (1.026 or more) these findings may be due to heart failure, per se, or heart failure in association with chronic renal disease and normal kidney function. With diuresis and restoration of cardiac compensation, proteinuria and azotemia disappear if these manifestations are the result of heart failure, per se; proteinuria persists despite disappearance of azotemia if chronic renal disease with normal kidney function is present. On the other hand, if the urinary specific gravity is in the vicinity of 1.018 during the oliguric-azotemic phase of congestive heart failure, impaired renal function is probably present even if the azotemia disappears with diuresis and restoration of cardiac compensation. Furthermore, if the urinary specific gravity is 1.012 or less during the oliguric-azotemic phase of congestive heart failure, significant renal insufficiency is probably present; with diuresis and restoration of cardiac compensation the azotemia persists, usually in a lesser degree.

**Treatment.** Kidney function should always be carefully evaluated before therapy of congestive heart failure in chronic renal disease is undertaken. Patients with chronic renal disease and normal kidney function may be treated in the same manner as those patients with congestive heart failure without renal disease. Excellent presentations of the management of congestive heart failure have recently appeared.

However, if either impaired renal function or renal insufficiency is present, the intelligent
management of congestive heart failure requires the awareness and recognition of the underlying abnormal physiology. Careful appraisals of the electrolyte equilibrium and the hemoglobin level are essential. Drug therapy should be undertaken with extreme caution since excretion of all medications may be delayed to such a degree that blood levels toxic to the patient ensue. Furthermore, measures employed to promote the excretion of salt and water and re-establish the balance between electrolyte and fluid intake and output may be responsible for electrolyte disturbances or for the aggravation of already existing electrolyte derangements. Besides, steps taken to correct the anemia and acidosis of chronic renal insufficiency may aggravate the existing cardiac problem by the development of pulmonary edema.

Intractability of congestive heart failure in chronic renal insufficiency is a common occurrence because of the difficulty in instituting a suitable program to restore cardiac compensation without aggravating the existing renal insufficiency, electrolyte derangements and cardiac failure. However, in spite of these problems, it is possible to improve the cardiac failure in some patients without intensifying the underlying renal insufficiency by the use of digitalis, dietary sodium restriction, mercurial and other diuretics, electrolyte replacements, transfusions of packed red cells, and the avoidance of administration of ammonium chloride, renal carbonic anhydrase inhibitors and cation exchange resins. The need for individualization in management cannot be over-emphasized. If renal insufficiency is severe as a result of chronic renal disease, measures employed for the restoration of cardiac compensation may be without any effect. In elderly diabetics, congestive heart failure may coexist with organic renal disease manifested by the nephrotic syndrome and renal insufficiency. The therapeutic approach in such patients is indeed a dilemma. Equally unsatisfactory is the management of the patient with chronic renal insufficiency and congestive heart failure who develops acute renal failure as a result of myocardial infarction or severe dehydration consequent to vomiting or diarrhea.

Emotion and the Heart in Chronic Renal Disease

Emotional disorders often coexist with cardiac and renal disease in many patients. In such cases, determination and evaluation of the causes of the multiple symptoms may be extremely difficult. Responses of the cardiovascular system to stress-producing situations include a change in heart rate, rise in blood pressure, increase in cardiac output, change in the contractile state of the blood vessels of the skin, and alteration in the respiratory rate and depth. Under emotional stress patients may complain of dyspnea, palpitation, chest pain, faintness and fatigue. Such complaints are not easy to evaluate in the presence of cardiac and renal disease. For example, the respiratory difficulty of anxiety is to be differentiated not only from the dyspnea of congestive heart failure but also from that due to anemia and acidosis in chronic renal insufficiency. Similarly, the chest discomfort of neurosis is to be distinguished from that due to coronary arteriosclerosis and uremic pericarditis. Faintness and fatigability may not only be caused by emotional disturbances but by congestive heart failure as well as the anemia of chronic renal insufficiency. Obviously, the appraisal of these complaints is difficult and can only be made on the basis of both the clinical and laboratory data and available information about the patient’s personality.

Altschule and others have emphasized the facts that the physiologic effects of emotion may exacerbate cardiovascular disease, that these manifestations may resemble those of coronary sclerosis and myocardial insufficiency, and that their occurrence may call attention to the presence of emotional disorders not previously recognized. In renal disease, symptoms associated with pericarditis, anemia and acidosis may further complicate the picture by causing manifestations difficult to distinguish from some of those encountered in neurosis. Successful management of emotional disorders in cardiac and renal disease is indeed complex, taxing the resourcefulness and understanding of the physician.

Summary

As a result of recent advances in our understanding of the pathologic and functional dis-
turbances of the heart in renal disease—that is, acute glomerulonephritis, acute renal failure and chronic renal disease—more rational and effective therapy has been developed. This progress has been reviewed.

REFERENCES


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