Colby PYELONEPHR[redacted]S

PYELONEPHRITIS

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PREFACE

Pyelonephritis is one of the most important present problems of modern medicine. Only within recent years has its seriousness been generally recognized. Studies of the pathology and the clinical course of pyelonephritis have made clear certain facts that previously were not appreciated and, although progress has been made in a better understanding of this disease, many of its problems remain unsolved.

When pyelonephritis is acute its symptoms are characteristic, diagnosis usually is evident, the response to modern treatment is excellent, and mortality is low. Acute pyelonephritis is no longer the problem of past years. Chronic pyelonephritis is different. Its symptoms often are vague and misleading, diagnosis may be difficult, treatment is unsatisfactory, and renal damage can be so severe that the result is uremia and death.

Recent literature concerning pyelonephritis has been extensive. Opinions expressed have varied to such an extent that it is apparent that there are many things about this condition that still are unknown. These many reports, however, have emphasized the frequency and seriousness of pyelonephritis and have made clear one important fact—that every effort should be made to prevent the disease from becoming chronic. This means early and adequate treatment of acute pyelonephritis.

This book describes the background of pyelonephritis and sum-

marizes what we now know about the disease. The development, anatomy, and physiology of the kidneys are presented. The pathology, symptoms, diagnosis, and treatment of acute and chronic pyelonephritis are described. Separate chapters are devoted to pyelonephritis in infancy and childhood, in pregnancy, in diabetes, and to the association of pyelonephritis and hypertension. Much of the text is based upon our own experience with pyelonephritis at the Massachusetts General Hospital.

The book should be useful to students, general practitioners of medicine, and to the occasional internist who may know less about this disease than I. It is written from the point of view of a urologist.

My sincere thanks go to my secretary, Miss Frances Schwab, for her meticulous preparation of the manuscript, to Donald C. Withee of the photographic department of my hospital for his help in preparing the illustrations, and to Dr. Wyland F. Leadbetter for valuable suggestions.

F. H. C.

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PYELONEPHRITIS

A Russian-born laborer of 48 came to the hospital with the complaint of increasing exertional dyspnoea for six months. He had been perfectly well until three years before when severe generalized headaches developed. However, he had continued to work until the recent shortness of breath made this impossible. Six weeks ago his appetite failed, he was nauseated, vomited frequently, and became more and more drowsy. Never had there been any urinary symptoms.

Upon admission, he was severely dyspnoeic. The breath was uremic. His blood pressure was 200/110. Moist rales were present at both lung bases and the heart was enlarged. The neck veins were distended and there was ankle edema. He obviously was in congestive heart failure. Eye grounds: narrowed retinal vessels and flame-shaped hemorrhages.

Significant laboratory findings were a cloudy urine of low specific gravity (1.008) with albumin 4 plus and many red and white blood cells (R. and W.B.C.) and granular casts in the sediment. Urine culture, no growth. Nonprotein nitrogen (N.P.N.),

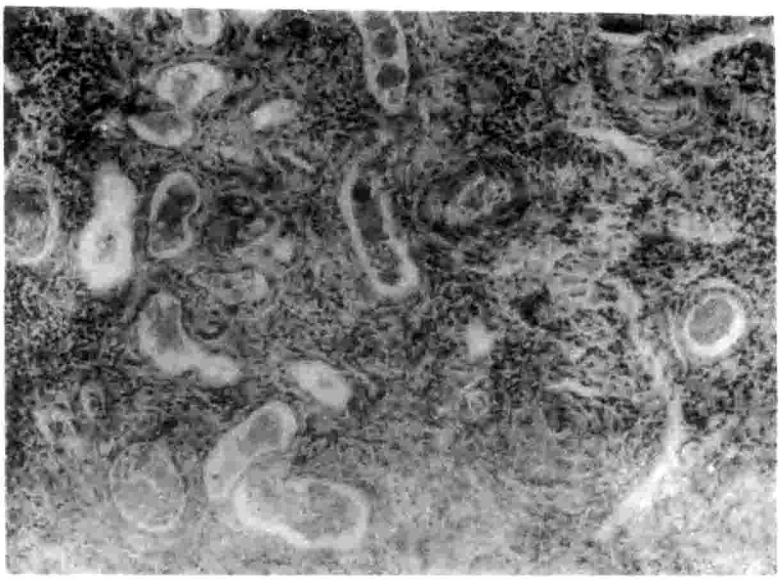

FIG. 1. Severe bilateral chronic pyelonephritis with hypertension. Death in uremia. Marked destruction of renal architecture with scarring, chronic inflammatory cellular infiltration and tubular dilatation with proteinaceous casts. Photomicrograph. Low power.

76 mg. per cent; CO_2, 21.5 m.eq.; Cl, 109 m.eq.; Ca, 9.0 m.eq.; P, 6.1 m.eq.; hemoglobin (Hgb.), 10.5 gm. Chest x-ray: cardiac enlargement and pulmonary edema.

His prognosis was considered to be grave, but he improved with digitalis and left the hospital, although the N.P.N. had risen to 82 mg. per cent. He became progressively worse with nausea, anorexia, muscular twitching, and disorientation. Within a month he was readmitted in advanced uremia, was comatose, and in 12 hours was dead.

At postmortem examination there was severe chronic pyelonephritis, cardiac hypertrophy, fibrous pericarditis, bilateral hydrothorax, and secondary parathyroid hyperplasia (Fig. 1).

This is the short history of renal failure, uremia and death from chronic pyelonephritis. The disease was insidious in nature, no urinary symptoms had preceded its onset, treatment was of no

avail, and an accurate diagnosis was made only at autopsy. *This was chronic pyelonephritis.*

The Past History of Pyelonephritis

For centuries pyelonephritis has been a common disease. Only within recent years, however, has it been generally appreciated that pyelonephritis, acute or chronic, has become one of the foremost problems in medicine. At present, the disease is recognized as an infectious process that involves not only the renal pelvis but chiefly the parenchyma of the kidney and particularly the interstitial tissues. In 1929 Wilson and Schloss (1) called attention to the fact that "pyelitis" was really a true suppurative lesion of the interstitial tissues of the kidney. This statement was based upon a postmortem study of 49 infants who had had pyuria. Pathological examination of the kidneys showed inflammatory foci in the interstitial tissues often adjacent to small blood vessels. Pyelitis obviously was a misnomer; the more correct term was pyelonephritis.

The contracted kidneys of chronic pyelonephritis had been described by Löhlein in 1917 (2). The natural history of the disease was suggested by many authors (3–5).

The publication of the clinical observations of Longcope and Winkenwerder (6) in 1933 built the foundation for the appreciation of the real character of chronic pyelonephritis. These authors emphasized the importance of recognizing this disease in its early stages, particularly in childhood, during the puerperium, and in obstructive lesions of the urinary organs. Their description of a small group of cases applies well today, particularly regarding the frequent occurrence in young women of recurring attacks of urinary infection accompanied by lumbar pain, cardiac hypertrophy, retinitis, nitrogen retention, occasionally elevated blood pressure, scanty urinary findings, pyelographic changes, uremia, and death.

Longcope observed that certain patients who died in uremia, supposedly from chronic Bright's disease, had, at autopsy, chronic pyelonephritis with shrunken kidneys and irregularly dilated renal pelves. He also noticed that some children who gave a

history of recurrent attacks of "pyelitis" and who died in uremia had chronic pyelonephritis. He realized that chronic pyelonephritis was different from the usual conception of Bright's disease and he emphasized the importance of chronic pyelonephritis as a cause of renal failure.

Most of Longcope's patients (7 of 9) were young women whose symptoms before renal failure often had been vague and slight but of long duration. Frequently, the history was one of poor health for many years with recurrent episodes of fever. Lumbar pain and cloudy urine accompanied these episodes. During childhood or adolescence pus or albumin had been present in the urine. The symptoms presented when these patients were first seen by a physician were those of renal failure. Medical advice was sought because of headache, loss of weight, lassitude, dyspnoea, nausea and vomiting, epistaxis, lumbar pain, and, at times, convulsions. *All were signs of renal insufficiency.* Anemia, sometimes severe, usually existed. Retinitis with hemorrhagic exudates often was present. Edema occurred only when there was cardiac failure. Cardiac enlargement or an elevated blood pressure were not always present but hypertension existed in over one-half of Longcope's cases. Urinary abnormalities occurred in all. Large quantities of urine were passed with the specific gravity fixed between 1.006 and 1.012. Only moderate traces of albumin were found and leukocytes almost always were present with few or no hyaline casts. *Escherichia coli* was the commonest organism found by culture. Distinct renal abnormalities were present in these cases as demonstrated by retrograde pyelography. The renal pelves were irregularly deformed and often slightly dilated. The calyces were distorted and blunted.

That serious renal damage was present in Longcope's small series was evident by renal function tests. Excretion of phenolsulfonephthalein often was less than 20 per cent. The nonprotein nitrogen usually was elevated and the urea clearance tests were lower than normal.

Five of Longcope's 9 patients died in uremia. At autopsy, the kidneys were smaller than normal, scarred, and distorted. The renal pelves were slightly dilated and inflamed in varying degrees.

On microscopic examination, areas of inflammation were present with marked replacement of normal kidney tissue by fibrosis.

It is evident that these early cases so well described by Longcope had advanced chronic pyelonephritis with considerable degrees of renal damage. His observations clearly showed that certain patients who died in uremia, supposedly from chronic Bright's disease, had chronic pyelonephritis. He also observed that some children who died in uremia, after a history of persistent so-called "pyelitis," had chronic pyelonephritis (7). Longcope's observations were an important contribution and an accurate description of chronic pyelonephritis as it exists today.

During the past thirty-odd years a great many authors have written about pyelonephritis. Certain communications in this mass of literature mark the progress that has been made in a better understanding of pyelonephritis. Although these studies have served to emphasize the frequency and importance of this disease and to give a clear picture of the pathological changes in the kidney, there still remain many unsolved problems.

In 1927 Braasch and Cathcart (5) made a study of 251 patients with chronic bilateral pyelonephritis. They emphasized the fact that symptoms often were vague or lacking and they described the typical pyelographic deformities that existed. In their experience, about one-third of these patients recovered, one-third were considerably improved, and one-third were not helped by treatment. Patients who had foci of infection removed fared better as a group than those in whom this was not done. Chown (3) in a study of pyuria in infants of two years of age or less also called "pyelitis" a misnomer since it seldom or never occurred without involvement of the kidney itself.

In 1929 Barash (8) favored an ascending route to the kidney for pyelonephritis in children and found *E. coli* the most frequent infecting organism. He also believed that focal infections were important contributing factors in etiology. In the same year Scott (9) reported 82 cases of blood stream infections following urological procedures. The urethra was said to be the portal of entry in 80 per cent. The mortality in these cases was 18 per cent and the commonest organism isolated was *E. coli*. Bacteremia with

chills following urethral instrumentation with positive blood cultures within a few minutes was reported also by Barrington and Wright (10).

At this time Campbell and Lyttle (11) in a report of 74 cases of ureteral obstruction in infancy, with pyuria usually the only diagnostic sign, called attention to the importance of urinary stasis as a predisposing and perpetuating cause of urinary tract infection. Ureteral obstruction was present in nearly 2 per cent of 2420 autopsies on pediatric cases.

The importance of an early recognition of pyelonephritis in children was stressed by Butler and Lanman in 1937 (12). They reported chronic pyelonephritis as a primary cause of death in about 2 per cent of 2043 autopsies, 63 per cent being under 2 years of age. Well over one-half of their children had some anatomical malformation of the urinary tract. The high incidence of pyelonephritis in children was emphasized along with its seriousness in infants with or without anatomical abnormalities. Chronic pyelonephritis, they stated, was the commonest cause of renal insufficiency with uremia. *A relationship between chronic pyelonephritis and hypertension was shown to exist.*

In a review of over 500 cases of pyelonephritis at the Mayo Clinic, Braasch (13) stated that the disease often is so mild and symptoms so vague that the condition is recognized only on urinalysis with culture and gram stains of the urinary sediment. About 20 per cent of his cases were said to recover without treatment. Secondary calculi formed in only 28 of 526 cases and their removal seldom was necessary. He also stressed the necessity of treating foci of infection and the importance of early and adequate treatment of acute infections.

The late effects of acute "pyelitis" in girls were reviewed by Wharton *et al.* (14) in a follow-up study of 30 patients. Nine had had one attack of "pyelitis" on an average of 13 years previously and, although 3 showed no abnormality, 9 had definite pathological changes in the urinary tract, although these girls were in good health. When there had been repeated acute attacks during the previous 10 years no permanent damage was found in any, but when these attacks were associated with persistent patho-

logical changes in the urinary tract all but 2 of 11 had continued symptoms. One had renal insufficiency, one ended with a shrunken, functionless kidney, and in 57 per cent there were definite urinary abnormalities. The authors stated that the effects of "pyelitis" often were more grave than had been expected.

In a study of 172 cases of chronic pyelonephritis by Nesbit and Conger (15) the diagnosis was made in 80 per cent by characteristic pyelographic changes or by pathological examination. Pyelograms were normal in 20 per cent. Girls predominated three to one and women two to one, but in the fifth to eighth decades men and women were even. Symptoms varied from 3 months to 20 years with cystitis the initial symptom in 61 per cent. It was felt that the diagnosis could have been made earlier in 84 per cent and that earlier treatment might have helped. Some degree of renal impairment existed in 75 per cent and was marked in 25 per cent. With progressive degrees of renal impairment, mortality increased and the response to treatment was poorer. Many cases, however, lived for years with little effect on renal function, blood pressure or pyelographic changes. At times, though, the disease took a rapid and fulminating course. After treatment, 37 per cent showed no great change, 34 per cent were improved in health and symptoms, but only 3 per cent became free of symptoms and subsequently had repeatedly normal urines. The authors felt that all patients with acute pyelonephritis should be treated, not only until they were symptom free, but until the urine was free of bacteria on many examinations.

Although the small contracted kidneys of advanced chronic pyelonephritis had been studied and reported early, particularly by German authors (2, 16), the studies of Weiss and Parker (17) were largely responsible for the recent interest in pyelonephritis. They described the vascular lesions of pyelonephritis as a feature of the disease since these were considered to be a factor in the production of hypertension. The relationship between renal and vascular changes and hypertension was as follows. (a) A mild degree of arteriosclerosis of both kidneys usually was associated with normal blood pressure. (b) A severe degree of arteriosclerosis in unilateral pyelonephritis might or might not be so associated.

(c) A severe degree of arteriosclerosis of both kidneys practically always was associated with severe hypertension. They considered that pyelonephritis was responsible for 15 to 20 per cent of cases of malignant hypertension.

Changes in the glomeruli with atrophy and hyalinization associated with pyelonephritis were described by Kimmelstiel and Wilson (18) in kidneys that showed arterial or arteriolar sclerosis.

With the stimulus provided by Weiss and Parker, more attention was directed to the pathology of pyelonephritis, combined with experimental work, in an effort to trace its origin. Unilateral pyelonephritis in rabbits was produced by Mallory *et al.* (19) by the intravenous injection of colon bacilli after partial ligation of one ureter. Acute pyelonephritis, similar to that in man, was produced in the partially obstructed rabbit's kidney in 25 per cent of the experimental animals. At the end of 2 months, the obstructed kidneys were markedly contracted and pale gray in color. No extensive pyelonephritis was found in the unobstructed kidney. These experiments demonstrated that urinary obstruction was a very important factor in the development of blood-borne pyelonephritis.

It was shown also by Bell (20) that the obstructive form of pyelonephritis was about 12 times as common as the nonobstructive type in autopsy material. In 32,360 autopsies, hydronephrosis was present in 1229 and pyelonephritis was present in 60 per cent.

The relationship between renal ischemia and hypertension was provided by the experiments of Goldblatt *et al.* in 1934 (21) by causing renal ischemia in dogs through narrowing the lumens of both renal arteries by means of adjustable clamps. Permanent hypertension was produced (22). If normal renal tissue was present, these experiments were not successful. There were two possibilities. As a result of renal ischemia a pressor substance was produced, but if a normal kidney was present this substance had no effect. The other possibility was that the pressor substance was neutralized by something produced by the normal kidney.

As Boyd (23) pointed out, in spite of this experimental evidence it has been shown that unilateral renal ischemia in man may result in hypertension and that pyelonephritis and hypertension

are associated and that occasionally in unilateral lesions the hypertension is cured by nephrectomy.

Homer Smith (24) took a cautious attitude in this respect. He felt that unilateral renal pathology might be the cause of hypertension in rare instances but that the 19 per cent of successes from nephrectomy and the fact that most urological disease did not cause hypertension, left a reasonable doubt about this hypothesis. If bilateral renal disease is present, as is usually so in advanced hypertension, nephrectomy may shorten life by the removal of an important fraction of total available renal function.

Since the production of hypertension by the pyelonephritic kidney is far from being completely understood, it can be stated with considerable emphasis that a careful evaluation of all available facts should be made before nephrectomy is considered.

It is well established that pyelonephritis is the result of invasion of the kidney by bacteria. The initial infection may be the beginning of a disease that can lead to renal failure, uremia, and death. The methods by which bacteria reach the kidneys have been debated for years. In obstructive lesions of the lower urinary tract with reflux of infected urine up the ureters the ascending route is obvious. The chills and fever with positive blood cultures that sometimes follow urethral instrumentation indicate that bacteria may reach the kidney by the blood stream. A spread of infection to the kidney from organs in the pelvis by the lymphatics has been a controversial subject but since most investigators have been unable to demonstrate lymphatic pathways by which this can occur such a route seems unlikely.

Acute pyelonephritis is readily recognized by its characteristic symptoms of chills, fever, loin pain, painful and urgent urination, and kidney tenderness. Modern therapy quickly relieves these patients but each attack of acute pyelonephritis may be serious because of the possible consequences. Repeated acute episodes mean that the initial infection has not been completely eliminated or that reinfection has occurred. In any event, repeated acute episodes of renal infection mean that progressive renal damage is taking place with the possibility of eventual renal failure.

Unlike acute pyelonephritis, chronic pyelonephritis often exists

without characteristic symptoms. Here, there may be little or no evidence of active infection and no local symptoms. Pallor, easy fatigability and loss of weight may be the only symptoms. A diagnosis is made largely by laboratory examinations. Large volumes of urine are passed with a low specific gravity, mild proteinuria, and with few leukocytes in the sediment. Pyuria often is intermittent and urine cultures may show no growth. However, repeated cultures and examinations of the stained sediment often reveal the presence of active infection. Pyelography may aid in the diagnosis by characteristic changes in the renal calyces and ureters but the pyelograms often have been normal in patients with chronic pyelonephritis.

It is agreed that acute pyelonephritis should be effectively treated by the appropriate chemotherapeutic agent after the infecting organisms have been identified and sensitivity tests have been done. The treatment of chronic pyelonephritis many times is unsatisfactory and intelligent therapy should take into consideration any complications that favor infection, the duration of the disease, arterial status and renal function. Pyelonephritis in diabetics often is impossible to cure. If hypertension exists, treatment is quite likely to be unsatisfactory.

From the foregoing it is apparent that progress has been made in a clearer understanding of pyelonephritis. Milestones in progress were Longcope's early and accurate descriptions of the disease. His reports made a great impression upon internists by differentiating chronic pyelonephritis from Bright's disease as a cause of failing renal function, uremia, and death. He pointed the way toward more accurate diagnosis and, eventually, to more intelligent treatment. Braasch brought to the attention of urologists the importance of pyelonephritis by his careful and comprehensive studies at the Mayo Clinic. Previous to this, the serious implications of this disease were scarcely appreciated by most urologists. The frequency with which pyelonephritis occurs in infancy and childhood and the high incidence of obstructive urinary tract lesions were demonstrated by Campbell. The seriousness of the condition in children and the relationship between hypertension and chronic pyelonephritis were pointed out by

Butler. The careful correlation between the clinical course of pyelonephritis and the pathological changes that were present, as portrayed by Weiss and Parker, gave impetus to the more careful study of patients with chronic renal disease and they demonstrated the association of chronic pyelonephritis with hypertension. Mallory's work resulted in a better understanding of the methods by which renal infection takes place. A great contribution toward the correlation of some types of hypertension and renal disease resulted from the experiments of Goldblatt. Homer Smith has tried to put the relationship between hypertension and unilateral renal disease on an even keel.

All of these investigators have added to our knowledge of this serious disease: pyelonephritis.

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