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Diagnosis and management

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The clinical syndrome [of acute renal failure] may be recapitulated briefly. In most cases the patient has been buried beneath fallen masonry or heavy debris and, on release, may appear well except for swelling of the affected limb. Should shock develop, the blood volume has usually been restored to a normal figure by transfusion and as a rule been well maintained. Some of these patients pass dark-coloured, smoky or red urine which contains albumin and gives a positive benzidine reaction, and on spectroscopic examination shows the absorption bands of myohemoglobin (Bywaters et al). The sediment is full of granular debris and brown pigmented casts, but only rarely shows red blood corpuscles. Subsequently oliguria or anuria may develop, and there is an increase in the concentration of urea, and of phosphate and potassium in the blood. Death may take place about the end of the first week, or recovery may follow upon a diuresis which occurs about this same time. With either course there is a falling off in the excretion of pigment and of casts, which become more cellular in character.

Although in the majority of cases there has been marked crushing injury of muscle, it is to be noted that a similar condition has been found in cases of muscular ischemia of different origin.

E. G. L. Bywaters, and J. Henry Dible
The renal lesion in traumatic anuria,
J. Path. and Bact. 54:111, 1942.

Foreword

Acute renal failure is a central theme of modern nephrology. Richard Bright did not recognize it and Volhard and Fahr did not understand it. Our view of it in 1969, which Dr. Robert Muehrcke presents so well in this book, starts with Eric Bywater's work, in 1940, on the brave fire-fighting citizens of London crushed by the falling walls and debris of buildings blown apart by the Nazi air force during the Battle of Britain. At that time, across the English Channel in Nazi-occupied Holland, a patient and ingenious Dutchman, Willem Kolff, was planning and developing machines that would do the work of the kidneys for the body, while the patients' organs, hopefully, were regenerating cells and lost functions destroyed by one or another of myriad aggravated bodily insults. Soon after 1945, when the war had ended, surgeons, obstetricians, industrial physicians, and toxicologists began to recognize that their patients, ill with acute renal failure, required modern treatment in special centers equipped to deal with their unique problems. These sprang up in Amsterdam, around Borst; in London, around Bull; in Copenhagen, around Iversen and Brun; in Boston, around Merrill; and in Cleveland, around Kolff. Borst and Bull developed conservative dietary regimens to save lives. Merrill and Kolff built practical kidney machines to do the job. The classical histologic studies of Lucké and the nephron dissections of Jean Oliver give no inkling of the early stages of renal pathology in the syndrome. Iverson and Brun developed renal biopsy to look for the common thread of pathophysiology in early or developing cases, and later Danish workers developed the radioactive xenon technique to look into renal blood flow failure as an etiologic factor in the disorder. Meanwhile, Merrill's work on potassium intoxication made nephrologists acutely aware of water and electrolyte disturbances as part of their specialty. By 1959 Doolan had developed a system of peritoneal lavage, which was perfected by nephrologists and anonymous colleagues in the pharmaceutical industry. Peritoneal dialysis brought the treatment of acute renal failure, except for the complicated cases, back to the community hospital.

From these beginnings Merrill and Hume began renal transplantation in twins

and revitalized the science of immunology. From these beginnings Scribner developed treatment for patients moribund with end-stage kidney disease by repeated dialysis, and made us ask "What is death?" and "Who shall live?" Dr. Robert Muehrcke in his scholarly book brings to bear his wide research and clinical experience and his deep knowledge of renal pathology to the story of acute renal failure outlined above. He has written a practical book of particular value to doctors in community hospitals, who will help patients by what they will learn from it.

This marvelous story of thirty years of research work and the practical results therefrom—which will continue to save innumerable lives in the future as it has in the past—would not have been written if Dr. Muehrcke's special education in clinical nephrologic research and his research on renal disease had not been supported, since 1950, by funds from the National Institutes of Health. The work could never have been written *now* without past U. S. Governmental research support to Doctors Kolff, Merrill, and Scribner, and particularly to the hundreds of other investigators whose names are listed in the bibliography. We may well ask in this age of restricted funds for renal and other clinical research, "What of the future?"

Robert M. Kark, M.D.

Preface

Since 1960, clinical nephrology has gradually become recognized as a well-established medical specialty. It has been defined as a comprehensive study of renal structure and function in health and disease, including the prevention and treatment of diseases involving the kidney and urinary tract. The development of an important diagnostic tool, the renal biopsy, began a steady, rapid, and burgeoning accumulation of basic knowledge on the kidney. The use of renal biopsy sharpened the physician's diagnostic acumen and established clinical nephrology on a firm footing. The strongest stimulus to the growth of nephrology has been the advent of dialysis and transplantation.

In this book, renal biopsy is applied to a dynamic and vivid correlative cinematographic study of structure and function in patients ill with acute oliguric renal failure. Emphasis is placed on the diagnosis of this well-established clinical syndrome, its meticulous treatment, and its dread consequences. This book is directed to all in medicine interested in patients with renal failure. It is directed particularly to the student, the practicing physician, the internist, the nephrologist, the urologist, and the pathologist.

This book illustrates the vast spectrum of acute oliguric renal failure: the complex etiology, the numerous pathogenic conditions, the tedious management, and varied prognoses in relation to the ever-changing renal morphology. I do not mean for this book to be an encyclopedia on acute oliguric renal failure. It is meant to serve as an illustration of the broad variation in the clinical course of patients with acute oliguric renal failure and to relate these clinical functional abnormalities to the numerous observations on renal structure as made by serial renal biopsy. The book emphasizes the natural history of the numerous ramifications of acute oliguric renal failure and the adverse effects of chemicals and drugs in producing functional and structural changes. Current medical progress in dialysis and transplantation is described in view of beneficial as well as adverse effects on patients with acute renal failure.

I am most grateful to Dr. Robert M. Kark, Dr. Geoffrey Kent, Dr. J. Charles

McMillan, Dr. Conrad L. Pirani, and Dr. Harry Lerner, and to research fellows, residents, interns, nurses, and dietitians on the medical wards of research and educational hospitals of the University of Illinois College of Medicine, Presbyterian–St. Luke's Hospital, Chicago, and West Suburban Hospital, Oak Park, Illinois. Acknowledgment is given these individuals for the care of patients discussed in this book and for their clinical and morphologic data.

Drs. Kark and McMillan made major contributions in reviewing the final manuscript. Dr. Pirani, of the Michael Reese Institute of Pathology, made available special morphologic studies. Mrs. Sofia Michevicius and Johanna Puniska provided technical assistance with electron microscopic studies and special stains. Mrs. JoAnn Cooney typed and edited the manuscript.

Robert C. Muehrcke, M.D.

Contents

Chapter 1

Introduction

Acute oliguric renal failure was first recognized by physicians at least 100 years ago.[252] Like many other clinical disorders, it remained dormant in medical literature except for sporadic reports in the English literature by such pathologists as Councilman[242] and Kimmelsteil[627] or in the German literature by Frankenthal[392] and Minami.[781] However, it was not until World War II that Eric Bywaters (Fig. 1-1) permanently established it as a clinical syndrome.[188-191]

Today acute oliguric renal failure is a well-substantiated clinical syndrome that occurs in a patient with previously healthy kidneys and that is characterized by a sudden decrease below 400 ml (less than 17 ml/hr) in the adult and 50 ml in the child in daily urinary output delivered to the urinary bladder. Acute oliguric renal failure is associated with acute clinical and biochemical manifestations of abnormal renal failure.[375] In some patients acute renal failure may not be associated with oliguria but rather with a "high urinary output" (nonoliguria).[996,1052a] In time both conditions can be reversible, either spontaneously by diuresis or by proper and effective management. On the other hand, acute renal failure can be irreversible, can produce a progressive deterioration in the clinical and biochemical status of the patient, and can lead to death.

The reversibility of acute renal failure depends on several important conditions. The most important is early diagnosis with differentiation from chronic "end-stage" renal disease, renal circulatory failure (prerenal), and obstructive uropathy (postrenal); it can also occur superimposed on chronic renal disease. Once an exact diagnosis is made, prompt and adequate intensive management must follow. An all-important factor in the outcome of the patient with acute renal failure is the pathophysiologic process, especially the specific site and severity of renal damage. There are few clinical disorders that demand of the physician scientific knowledge, practical skill, and clinical common sense as does acute renal failure. The gravity of the disorder and its complete and dramatic reversibility greatly tax physicians' ability; yet, he may experience tremendous gratification once the patient recovers.

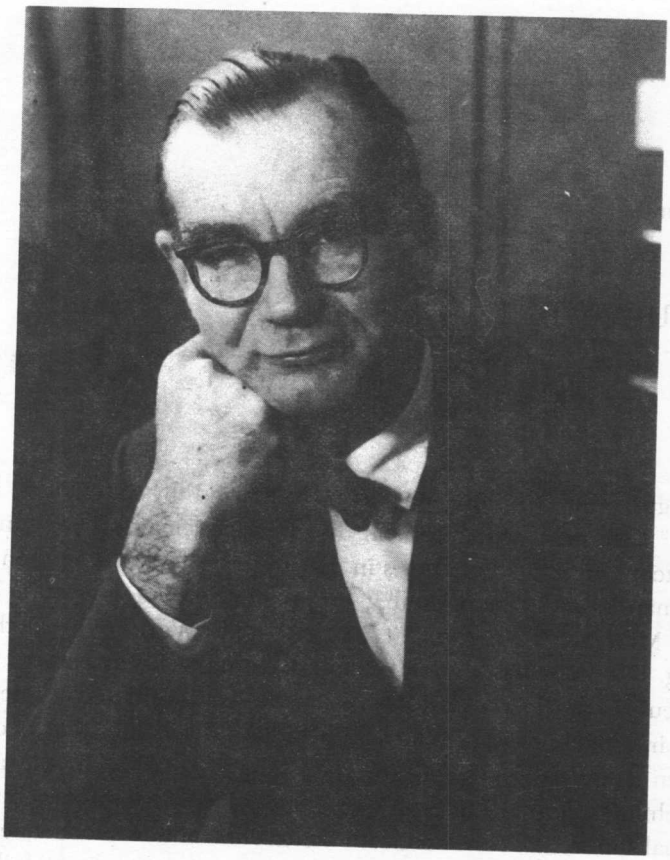

Fig. 1-1. Professor Eric G. L. Bywaters of the Royal Post-Graduate Medical School. In 1942 he described the clinical syndrome of acute oliguric renal failure that roused considerable interest of physicians throughout the world.

Acute oliguric renal failure as known today is a by-product of military and civilian casualty medicine from World Wars I and II. It has long been known to result from shock.[486] Although shock was effectively treated, progressive and fatal renal insufficiency contributed significantly to the final outcome of the battle casualty. During World War I, studies made on combat and civilian casualties with shock revealed the frequent occurrence of renal involvement with progressive azotemia and death.[781] In 1939, Jeghers and Bakst reviewed acute renal failure under the term "extra-renal azotemia."[858] These reports attracted little attention or interest from the medical profession.

During the years 1939-1945, Bywaters and colleagues[188-191,325] aroused considerable attention and stimulated the military physicians' interest in acute oliguric renal failure. During the 1940 bombardment of London, they studied air raid casualties injured by fallen masonry or heavy material. Their patients

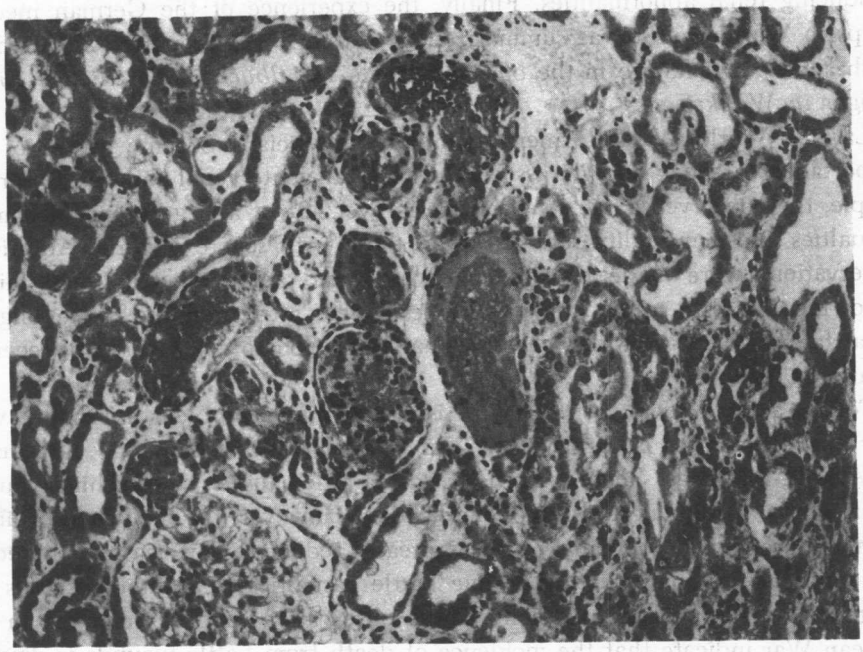

Fig. 1-2. "Crush kidney" described by Bywaters. Patient with acute anuria was found to have acute tubular necrosis. Numerous hemoglobin casts were noted within the renal tubular lumen. Note the necrotic tubules filled with cellular debris and pigmented casts. There were tubules with regenerative changes. There was considerable interstitial edema with mild inflammation. The glomerulus was unremarkable. (H & E × 240.)

recovered from shock but sustained crushing and compressing muscle injuries. Renal insufficiency followed and, in many, was fatal. They designated this disorder the "crush syndrome." At autopsy they found acute necrosis of renal tubules and blanched necrotic muscle. Bywaters' original and accurate drawings of abnormal renal morphologic findings are most impressive and should be reviewed by those interested in this disorder (Fig. 1-2).

Originally Bywaters and associates thought that the crush syndrome was a "hitherto undescribed condition." However, later he called attention to previous reports in the German literature and acknowledged them in a chapter of *History of World War II*, published in 1953.[194] The "compression muscle necrosis with renal failure syndrome" was first described by Frankenthal[392] in 1916 and again 2 years later when he reported a review of thirty patients with muscle necrosis and enlarged kidneys.[393] That same year, Kuttner[657] reviewed the entire subject and added seven patients with compression muscle necrosis. In addition, he referred to Colmers'[229] reports of patients suffering compression muscle necrosis and renal failure in the Messina earthquake of 1909.

The most complete pre–World War II report of acute renal failure was made by Minami in 1923.[781] He suggested that myohemoglobinuria was involved in

producing renal abnormalities. Finally, the experience of the German medical corps in World War I was summarized by Kayser.[614] He reported 126 patients with acute renal failure in the official German *Handbuch der arztlichen Erfahrungen im Weltkriege.*

Late in World War II American military physicians became aware of the importance of shock and its association to fatal acute renal failure.[781] For example, they observed acute renal failure in over 40% of a large group of combat casualties and a mortality rate of 90% in those with severe oliguria. Additional observations were made by Mallory, who found acute oliguric renal failure following shock in army battle casualties.[737] He attributed the acute oliguric renal failure to the considerable time that elapsed before the casualty received treatment for shock.

Today, acute oliguric renal failure is still a major problem associated with war and other mass catastrophes.[180] For example, during the 1960 earthquake in Agadir, Morocco, acute oliguric renal failure caused by crushing muscle injuries was a frequent and fatal complication. However, the incidence of acute renal failure in the Vietnam War was greatly reduced. This was attributed to the rapid air evacuation of front line battle casualties to station hospitals for prompt and appropriate treatment. These observations and those made in the Korean War indicate that the incidence of death from battle wounds is directly related to the incidence of acute renal failure. The greater the percentage of acute renal failure the greater the number of deaths from war wounds.

In civilian life acute renal failure is by no means related exclusively to catastrophes. In general, traumatic shock produces an extremely small proportion of acute oliguric renal failure. Because the causes of acute oliguric renal failure are innumerable and diversified, the syndrome becomes very important to physicians in every branch and speciality of medicine.

DIFFERENTIAL DIAGNOSIS OF ACUTE OLIGURIC RENAL FAILURE

The physician must make a prompt differentiation between sudden oliguria or anuria caused by acute renal failure and chronic "end-stage" renal failure.[942] Patients with acute renal failure may not display the typical course, in which there is an onset stage or in which oliguria may not be striking.[339,1057] For further differentiation it seems important to subdivide acute oliguric renal failure into three distinct clinical groups: acute parenchymal disease, acute renal circulatory failure (prerenal),[85] and ureteral obstructive uropathy (postrenal).

Prompt and accurate differential diagnosis is very important for two reasons. First, if acute circulatory failure is not corrected it may progress to parenchymal lesions. Second, hasty and poorly considered management using fluid and electrolytes may be extremely hazardous if parenchymal abnormalities are present. The prerenal disorders include renal circulatory insufficiency due to a variety of causes: acute myocardial infarction, dehydration, and electrolyte and acid-base

Table 1-1. Differential diagnosis of acute renal failure from water and electrolyte depletion

Clinical features	*Acute renal failure*	*Water and electrolyte depletion*
History of excessive salt or water loss	Usually absent	Present
Precipitating factor	Present	Absent
Thirst	At first usually absent	Present
Dryness of mouth	Absent	Present
Hyponatremia without evidence of NaCl depletion	If present—diagnostic	Absent
Hypernatremia	Usually absent	If present very helpful
Urinary specific gravity	Usually 1.010 higher in glomerular disease	1.010 usually excludes
Blood urea nitrogen (BUN) BUN/creatinine ratio	High value favor this diagnosis	Usually only slightly elevated
Urinary chloride (mEq/L)	10 to 50	Over 50
Urinary–plasma urea ratio	Less than 5 : 1	Greater than 10

deficiencies such as hyponatremia, hypopotassemia, and acidosis. Clinical features helpful in differentiating dehydration or water depletion from acute oliguric renal failure are listed in Table 1-1.

In the differentiation of prerenal failure from acute oliguric renal failure, 1 liter of 5% glucose in water may be infused over 30 to 45 minutes into a patient not overhydrated or edematous. If the patient has prerenal dehydration, the urinary specific gravity decreases and the urinary volume increases. In patients with prerenal circulatory failure and daily urine volumes less than 400 ml because of dehydration, the urinary specific gravity is approximately 1.030 or greater with an osmolarity of 1,200 milliosmols per liter (mOsm/L). The ratio of urinary urea to plasma urea is usually greater than 10. In "acute tubular necrosis" or severe parenchymal disease the urinary specific gravity approaches 1.010 and the ratio of urinary urea to plasma urea decreases to less than 5 to 1.[454]

First, the physician must exclude all precipitating episodes such as medical and surgical conditions known to be associated with acute renal failure. Then he may concentrate on the possible preexistence of chronic renal disease, which can be done by making careful inquiries into a history of previous renal disease. The best clues are previous hematuria, proteinuria, hypertension, edema, muscle cramping, twitching, toxemia of pregnancy, urine-like taste in the mouth, recurrent renal infections, and the chronic ingestion of nephrotoxic drugs such as analgesic agents.

Physical findings suggestive of chronic renal failure include hypertension, skin discoloration caused by retained urinary chromogen, pallor, ammonia on the breath, red eyes,[99] funduscopic abnormalities, cardiomegaly, pericardial friction rubs, flank pain or tenderness, gross edema, flapping tremor, uremic

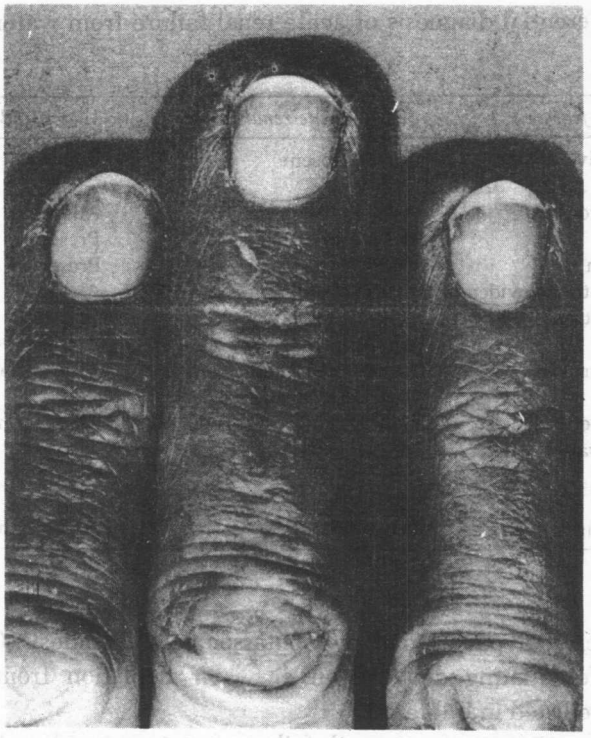

Fig. 1-3. White fingernails, described by Dr. Richard Terry, indicate chronic disease, usually of the liver or the kidney. This clinical finding can be used to distinguish acute from chronic renal failure.

frost, half-and-half nails,[699] white fingernails (Fig. 1-3) or fingernails with a single transverse white band (Fig. 1-4), periorbital edema, and circumflex oral pallor. In prerenal failure caused by dehydration, numerous physical findings are noted. They are decreased turgor of the skin—especially the forehead skin in the elderly—and a dry parched tongue. (Care should be taken to ensure that the dry tongue is not the result of mouth breathing.)

Laboratory findings suggestive of chronic renal diseases are anemia, elevated serum creatinine,[144] elevated serum phosphorus, decreased serum calcium, normal leukocyte counts, and low serum proteins, especially albumin. In prerenal failure caused by dehydration, hematocrit and total protein may be elevated. In addition, the serum uric acid level has been found to be increased out of proportion to the urea nitrogen levels; there has been fixed urinary specific gravity and a serum and urinary urea ratio of more than 10 to 1; and small kidneys have been disclosed by either x-ray studies or by a renal scan study using orthoiodohippurate (Hippuran I^{131}).[199] Finally, a percutaneous renal biopsy study may provide the exact renal pathology.[805a]

It must be pointed out that acute oliguric renal failure can be superimposed

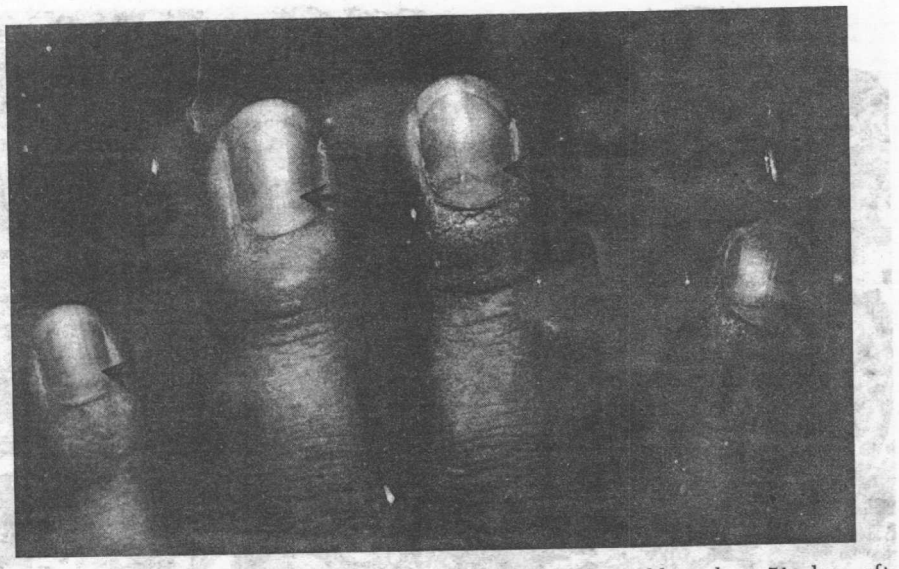

Fig. 1-4. Single transverse white strip in fingernails of 23-year-old student 51 days after onset of oliguria. He sustained a crush injury with intra-abdominal hemorrhage due to fractured liver. Oliguria lasted for 14 days before diuresis occurred.

on chronic renal diseases. For example, patients with advanced renal insufficiency caused by diabetic glomerulosclerosis or by amyloidosis may develop superimposed renal vein thrombosis. This occurs by the abrupt and massive thrombosis of the small intrarenal veins. As a result, the patient develops sudden and absolute anuria.

The clinician should carefully evaluate the patient's chart to appraise intake-output records, blood loss, fall in blood pressure, and the prolonged administration of large quantities of fluids containing glucose. In addition, the physician should check on drugs administered to the patient, surgical reports, hypovolemia, and peripheral vasoconstriction.

The differential diagnosis of acute oliguric renal failure from end-stage renal disease can be most difficult. This is illustrated by the following two cases. In the first patient, chronic end-stage renal diseases could be diagnosed only by percutaneous renal biopsy. Based on a diagnosis of chronic renal disease, prolongation of life by peritoneal dialysis was interrupted. In the second patient, acute anuria resulted from renal vein thrombosis associated with renal cortical necrosis; the nephrotic syndrome was caused by primary amyloidosis.

CASE PRESENTATION

R. S., age 50 years, was transferred to Presbyterian–St. Luke's Hospital on August 1, 1962, with acute oliguric renal failure. He was found to have had "congenital" renal disease in his childhood. On June 15, 1962, he developed fatigue and epigastric pain. His family physician admitted him to a community hospital. He was evaluated and was found to have azotemia.

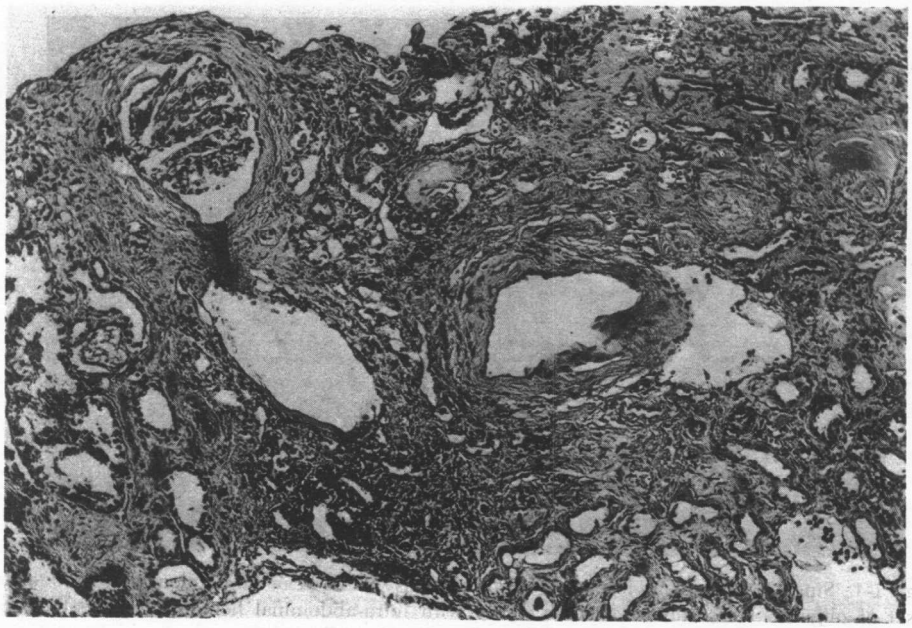

Fig. 1-5. Advanced chronic renal disease. A 50-year-old executive had sudden oliguria. Congenital renal disease was diagnosed in childhood. On the eleventh day of oliguria a renal biopsy study was done to determine the acuteness of renal failure. Chronic renal disease was found. Small cystic lesions were noted with chronic findings of tubular atrophy and interstitial fibrosis. (H&E ×225.)

On physical examination he had marked edema of the neck and face, with periorbital edema and hypertension. His blood pressure was 190/118 to 190/120 mm Hg. His hematocrit was 32%. The leukocyte count was 8,250 per mm^3. Urinalysis revealed gross hematuria, mild proteinuria, and leukocyte casts. The blood CO_2 was 24.5 mM/L. The serum potassium was 5.0 mEq/L. The serum sodium was 135 mEq/L. The blood urea nitrogen (BUN) was 150 mg per 100 ml and rose to 347 mg per 100 ml. The serum creatinine was 9.9 mg per 100 ml and rose to 12 mg per 100 ml.

On admission he received a rapid injection of 25 gm of a 20% mannitol solution without increased urinary output. Peritoneal dialysis was started. The BUN dropped from 150 mg per 100 ml to 96 mg per 100 ml. On August 11, 1962, a percutaneous renal biopsy was done. Chronic pyelonephritis with polycystic renal disease was found (Fig. 1-5). Because of the finding of chronic renal disease, peritoneal dialysis was discontinued. He developed pulmonary edema and was rapidly digitalized. On August 23, 1962, the BUN was 143 mg per 100 ml and the serum creatinine was 16.5 mg per 100 ml. He died on September 5, 1962.

At autopsy the renal biopsy findings were confirmed; bilateral polycystic renal disease was found. On microscopic study there was chronic pyelonephritis.

The following case illustration concerns a patient who presented with all features of the nephrotic syndrome, which was believed to be the result of amyloidosis. He was in shock because of a severe upper intestinal tract hemorrhage. Oliguria followed; a differential diagnosis was between acute tubular necrosis and renal vein thrombosis as the cause of sudden oliguria.