

## DISORDERS OF URINARY TRACT

*(In March 1949 the Frank E. Bunts Educational Institute presented a continuation course on Diabetes, the proceedings of which were later published in the Cleveland Clinic Quarterly. These proved so popular that it has been decided to publish the proceedings of the similar course on Medical and Surgical Disorders of the Urinary Tract held on November 17, 18, and 19, 1949.—Ed.)*

### **PYELONEPHRITIS AND GLOMERULONEPHRITIS**      *Robert D. Taylor, M.D.*

Both pyelonephritis and glomerulonephritis can cause proteinuria, pyuria, hematuria, cylindruria, and eventually hypertension and renal failure. Glomerulonephritis has been more widely studied and hence, in spite of an incidence of only 0.7 per cent, is a more common diagnosis in the presence of abnormal urinary findings than is pyelonephritis which was observed in 5.6 per cent of 3607 postmortems. Glomerulonephritis is a relentlessly progressive disease while pyelonephritis can be cured or controlled.

#### **Clinical Differential Diagnosis**

##### **A. Chronic Pyelonephritis**

###### **1. History**

More common among women; often follows marriage or pregnancy. Recent or remote history of chills, fever with dysuria. Nocturia is more frequent during active phase. Edema is rare save in terminal state.

###### **2. Physical Findings**

Patients may appear acutely or chronically ill. Blood pressure is usually normal and becomes elevated only as renal failure supervenes; occasionally acute hypertension is present. Costovertebral angle tenderness is demonstrable. No edema. Fever is common and may be of septic type.

##### **B. Chronic Glomerulonephritis**

###### **1. History**

There is no sex predominance. There is sometimes history of acute hemorrhagic glomerulonephritis. More often proteinuria is discovered during routine examination. Edema is frequent. Nocturia gradually increases and becomes continuous.

###### **2. Physical Findings**

Unless the process is acute or terminal, patients appear well. Blood pressure is often normal, commonly moderately elevated early in course; high in later phases. Dependent edema. Mucous membranes and skin appear moderately pale. Fever rare, due to intercurrent infection or massive edema.

#### **Laboratory Findings**

##### **1. Addis Test**

###### **a. Tubular Function**

Ability to concentrate urine is usually fairly well preserved. If depressed, the change is proportionate to decrease of glomerular filtration. Concentrating ability may improve with treatment.

##### **1. Addis Test**

###### **a. Tubular Function**

Until advanced and terminal phases, concentrating power moderately depressed. Not impaired in proportion to filtration rate. (Measured from urea clearance)

## URINARY TRACT

### b. Proteinuria

Usually not more than 1 to 2 Gm. per 24 hours.

### c. Cylindruria

May be excessive during active inflammation and remittent at intervals. Casts are usually granular or cellular. (Leukocytes)

### d. Hematuria

During active infection may be considerable. Clears with treatment.

### e. Pyuria

May be severe. Leukocytes show pronounced cytoplasmic motion (vital stain or phase microscope).

## 2. Urea Clearance

### a. Filtration Rate

Moderately depressed and in proportion to tubular damage.

### b. Blood Urea

May be elevated to 50 to 60 mg. per 100 cc. in spite of adequate filtration because of fever-induced, excess protein catabolism.

## 3. Blood

### a. Hemoglobin

Normal or depressed if disease is longstanding.

### b. White Cells

Often moderate leukocytosis.

### c. Proteins

Usually normal.

## 4. Urine

### a. Culture

May at times be sterile, but the same organism can usually be recovered on repeated culture.

## 5. X-rays

In primary pyelonephritis, kidney pelves,

### b. Proteinuria

Usually above 2 Gm. per 24 hours, commonly 4 to 10.

### c. Cylindruria

Casts are constantly increased in number and until terminal are predominately hyaline; if cellular, show red cells and epithelium.

### d. Hematuria

Varies in degree but is almost constantly present.

### e. Pyuria

Moderate. Leukocytes inert.

## 2. Urea Clearance

### a. Filtration Rate

Excessively depressed, more so than tubular function.

### b. Blood Urea

May be normal in spite of depressed clearance.

## 3. Blood

### a. Hemoglobin

Early—normal. With appearance of azotemia—progressive anemia.

### b. White Cells

Normal.

### c. Proteins

Albumin fraction often low.

## 4. Urine

### a. Culture

Sterile.

## 5. X-rays

Normal.

ureters and bladder have normal shadows until late in the disease. Then blunting of calyces and distortion of pelves may appear. In secondary types an obstructive lesion is demonstrated by intravenous or retrograde pyelograms.

### Treatment

1. Selection of proper antibacterial drug.
2. Proper follow-up.

### Symptomatic

1. Alphalin.
2. Potassium citrate.
3. Thiocyanate.
4. Low sodium diets.
5. Adequate fluid intake.

### Results

Cure or arrest of disease.

Progressive renal failure.

---

## TECHNIC AND SIGNIFICANCE OF ADDIS COUNT AND UREA CLEARANCE

*Harriet P. Dustan, M.D.*

Because urea is always present in blood and urine and because the methods for its measurement are not too exacting, simultaneous estimates of blood and urinary urea have been used for a long time as tests of renal function. The most practical of these tests is the urea clearance of Van Slyke. In principle, the test measures the volume of blood equivalent to one minute's urinary excretion of urea. The formula used in its calculation expresses this ratio as  $UV/B$ , for "maximum" clearance at high urine flows ( $C_m$ ; normal 75 cc./min.) and  $U\sqrt{V}/B$  for "standard" clearance at urine flows of less than 2 cc. per minute ( $C_s$ ; normal 55 cc./min.). For convenience in interpretation, the values are reported as per cent of normal by multiplying observed  $C_m$  by 1.33 and observed  $C_s$  by 1.85.

The disparity between  $C_s$  and  $C_m$  results from the diffusion and reabsorption of urea from the tubular fluid. At rapid, steady, or slowly decreasing rates of urine flow, the proportion of urea reabsorbed is constant at about 40 per cent of that filtered. Consequently, changes in urea clearance can be interpreted in terms of changes in glomerular filtration. Variations in reabsorption of urea incident to the onset of diuresis, to exercise, pain or inadequate hydration, disturb this relationship and render the test uninterpretable.

From the Addis examination, one obtains three types of information: (1) the ability of the kidney to concentrate urine in response to water deprivation as indicated by the nonprotein specific gravity, (2) a quantitative determination of urinary protein, and (3) a quantitative determination of the numbers of casts, red cells, white cells, and renal epithelial cells in the urinary sediment.

The patient is deprived of water for a 24 hour period, and the determinations are made on the urine collected during the last 12 hours of water deprivation. Normally, the nonprotein specific gravity of this specimen will be 1.026 or above. If the patient misunderstands the instructions and takes fluids, if he has congestive cardiac failure or increased extracellular fluid from any cause, or if he has been on an exceedingly low-protein intake such as a rice diet, a falsely low value will be obtained. In a test in which

these conditions are not present, the nonprotein specific gravity is a reliable indication of tubular integrity.

Normally, the urine contains less than 0.2 Gm. of protein in 24 hours. In diseases which increase the permeability of the glomerular capillary membrane, there is an increase in urinary protein. The cells and casts of the urinary sediment can be considered as a renal biopsy. The quantitative estimation of components of the sediment is exceedingly valuable, not only in diagnosis but in following the course of renal disease.

## RENAL DISEASE OF HYPERVITAMINOSIS D

*Leonard L. Loushin, M.D.*

### I. Introduction

- A. Vitamin D intoxication becoming more common with the increased use of high potency preparations.
- B. Used chiefly in the treatment of arthritis, sarcoid and lupus vulgaris.
- C. No good evidence that Vitamin D is useful in the treatment of arthritis.
- D. All forms of Vitamin D probably can cause intoxication.
  1. Whittier process (Ertron) has caused intoxication in many instances.
  2. Excess cod liver oil in children.

### II. General Aspects of Hypervitaminosis D

- A. Dosage.
  1. Individual variation.
  2. May occur with therapeutic doses as small as 100,000 units daily.
- B. Symptoms—nausea, vomiting, anorexia, weakness, malaise, polydipsia, polyuria, headache, diarrhea, weight loss.
- C. Objective Findings.
  1. Signs of renal damage.
  2. Metastatic calcification—arterial, around joints, renal.
  3. Anemia common; may be out of proportion to the amount of renal failure.
  4. Increased blood calcium; normal blood phosphorus; increased urinary calcium.
- D. Mechanism.
  1. Many of toxic symptoms may be due to hypercalcemia. (Increase of ionized portion)
    - a. Similar picture in hyperparathyroidism.
    - b. No clinical symptoms with multiple myeloma. (Increase in protein-bound fraction)
  2. Theory that cellular damage is due to the metastatic calcification. (Ham)
  3. Theory that cellular damage precedes calcification. (Steck)

### III. Renal Disease in Hypervitaminosis D

- A. Kidney damage the most constant feature. May be easily missed because of paucity of urinary findings.
  1. (Howard and Meyer)—Series of 10 cases; all showed signs of some renal failure.
  2. (Schneider and Kammer)—Series of 9 cases; all 9 had renal disease.
- B. Clinical Findings.
  1. Slight to moderate albuminuria; usually below 0.5 Gm. per liter.
  2. Occasional granular casts.
  3. Elevated blood urea.
  4. Loss of concentrating power.

## URINARY TRACT

5. Decreased urea clearance and P.S.P. excretion.
  6. Picture most resembles old chronic pyelonephritis or nephrosclerotic kidney.
- C. Pathologic Findings.
1. Calcification in renal tubules—either in lumens or tubular cells.
  2. Arterial calcification.
- D. Prognosis.
1. Renal damage reversible if found early.
  2. Amount of residual damage depends on amount of fibroblastic proliferation around calcium.
  3. Renal damage persisting over 6 months after discontinuance of Vitamin D is usually permanent.
  4. In Howard's series of 10 cases only 2 returned to normal.
- E. Treatment.
1. Discontinuance of Vitamin D.
  2. Force fluids—3000 to 4000 cc. per day.
  3. Low calcium diet.

Because symptoms often suggest primary gastrointestinal disease, patients are often on milk diet. (High calcium)

### IV. Analysis of 12 cases at Cleveland Clinic

- A. Blood calcium elevated in all 12. Range 11.9 to 15.5 mg. per cent.
- B. Blood phosphorus elevated in 4. Highest 6.1 mg. per cent.
- C. Blood urea elevated in 11 of 12.
- D. Urea clearance definitely decreased in 10 of 11 determinations.
- E. Anemia in 10 of 12. (Below 11 Gm. hemoglobin)  
Red blood cells below 4,000,000 in 9; on 4 occasions below 3,000,000.
- F. Albumin in urine in 10 of 12. (1 and 2 plus)  
Addis determinations in 5; protein was below 0.5 Gm. per liter in all.

---

## MYELOMATOSIS, PERIARTERITIS, AND LUPUS ERYTHEMATOSUS

*Donald W. Bortz, M.D.*

In multiple myeloma the renal lesion may be manifest by proteinuria or, most commonly, albuminuria, hematuria, elevation in blood pressure, impaired renal function and edema. Renal insufficiency is invariably present at some stage of the disease and most commonly appears as part of the terminal picture as manifested by an elevated blood urea. The alteration in serum proteins as is usually noted in a high total serum protein is not actually the result of any structural kidney lesion, but is usually attributed to the fact that plasma cells serve as the origin of the increased amount of serum protein. One of the most common, and certainly the most characteristic laboratory observation in multiple myeloma is the presence of Bence-Jones protein in the urine. This protein precipitates at a relatively low temperature, usually 50 to 60 C and is partially or completely dissolved at 100 C, the precipitate reappearing upon cooling. It is usually present in 60 to 70 per cent of all cases of myelomatosis, but may occasionally be seen in myelogenic osteosarcoma, carcinomatous metastases to the bone marrow, and rarely in leukemia. Dr. Lena Lewis in our laboratories has studied the Bence-Jones protein in the urine by electrophoretic methods and has noted a usually constant change.

Pathologically, the kidneys are of normal size, unusually pale and firm to the touch. They present a characteristic pattern of protein deposition. Not infrequently, deposits of calcium, presumably resulting from the osteolytic bone lesions, may be seen in the

## URINARY TRACT

convoluted tubules. The tubules may also be dilated, but this dilatation occurs only at the site of either the protein or the calcium deposition.

The diagnosis of periarteritis nodosa, now being made with increasing frequency ante mortem, must always be entertained when the urine shows hematuria or at least the presence of erythrocytes microscopically, albuminuria, cylindruria and an elevation of the blood urea.

Periarteritis involves the medium sized arteries and arterioles and in the acute phase may involve one or all coats of the vessel. A large number of polymorphonuclear leukocytes and eosinophils present in the acute phase become replaced by a predominance of lymphocytes and monocytes as the chronic phase of the disease is reached. Characteristically the involvement of the vessel is usually segmental in nature. The changes are within the vascular bed whereas the usual changes in myeloma are secondary to protein deposition in the tubules.

Although Bence-Jones proteinuria is never observed, albuminuria, cylindruria, and erythrocyturia are all present in the urine of the lupus suspect. An increase in the cellular contents of the Addis count, which may be noted in any of the diseases under discussion, is present also in lupus erythematosus, although these changes are never as severe as those observed in the typical nephritides. Just as in myelomatosis, albuminuria is invariably present at one time or another in the disease. It may be associated with hematuria or cylindruria. While terminally an acute infectious process may intervene, evidences of renal failure as manifested by an elevation in the blood urea may occur. *All changes in this disease are secondary to the involvement of the connective tissues of the body.*

It is only by combining the information from the clinical laboratory with that obtained from the clinician's examination that the presence of any of these entities may be suspected. Confirmation of the clinical diagnosis awaits the pathologist; deposition in the tubules of the kidney in myelomatosis; arterial or arteriolar involvement in periarteritis nodosa; and the typical connective tissue changes of lupus erythematosus.

---

## MANAGEMENT OF URINARY TRACT INFECTIONS INCLUDING TUBERCULOSIS

*Eugene F. Poutasse, M. D.*

With the advent of new chemotherapeutic drugs the treatment of urinary infections has become much more effective, provided that certain fundamental principals are adhered to.

1. A large number of uncomplicated cases of urinary tract infection will clear up readily with fairly simple treatment.
2. Any serious, recurrent, or persistent infection should be carefully investigated for stone, obstruction, anomaly, or other lesions acting as a source of infection, and treated as indicated.
3. A Gram stain of fresh urinary sediment gives immediate and valuable information regarding type and degree of infection. Cultures should be made in all cases. In serious infections the organism should be tested for sensitivity to various antibiotics to determine the most effective agent.
4. Several drugs are available for the treatment of urinary tract infections. The development of bacterial resistance, which applies particularly to streptomycin, should be distinguished from innate ineffectiveness of a given antibiotic against a specific type of bacteria.

Mandelic acid is a cheap, effective agent against *B. coli* and *Streptococcus faecalis* provided urine is maintained at a pH of 5.5 and the concentration in the urine is about

## URINARY TRACT

1 per cent. The sulfonamides act best in alkaline urine and are useful against coliform bacteria, but toxic reactions must be watched for. Sulfisoxazole (trade name gantrisin) may prove useful in controlling proteus infections, particularly when combined with chloromycetin. Penicillin, aside from being the drug of choice against the Gram negative gonococcus, is useful only for Gram positive organisms. Dihydrostreptomycin, highly effective against Gram negative organisms, must be used only when urine is alkaline, as resistant variant strains develop more readily in acid urine and limit its usefulness.

Aureomycin and chloromycetin have a similar wide rapid bacteriostatic action against both Gram negative and positive organisms. Therapeutic dosage varies considerably with the degree of infection.

5. The pathogenesis of genitourinary tuberculosis must be thoroughly understood. The use of long term streptomycin therapy is gradually evolving and must be integrated with appropriate surgery as indications arise. New drugs to be used either with or without streptomycin are under investigation.

	Mandelic Acid	Sulfa	Penicillin	Streptomycin	Aureomycin	Chloromycetin
<i>B. coli</i>	+	+		+	+	+
<i>Streptococcus faecalis</i>	+		±		+	+
<i>Staphylococcus albus</i>			+		+	+
<i>Proteus vulgaris</i>		gantrisin ±				±
<i>Pyocyaneus</i>				±	±	
<i>Aerobacter aerogenes</i>				+	+	+
Diphtheroids			+		+	+
<i>Alcaligenes faecalis</i>		+			+	+

This table illustrates the effective antibacterial activity of the drugs discussed.

### CRUSH SYNDROME

*A. C. Corcoran, M.D.*

The term "crush syndrome" is restricted to that form of lower nephron nephrosis which follows trauma of the type experienced during urban bombing. The lesion, as in other forms of this condition, is characteristically one of obstruction and necrosis of distal convoluted tubules with proximal damage also. Clinical course is one of oliguria or anuria with the onset of diuresis delayed for 10 to 14 days, during which time death may result from potassium intoxication. After this time the course is toward recovery. The onset of diuresis probably coincides with adequate regeneration of renal epithelium.

Mechanism of the condition illustrated by studies on animals evidently involves

multiple factors: (1) renal vasoconstriction, (2) oliguria and aciduria, and (3) excretion of hemoglobin pigment.

Treatment: (1) Preventive: block of afferent impulses, vigorous treatment of shock and hypotension, pressure bandaging and establishment of diuresis; (2) Supportive: see Management of Acute Anuria.

## UNILATERAL RENAL DISEASE AND HYPERTENSION

*Robert D. Taylor, M.D.*

The concept of unilateral renal disease and hypertension as a syndrome had its inception following the report of Goldblatt and his associates that a constricting clamp applied to the renal artery of dogs caused persistent arterial hypertension. It was given further support when Page produced arterial hypertension by cellophane-induced perinephritis. In spite of the appeal of this concept as a cause of human arterial hypertension, too frequently nephrectomy has no effects upon the blood pressure of hypertensive human beings. However, an occasional patient has disease of a single kidney that produces hypertension.

If signs of unilateral renal disease exist, final decision about nephrectomy must be empirical and depend upon knowledge gained from animal experiments and the nephrectomies done over the past 15 years.

In rats, experiments of but a few weeks duration have shown that removal of the kidney causing hypertension is followed by return of the blood pressure to normal. However, after months and years of hypertension, little change in blood pressure occurs after nephrectomy. Experience has been similar among human beings. Those benefited by nephrectomy have been children or patients with a short history of hypertension.

The chief indications for nephrectomy are those which would lead to operation whether or not hypertension was present. Exceptions occur, however. If the presence of unilateral renal disease can be established in a patient who gives no family history of hypertensive disease, the chances are greater that his hypertension is due to the acquired lesion than among those patients who have a strong familial background. Furthermore, nephrectomy may be justified if there is little or no arteriolar disease, which indicates that the affection is probably of comparatively short duration.

## CYSTIC DISEASES OF THE KIDNEY

*William J. Engel, M.D.*

There are several different forms of renal cysts. (a) Polycystic disease occurs both in the newborn and in adults. (b) Multicystic disease of the kidney can be either congenital and unilateral or acquired and bilateral. (c) Simple serous cysts may occur either in solitary or multilocular form and either unilaterally or bilaterally. Among the rare types of cysts are: echinococcus; lymphatic; cystadenoma.

Polycystic kidneys are not rare, being found in about 1 out of 1000 autopsies and once in 3500 clinical urologic patients. There are two types of the disease: that occurring in the newborn which is usually fatal and the adult type which is more common and generally recognized in the third or fourth decade of life. Cause of polycystic kidneys is not known. Two prominent theories are failure of union of the collecting and secreting portions of the tubules or obstruction of the tubules. In any event, this is an hereditary disease with the basic fault probably lying in the germ plasm; it is always bilateral, producing multiple cysts which grow and multiply. The kidney becomes large, the



pelvis deformed, compression destroys the adjacent renal tissue, and death is usually the result of renal failure. Hemorrhages may occur into the cyst, infection is not uncommon, and cysts are frequently found in other organs such as the liver or lungs.

The most common symptoms are the presence of a bilateral abdominal mass, renal failure, hypertension, hematuria, or infection of the urinary tract. The urine generally contains albumen, red blood cells, and has a low specific gravity. The diagnosis depends on the performance of bilateral pyelograms. The kidneys are large with large pelves. There is variability of the calyces, dilation of the calyces, and circular indentations: The calyces are also elongated and stretched and variable in configuration. The pyelographic media show a variable density. The treatment is conservative and nonsurgical unless the cysts become large and painful, infected, with the presence of fever (and here antibiotics should be tried before surgery) or hemorrhage into the cysts. When operation is necessary, multiple puncture and drainage of the cysts is indicated.

Multicystic kidneys may be congenital and unilateral. They usually are recognized in children because of the presence of pain, chills and fever, persistent pyuria, and, rarely, a palpable mass. Surgical removal is the treatment of choice. In the adult form the cysts are more often bilateral and the etiology is probably tubular obstruction. There may be no clinical manifestations, but the condition should be suspected in the presence of unexplained azotemia, diminished renal function of obscure nature, and hypertension. The diagnosis is made by x-ray and pyelograms. Treatment is nonsurgical and is similar to that employed for other forms of renal failure.

Simple cysts, often called solitary, are either unilateral or bilateral. They are not connected with the pelvis, calyces, or ureter. They may be multilocular and grow to a large size. Complications of hemorrhage or infection are not unusual. Frequently there are no symptoms and the condition is found accidentally because of a palpable mass. Occasionally dull, indefinite, aching pain or acute symptoms of hemorrhage or infection are present. Treatment consists of simple aspiration or surgical removal. The cyst frequently does not recur following aspiration. Excision of the cyst or unroofing and packing, if it lies in the central portion of the kidney, may be advisable in some cases.

---

## INTERCAPILLARY GLOMERULOSCLEROSIS

*Max Miller, M.D.\**

In 1936 Kimmelstiel and Wilson first described a distinctive lesion of the renal glomeruli which they associated with a clinical syndrome of diabetes, hypertension, and a nephrotic syndrome. Since then the work has been confirmed by many investigators, the majority of whom have agreed upon the specificity of the lesion.

Although Kimmelstiel and Wilson described the lesion as consisting of hyaline thickening of the intercapillary connective tissue, in recent years careful studies have shown that it is really the result of profound focal thickening and hyalinization of the capillary loops or their basement membranes. "Intercapillary," therefore, is a misnomer.

The glomerular lesions are of two distinct types, the nodular and the diffuse. The nodular hyaline lesion is of a spherical shape and occupies the center of a glomerular lobule, varying in diameter from 20 to more than 100 microns. The second lesion consists of focal fibrosis of the majority of glomeruli without spherical hyaline masses. In many cases there may be definite transitions between these two types. The nodular lesions are almost pathognomonic of diabetes according to Ball and Laipply.

The latter author has also emphasized the specificity of glomerular focal fibrosis for the diagnosis of diabetes pathologically. The focal fibrosis is present in nearly all the

glomeruli in an approximately equal degree in diabetes, as contrasted with the variation in degree and the presence of many normal glomeruli in nephrosclerosis, pyelonephritis, and glomerulonephritis. These lesions occur in from 30 to 60 per cent of diabetic patients, predominantly in the older age group. The longer the duration of the diabetes, the more frequently do the lesions occur and the greater the degree of involvement. Except for the study of Horn and Smetana all writers are agreed that it is present only rarely in other conditions. Thus Siegal found the lesions in only 1 of a series of 200 patients without diabetes and Laipply found 4 in 208 cases of various other types of kidney disease without diabetes.

Albuminuria is common in patients with typical glomerular lesions, being present in at least 80 per cent. When the lesions are severe, albuminuria is present in practically all instances. Contrary to Kimmelstiel's original description, the full nephrotic syndrome is relatively uncommon (6 per cent). However, when present, it is usually associated with severe glomerular changes. Renal failure may occur occasionally. Hypertension occurs frequently but probably no more so than in diabetic persons in the same age group without intercapillary glomerulosclerosis. Intercapillary glomerulosclerosis probably is not of too great significance because of the frequent lack of clinical manifestations. Nevertheless, it is important in that glomerulonephritis or nephrosclerosis need not be diagnosed in every diabetic patient who develops albuminuria.

---

*\*By invitation. University Hospitals.*

---

## RENAL LESIONS IN CHILDHOOD

*William J. Engel, M.D.*

Lesions of the kidney in children are similar to those in adults and methods of examination are identical; symptoms of renal disease should not be minimized. Persistent or recurrent pyuria, gross hematuria, incontinence, unexplained anemia, or a palpable abdominal mass should all be investigated from the urinary standpoint. Among the congenital anomalies, obstructions of the vesical neck and posterior urethra are common. These may produce bilateral renal damage. They should be recognized early and subjected to surgical correction as soon as possible. Ureterovesical obstructions are usually unilateral and result in hydroureter and hydronephrosis. Pain and chronic urinary infection are the usual complaints. A retrograde pyelogram or intravenous urogram should be used for diagnosis. Infection is combated with antibiotics and sulfa drugs. Surgical correction of obstruction is indicated. Hydronephrosis due to ureteropelvic obstruction is more often unilateral than bilateral. It may be caused by aberrant vessels, congenital stenosis, or periureteral bands and adhesions. Pelvioplasty to relieve the obstruction or nephrectomy, when a serious obstruction is present, are the indicated treatments. Ectopic ureter usually produces persistent pyuria and recurrent infection. Cystoscopic examination and retrograde pyelograms are indicated. The surgical treatment consists of heminephrectomy and removal of the infected ureter.

Renal tumors of the Wilms' type account for 20 per cent of childhood malignant tumors. The most common symptom consists of a tumor mass. Chills and fever and hematuria may occur. These tumors are rare in children over 10 years old. Treatment includes irradiation therapy and early nephrectomy when possible. The prognosis, however, is unfavorable.

Renal calculi are less common in children than in adults. The management, however, is similar. Cystinuria, an hereditary metabolic disorder, must be considered in children with renal colic and passage of stones. Nephrocalcinosis is uncommon in chil-

dren but is perhaps increasing in frequency. The most frequent symptoms are fatigue, anemia, anorexia, polyuria, and polydipsia. The significant laboratory findings consist of hyperchloremia, acidosis, azotemia, diminished renal function, and anemia. The x-ray reveals multiple pinpoint calcifications clustered at the renal pyramid. The pyelogram aids in localization.

## THE NEPHROTIC SYNDROME

*A. C. Corcoran, M. D.*

The nephrotic syndrome (edema, gross albuminuria, hypoalbuminemia and hypercholesterolemia) occurs most often in chronic glomerulonephritis, not infrequently as part of the Kimmelstiel-Wilson syndrome, infrequently and only in children as true lipid nephrosis; as a rarity it may be caused by secondary syphilis, leptospirochetosis or toxic nephrosis. It almost never occurs in chronic pyelonephritis.

The presenting defects are in protein and water-salt metabolisms.

**Protein:** The proteinuria is probably due to glomerular leakage with secondary hydrops of tubule cells due to protein stuffing. Albuminuria contributes to hypoalbuminemia, especially when diet is restricted, and thus to edema, but is not the sole cause of hypoproteinemia. The loss of  $\gamma$  globulin in urine, carrying with it complement and other antibodies, may explain some of the increased susceptibility to infections. A particular aspect of the protein defect is the hypoaminoacidemia associated with nephrotic crises. Proteinuria may of itself contribute to renal failure by obstruction of tubules; this is most likely where there is a large globulinuria. It is countered by urinary alkalization with potassium citrate.

**Water:** The edema is due in part to hypoproteinemia; it is also associated with a decreased ability to excrete salt and water. It is increased by NaCl and held in check by Na restriction. The multiple mechanisms may include the posterior pituitary. Diuresis and loss of edema may precede improvement in plasma protein. Salt-poor albumin intravenously is used in emergent treatment of edema; most of the administered albumin appears in the urine.

**Course:** In most cases the progression is towards renal failure; in lipid nephrosis usually toward recovery if complications are prevented. Basic principles: moderate rest, sodium restriction, protein replacement, prevention of infection, urinary alkalization. Other modes: thyroid—in some disrepute since low basal metabolic rate probably due to water logging and not tissue defect in metabolism; remissions after measles or occasionally other infections not infrequent; thus pyrogens have been used and even yellow fever vaccine. There is probably some effectiveness of ACTH, although no adequate reports have been published.

## KIDNEY TUMORS—CLINICAL ASPECTS

*Charles C. Higgins, M.D.*

Most malignant tumors of the kidney arise on the renal parenchyma and are most frequently observed in the sixth decade. The epithelial parenchymal tumors, namely adenocarcinomas and alveolar carcinomas, are the common types in adults.

The classical triad of symptoms is hematuria, pain, and tumor. Such symptoms may also be associated with other pathologic lesions of the kidney. By the time these three symptoms are present the favorable opportunity for a surgical cure has frequently passed.

Hematuria in our series was the initial symptom in 49 per cent of the cases. The

bleeding is usually intermittent and not profuse, the blood being well mixed with the urine. When profuse bleeding is present, blood casts of the ureter may be observed.

Pain was present in 46 per cent of our cases and was the initial symptom in 28 per cent. This is a dull, aching pain in the renal area or at times, when more profuse bleeding is present, it may be a colicky pain caused by obstruction of the ureter from clots and back pressure.

A demonstrable tumor was the initial symptom in 10 to 12 per cent of the cases.

Occasionally a metastatic lesion, cachexia, or an unexplained fever may, in the course of examination, lead to the detection of a renal neoplasm. The diagnosis is established by the history, physical examination, laboratory data, and pyelography. The retrograde pyelogram reveals deformity of calices or pelvis or both.

Primary tumors of the kidney pelvis are relatively rare as compared to tumors arising in the renal parenchyma. We have observed 37. Swift-Joly collected 337 such tumors from the literature. The symptoms are hematuria, pain, and tumor.

Hematuria is the most frequent symptom and occurs in 75 to 80 per cent of cases. In 33 of our 37 cases gross hematuria was present, the duration from 1 day to 3 years. In 4 instances blood cells were detected on microscopic examination of the urinary sediment.

The next most frequent symptom is pain which occurred in 24 of the 37 cases. The pain is usually dull, boring-like, a heavy, uncomfortable feeling in the renal area. Six patients experienced renal colic due to clots.

A mass was palpable in 13 of the 37 patients. The tumor frequently involves the ureteropelvic junction thereby producing varying degrees of hydronephrosis. Loss of weight, cachexia are late manifestations of the disease. Fever was present in 11 of the 37 cases.

Papillary tumors of the renal pelvis involve the ureter or the immediate vicinity of the ureteral orifice in the bladder whether the tumor is benign or malignant. This demands a more radical surgical procedure than that necessary for squamous cell carcinoma of the kidney pelvis or primary tumors of the renal parenchyma. The diagnosis is established by the history, physical examination, microscopic examination of the urinary sediment and retrograde pyelography. The Papanicolaou examination is of considerable importance in the diagnosis of such tumors.

A nephrectomy is the treatment of choice for carcinomas of the renal parenchyma. Due to the frequent involvement of the renal vein by tumor thrombi, the renal pedicle must be ligated before manipulating the kidney. Therefore, when dealing with large tumors, the transperitoneal approach is preferred as it permits ligation of the pedicle before manipulating the kidney, thus preventing the dissemination of tumor cells into the circulation from the renal vein.

For papillary tumors of the renal pelvis (benign and malignant) a nephroureterectomy with excision of a portion of the bladder about the ureteral orifice is indicated and required. A nephrectomy suffices for the treatment of squamous cell carcinoma of the renal pelvis.

Early diagnosis is essential in the treatment of malignant tumors of the kidney. To minimize the clinical significance of hematuria is exceedingly dangerous. Blood in the urine is a symptom demanding complete urologic investigation and is not a disease for which a prescription is to be offered the patient.

**PRIMARY EPITHELIAL NEOPLASMS OF THE KIDNEY***John B. Hazard, M.D.*

Renal neoplasms with epithelial components may be classified as follows:

## A. Benign

1. Adenoma
2. Papilloma

## B. Malignant

1. Embryoma (Wilms' tumor), including embryonal carcinoma and sarcoma.
2. Renal cell carcinoma (hypernephroma).
3. Transitional cell carcinoma.
4. Squamous cell carcinoma.
5. Mucinous adenocarcinoma.
6. Tubular carcinoma.

Certain embryologic features are of interest in the derivation of some of these neoplasms. The renal 'cap' provides the genesis for renal cell carcinoma and adenoma and is formed from the metanephros. Papillomas and carcinomas of the renal pelvis and adenomas and carcinomas of the collecting tubules, arise from adult structures whose anlage is the Wolffian duct. Embryoma (Wilms' tumor) finds its origin in remaining primitive elements of the renal blastema (mesonephros).

Adenomas of the kidney are most always of renal cell origin, only rarely being derived from the collecting tubules. They are of two types: (1) Small adenoma, often multiple and nonencapsulate. (2) Large adenoma, solitary and with well-defined capsule. The small adenomas may be bilateral and may bear a genetic relationship to renal cell carcinoma. They vary in size from a few millimeters to 2 cm., the larger forms rare, and all incidental findings in the pathologic examination of the kidney. The majority are papillary, wholly or in part. The large adenomas may measure 10 cm. or more in size and are of much less common occurrence. They may be papillary or nonpapillary.

Papillomas are of transitional cell type and may be multiple in the renal pelvis. Similar tumors are often concomitant in the ureter and bladder. Transitional cell carcinoma and squamous cell carcinoma may find origin in these tumors.

Carcinomas of the kidney are divided into two general groups, one of renal cell origin, the other of transitional cell derivation. The renal cell carcinomas arise in the cortex of the kidney, are over 1.5 cm. in diameter and grossly may be circumscribed or infiltrating. They are yellowish, often with areas of hemorrhage and with zones of degeneration evidenced by necrosis and fibrosis. Histologically, the cells usually have well defined margins and clear cytoplasm, the so-called clear cell variant or hypernephroma. These neoplasms, however, are rarely of pure type, and in addition to the characteristics mentioned there are cells of smaller size with granular pink staining cytoplasm forming lumina or tubular structures, spindle cell forms, at times simulating sarcoma, and areas of papillary architecture. The pure types are rare; they may be found as the clear cell carcinoma, granular cell carcinoma, or tubular carcinoma of the kidney. The renal cell carcinomas often invade the renal pelvis and extend into the veins, at times invading the main renal vein or even growing into and filling the inferior vena cava. Occasionally the renal capsule is penetrated and the neoplasm extends into the perirenal fat tissue. Distant metastasis occurs most commonly to bones, and lungs, but other sites may be secondarily involved; several instances of thyroid involvement have been recorded. Solitary metastases may occur and there have been reports of long survival following removal of the metastatic tumor and the primary neoplasm of the

kidney. Transitional cell carcinomas are derived from the epithelium of the renal pelvis and may occur as a neoplasm formed of tissue resembling the usual epithelial lining of the pelvis, or as squamous cell carcinoma. As to gross appearance, they may be villous or solid. They may grow superficially or show definite infiltrating properties. They are generally of gray or gray-white color. Microscopically, the transitional cell type is most common and a papillary configuration usual, although at times they may show a non-papillary arrangement. They invade veins less frequently than renal cell carcinoma, but have a greater tendency to extend into the tissues about the renal pelvis. The ureter and bladder may show concomitant occurrence of transitional cell carcinoma which may be regarded as either implant or as tumors of multicentric derivation. The neoplasms metastasize to regional lymph nodes and distant organs. Squamous cell carcinoma of the renal pelvis has an especially poor prognosis.

Embryoma is commonly known as Wilms' tumor and belongs to the group of mixed neoplasms. In gross appearance it is of large size, circumscribed, often encapsulate and gray to yellowish in color. Microscopically, it is of mixed structure, growing as embryonal carcinoma, as embryonal sarcoma, or at times as an undifferentiated cell type defying classification. Primitive elements simulating embryonic glomerular structures are found in typical specimens. The mesenchymal elements may at times predominate to form a firm, tough tumor mass which, because of its encapsulate appearance, may be grossly mistaken for a fibroma. However, if sufficient sections are taken, embryonal elements are always found to be present. These tumors metastasize regionally and often show extensive distant metastases.

There are certain morphologic features which bear a relation to the prognosis of primary carcinoma of the kidney. Among those indicative of a poor prognosis are: direct extension to perirenal tissues; microscopic dedifferentiation; growth activity as evidenced by frequency of mitoses; angio-invasion, especially by transitional cell carcinoma and the more dedifferentiated forms of renal cell carcinoma.

---

## ELECTROLYTE AND CHEMICAL FEATURES OF UREMIA

*A. C. Corcoran, M.D.*

The chemical features of uremia can be classed as (1) those due to retention of substances in blood, (2) those due to uncontrolled excretion of substances in urine, and (3) reactive changes.

In uremia due to acute and total loss of renal function, e.g. in lower nephron nephrosis, the most important changes are due to retention. Potassium intoxication is a common immediate cause of death. Acidosis, anemia, and hypocalcemia are not major features.

In contrast in slowly developing uremia, the clinical syndrome is marked by a preponderance of evidences of central nervous disturbance. These have been ascribed to a hypothetical "uremic toxin," the activity of which is somehow associated with protein catabolism. Azotemia can reach tremendous levels. Acidosis, due in part to failure of renal ammonia-formation and in part to retention of phosphate and sulfate, is an important complication, and anemia is often severe. The reactive changes of parathyroid hyperplasia due to phosphate retention may be of both diagnostic and clinical significance. Inability to retain sodium, water, and even potassium may also precipitate remediable complications. Interestingly, a similar inability to retain electrolytes occurs during the first days of recovery from acute anuria.

**NEPHROSCLEROSIS AND HYPERTENSIVE RENAL DISEASE***Robert D. Taylor, M.D.*

The nephrosclerosis of hypertensive disease differs from nephrosclerosis of old age only in the period of life at which it becomes apparent and the rate with which it progresses. The changes consist of hyalinization of the media and proliferation of the intima so that the vascular lumen is greatly narrowed and eventually obliterated. The natural consequence is impaired function and death of the tissues nourished by the diseased vasculature.

In the case of essential hypertension this process is slowly progressive and only 2 to 4 per cent of such patients die of renal failure. Cardiac or cerebral diseases are more common causes of death. In the malignant phase the sclerotic process is replaced by a much more fulminating process of necrosis. There is some evidence that this is due to sudden and sustained elevation of arterial pressure, while some observers feel it is the result of a specific necrotizing agent elaborated by the kidney. Be that as it may, the end result is necrotizing arteriolar inflammation, and well over 75 per cent of patients with malignant hypertension die of renal failure.

The laboratory and clinical signs of the renal disease of hypertension are characteristic. Because of arteriolar sclerosis and resulting decreased perfusion, tubular function is impaired relatively earlier than glomerular function which is maintained at or above normal by increased filtration pressure resulting from hypertension and increased arteriolar resistance to the flow of blood leaving the glomeruli. Hence, the ability to concentrate urine will be decreased while the urea clearance may be comparatively normal. Thus, one of the early signs of hypertensive renal disease is nocturia.

The urinary sediment is not greatly different from the normal in essential hypertension and proteinuria may amount to less than 0.4 Gm. per 24 hours. In the malignant phase of the disease there is hematuria, often gross, and proteinuria greater than 0.4 Gm. per 24 hours. Filtration rate falls rapidly and azotemia soon appears.

**DERMATOLOGIC PROBLEMS ENCOUNTERED IN MANAGEMENT OF URINARY TRACT DISORDERS***Earl W. Netherton, M.D.*

Pruritus commonly accompanies uremia regardless whether this has developed from nephritis, prostatic hypertrophy, or cardiorenal disease. Pallor and discoloration of the skin may result from edema of the tissues in nephrosis or the nephrotic stage of glomerulonephritis. Sallowiness and pallor are often seen in the terminal stage of glomerulonephritis. Hemosiderin may be deposited on the skin as a result of purpura which may be associated with several urinary tract disorders. Urea frost may be seen on the skin in terminal stages of uremia and is best observed in negroes.

Numerous other manifestations on the skin are often associated with uremia including xeroderma, eczematoid dermatitis, miliaria crystallina or sudamen, and acne vulgaris and rosacea, and pyoderma. Impetigo, furunculosis, and other infections are at times aggravated by uremia. Keratoderma blennorrhagicum is characterized by urethritis, arthritis, and an eruption consisting of vesicles, vesiculopustular and adherent waxy, semitransparent, thick, horny crust. The areas of predilection are the hands, feet and distal portions of the extremities. It is caused by the gonococcus. Reiter's disease, which is a condition of unknown origin, is characterized by conjunctivitis, arthritis, and urethritis and is at times associated with lesions simulating those of keratoderma blennorrhagicum. In paroxysmal hemoglobinuria urticarial and vesicular

lesions on the skin may develop. Porphyruria, which is a rare constitutional anomaly, is associated with sensitivity of the skin to sunshine. Exposure to the sun may produce vesicular and bullous eruptions in this disease. Perhaps the most common dermatologic manifestation associated with urinary tract disorders are the drug eruptions resulting from treatment of the underlying urologic disorder. Eruptions resembling purpura, erythema multiforme, urticaria, eczematoid dermatitis, scarlatina or measles are not uncommon results of drug therapy.

---

## THE HEART AND ELECTROCARDIOGRAM IN UREMIA

*William L. Proudfit, M.D.*

The characteristic electrocardiographic alterations in uremia are due to disturbance in the electrolyte balance and pericarditis.

Hypocalcemia is frequent in uremia. It is due to the retention of phosphates secondary to kidney disease. The characteristic electrocardiographic finding in hypocalcemia is an unusual prolongation of the Q-T interval. The form of the T-waves is normal, but there is an unusually long, flat RS-T segment.

Hypopotassemia may occur in uremic patients. The Q-T interval is prolonged as in hypocalcemia, but the configuration of the RS-T segments and the T-waves is characteristic. In contrast to hypocalcemia, the RS-T segment is of normal duration, and the Q-T interval is prolonged due to increased duration of the T-waves. Prominent U-waves are frequent in hypopotassemia, and at times the U-waves appear to be incorporated with the T-waves, causing further apparent prolongation of the Q-T interval. These changes disappear entirely after the administration of potassium salts by mouth or parenterally.

Hyperpotassemia may develop, either as a result of increased tissue breakdown with retention of the potassium liberated or retention of potassium salts given by mouth. The heart sounds may be muffled. The earliest electrocardiographic change secondary to hyperpotassemia is an increase in the height of the T-wave with a peaking of the crest of the wave. Subsequently the QRS complex may become wider, and finally auricular asystole may appear. The heart stops in diastole.

The clinical and electrocardiographic changes of fibrinous pericarditis in uremic patients differ in no way from those in nonuremic subjects. In some cases of uremic pericarditis the electrocardiographic changes may not be striking, or may be absent.

Combinations of these disturbances may occur in uremia. The presence of changes indicative of both hypocalcemia and hyperpotassemia is highly suggestive of uremia.



## APPOINTMENTS

Dr. Fred R. Tingwald has been made a member of the staff in the Department of Otolaryngology. Dr. Tingwald was graduated from the State University of Iowa in 1937 and received the M.D. degree from that institution in 1938. Following a two year internship, he served a residency in pathology for one year at the Youngstown (Ohio) Hospital Association. Dr. Tingwald was with the U. S. Army from 1941 to 1945. He then returned to the University Hospital, Iowa City, where he spent three years as resident in otolaryngology. On completion of this residency he was made assistant in otolaryngology at the State University of Iowa College of Medicine. Dr. Tingwald was certified by the American Board of Otolaryngology in 1948.

On March 20, Dr. Willem J. Kolff joined the assistant staff in the Research Division. Dr. Kolff studied at the University of Leyden and was assistant in the Department of Pathology at that university. On completing his medical studies in 1938, he was assistant in the Department of Internal Medicine at the University of Groningen and in 1941 became head of the medical department of a small municipal hospital in Kampen, Holland. Dr. Kolff received his doctor's degree at the University of Groningen in 1946. During 1947 he made a lecture tour of four months in the United States, received the Amory Award in Boston presented by the American Academy of Arts and Sciences, and was made an honorary fellow of the American Medical Association. In 1947 Dr. Kolff's monograph "New Ways of Treating Uremia" was published by J. and A. Churchill, London.