



# Pyelonephritis

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The purpose of this paper is to review current thinking about pyelonephritis. Pyelonephritis may be defined as a "bacterial infection of the kidney which affects the parenchyma, the pelvis, and the calyces. It occurs in two forms, acute and chronic."<sup>1</sup>

Clinically, acute pyelonephritis is characterized by the symptoms of dysuria, frequency, urgency, chills, fever, and flank pain. The urine sediment contains numerous white blood cells, bacteria, and white blood cell casts (Fig 1). A quantitative culture of the first voided urine in the morning yields a growth of greater than  $10^5$  colonies per ml. Renal histologic examination reveals an acute interstitial inflammatory reaction with polymorphonuclear leukocytes and microabscess formation (Fig 2). If the infection remits either spontaneously or with antibiotic therapy, the involved areas may heal with formation of a contracted, fibrotic scar. In contrast to the acute infection, chronic pyelonephritis may be totally asymptomatic. Examination of the urine sediment usually shows changes similar to those in acute disease except that the quantities of cells and casts may be less remarkable. The classic pathologic picture of chronic pyelonephritis includes interstitial infiltration by mononuclear cells, scarring, tubular dilatation (thyroidization) and periglomerular fibrosis (Fig 3). The typical chronic pyelonephritic kidney is shrunken, contains multiple scars, and is atrophic.

The pathologic picture of pyelonephritis is not entirely specific, particularly in the chronic state where other processes which cause an interstitial inflammatory reaction may give a similar appearance. An incomplete list of nonbacterial causes of

chronic interstitial nephritis includes: analgesic abuse, other drug toxicity, tuberculosis, sarcoidosis, gouty nephropathy, hypercalcemic nephropathy, and ischemic vascular disease.<sup>2</sup> Initially, these disorders may be suspected because of the presence of sterile pyuria, but later, superimposed bacterial infection may cloud the picture.

Bacteria invade the kidney by two principal routes: hematogenous and retrograde.<sup>3</sup> Hematogenous spread occurs infrequently, but when it does, it is the means whereby most staphylococcal and streptococcal infections are initiated in the kidney. These infections may be severe and associated with multiple abscess formation. Most bacterial infections of the kidney are caused by gram-negative organisms that reach the kidney via retrograde spread from the lower urinary tract; the natural habitat of the majority of these organisms is the gastrointestinal tract from which they spread to the urethra and then into the bladder and up the ureters. Approximately one fourth of all bacterial infections involve the urinary tract, but only a portion of these ascend above the bladder to the renal parenchyma.

Several factors are now recognized as being of major importance in the pathogenesis of urinary tract infection, the first of which is sex. There is clearly a higher incidence in females at all ages but particularly in the childbearing years. Only in later life with the advent of prostatic hypertrophy and associated obstructive uropathy does the incidence tend to increase in the male. The increased incidence in females probably relates to the shorter urethra, the absence of the antibacterial action of prostatic fluids, and trauma during intercourse. Recently it has also been recognized that disturbances in the bacterial resistance of the vaginal vestibule secretions may be the factor

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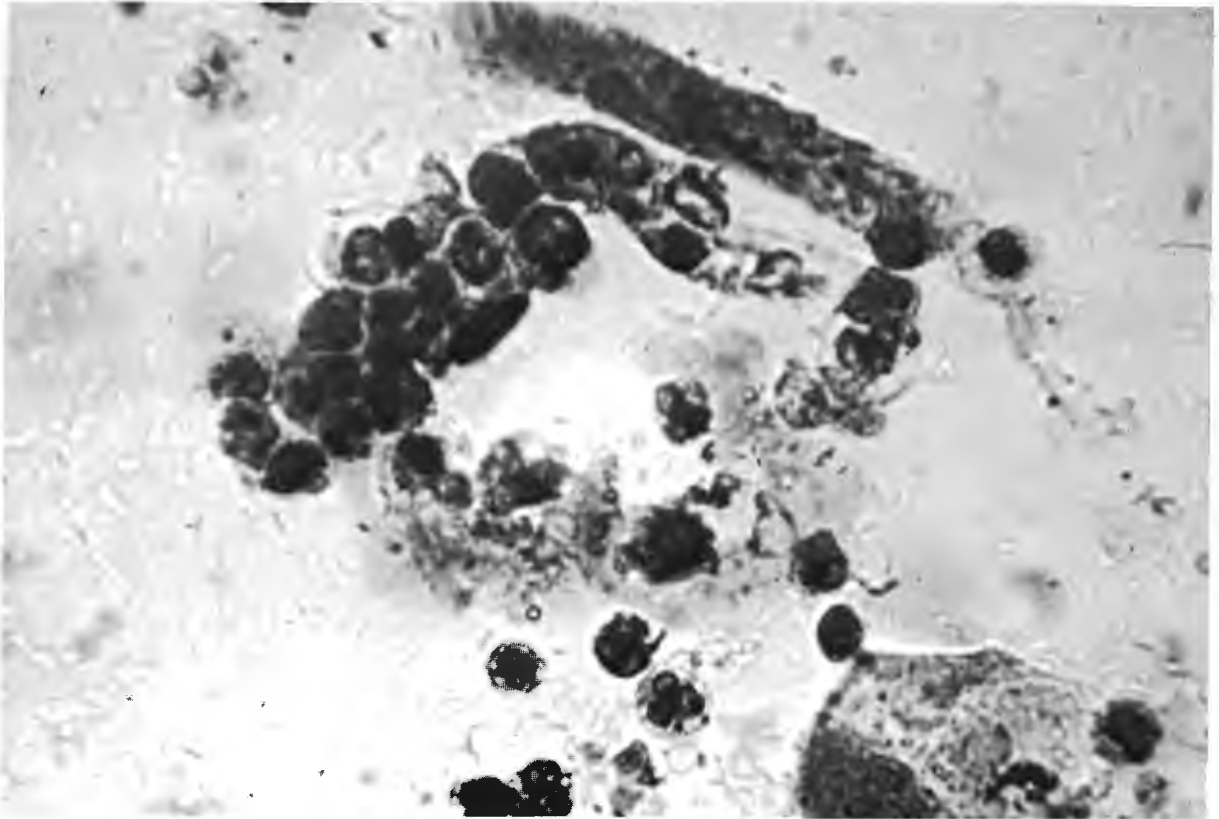


Fig 1—Urine sediment from a patient with acute pyelonephritis, showing white blood cells, a white blood cell cast, a granular cast and numerous bacteria ( $\times 1,000$ ).

which initially allows bacterial colonization of the urethra in females.<sup>4</sup>

Instrumentation of the urinary tract is frequently associated with introduction of bacteria into the bladder. Unfortunately, the instrumentation is usually undertaken for evaluation of an anatomically abnormal tract. Bladder urine is normally sterile. When pathogenic organisms are introduced into the bladder of a normal, unobstructed animal or man, they are rapidly cleared because of the combined effects of the bacteriostatic properties of normal urine, the dilution of organisms by voiding, and the resistance of the bladder mucosa to bacterial colonization.<sup>5</sup> On the other hand, in the obstructed state there is a residual pool of relatively stagnant urine; the bacterial clearing mechanisms are no longer operative and infection ensues. In this context neurogenic bladder dysfunction may have the same propensity to infection as overt obstructive uropathy.

In recent years numerous studies have indicated that ureteral reflux is probably the most important factor which allows for initiation and perpetuation of renal parenchymal infection. Congenital reflux becomes a problem in early childhood and is usually caused by an abnormal placement of the ureter in the bladder wall.<sup>6</sup> In the immature kidney it is likely that even sterile reflux may result in calyceal scarring and contracture of the parenchyma. This type of reflux carries an ominous prognosis and frequently requires surgical correction. Acquired reflux (Fig 4) may appear in older individuals and may be related to bladder infection, adjacent bladder diverticulae, or neurogenic mechanisms.<sup>7</sup> When reflux is severe, it may be associated with intrarenal reflux in the polar regions of the kidney. Some authorities think that this may be the cause of atrophic pyelonephritis.<sup>8</sup>

Dilatation of the ureters, because of pressure from the expanding uterus, and the smooth muscle

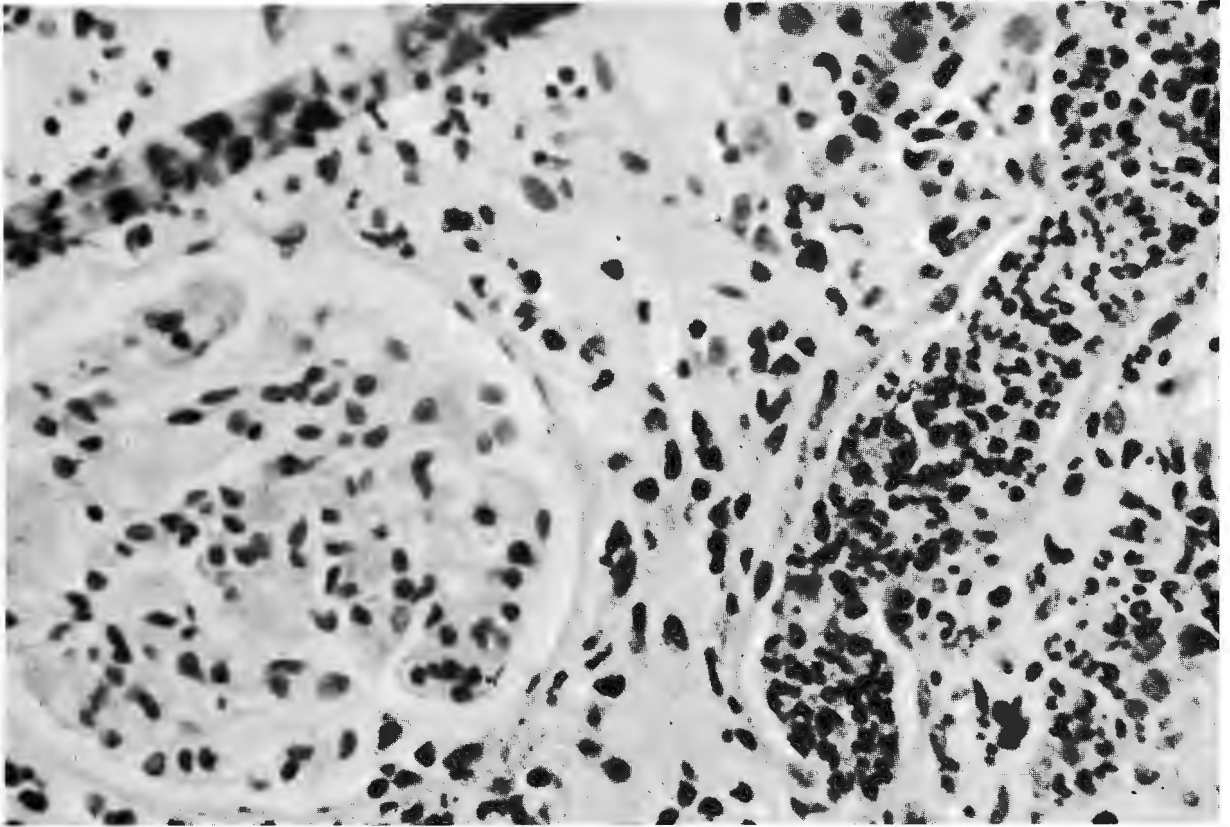


Fig 2—Light microscopic representation (H & E stain) of a renal biopsy section, showing the picture of acute pyelonephritis. Glomerular architecture is relatively well maintained, but there is a marked interstitial inflammatory reaction with both polymorphonuclear and mononuclear leukocytes. A white blood cell cast fills the collecting duct on the right. ( $\times 80$ ).

relaxing effects of high estrogen concentrations, may predispose to the development of pyelonephritis in pregnancy.<sup>8</sup> Fully 30% of pregnant patients with asymptomatic bacilluria will have an episode of acute pyelonephritis during a given pregnancy if left untreated.<sup>9</sup>

Controversy continues to surround the issue of whether or not diabetes mellitus predisposes to the development of pyelonephritis, and recent evidence suggests that its incidence is higher in diabetic women.<sup>10</sup> Clearly, when pyelonephritis develops in a diabetic patient, the infection itself is more likely to be severe.

The cortex appears to be relatively resistant to bacterial colonization, and most parenchymal infections begin in the medulla where increased susceptibility to infection probably relates to the lower blood supply to the medulla, the hypertonicity of the medullary interstitium which depresses phagocytosis, the

high level of ammonia which interferes with activation of the complement system, and the tendency for granulocytes to emigrate from the medullary area.<sup>8</sup>

Eighty-five percent of new urinary tract infections which develop outside the hospital are caused by *Escherichia coli* organisms and the remaining 15% by other organisms, most of which are also gram-negative.<sup>11</sup> When infection develops in the hospital setting or occurs after instrumentation, the bacterial flora is likely to be different and is usually composed of gram-negative organisms with a greater degree of bacterial resistance than *E coli*.

The main danger of bacterial infection of the kidney relates to its complications. There are a number of these and one which has generated much recent interest about its pathogenesis is atrophic pyelonephritis.<sup>8</sup> It is now clear that this condition develops in early life, is associated with high grades of reflux, and may terminate in end-stage renal disease at an early

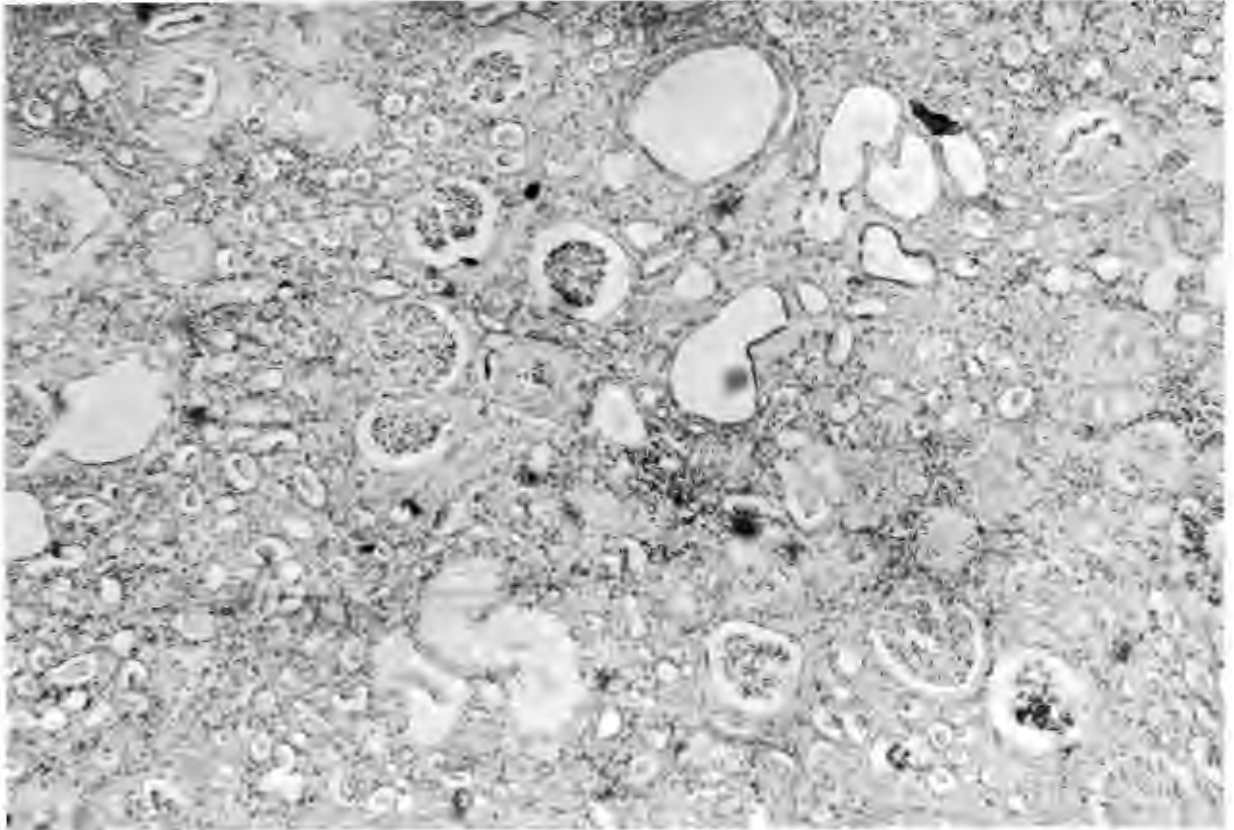


Fig 3—Light microscopic autopsy section (H & E stain) from a patient with chronic pyelonephritis. Marked interstitial inflammatory reaction in association with scarring, tubular dilatation, and periglomerular fibrosis is present. Secondary arteriolar thickening has also occurred ( $\times 20$ ).

age if the reflux is not corrected. It has been suggested that the small shrunken kidney seen in later life may be the result of atrophic pyelonephritis in childhood.

Papillary necrosis may be one of the most devastating complications of urinary tract infection, particularly if it occurs in diabetes mellitus with obstruction. This constellation of disturbances was formerly associated with a high frequency of sepsis and death, but it is seen less frequently since the advent of modern antibiotic therapy. At the present time it is more likely that papillary necrosis may present insidiously with slow deterioration in renal function, perhaps in conjunction with the passage of small pieces of papillary tissue in the urine. Contemporary studies<sup>12</sup> suggest that this latter picture may be seen more frequently with another underlying disease such as analgesic abuse or sickle cell disease, rather than as a manifestation of pyelonephritis (Fig 5).

Struvite stone formation is another common complication of urinary tract infection and is caused by infection with urea-splitting organisms, particularly those of the proteus species. This type of infection is seen all too frequently in patients with obstructive uropathy or neurogenic bladder dysfunction. Under either of these circumstances a continuous cycle of stone formation-infection-stone formation may develop. The composition of most "staghorn" calculi which develop in an obstructed, infected urinary tract is struvite. Infection is virtually impossible to clear from the urine in this situation.

Perinephric abscess is an infrequent but important complication of urinary tract infection because its onset may be insidious and it may be associated with remarkably minimal changes in the urine sediment. It may present as a fever of unknown etiology, and the use of modern radiographic techniques, such



Fig 4—Voiding cystourethrogram in a patient with acute cystitis and bilateral reflux. Moderate ureteral dilatation is present and the contrast medium refluxes into the calyceal system. The left calyceal system is also clearly dilated.



Fig 5—Retrograde urogram in a patient with papillary necrosis secondary to analgesic abuse. There is marked distortion of the calyceal system on the right. Necrotic, papillary debris is present in several calyces, displacing the contrast medium and giving rise to the characteristic "ring" sign.

as gallium scanning and CT scanning, may be of great diagnostic aid. In addition, sonography of the retroperitoneum and abdomen may be of diagnostic help.

Gram-negative sepsis remains a frequent complication of urinary tract infection and may be associated with instrumentation or the presence of an indwelling urethral catheter; therapy requires aggressive treatment with measures to support the circulation while administering a bactericidal antibiotic.

Whether or not chronic pyelonephritis predisposes to the development of severe hypertension continues to be a subject of debate. Some evidence in both children and adults would suggest that the chronically scarred kidney may be associated with

activation of a pressor hypertensive mechanism;<sup>13</sup> however, most patients with chronic infection remain normotensive or, at worse, mildly hypertensive. Perhaps a more important aspect of the association is the fact that progression of pyelonephritis, like that of any other type of renal disease may be accelerated by the presence of superimposed hypertension; therefore, elevated blood pressure in a patient with pyelonephritis should be treated vigorously.

A number of disturbances in relation to pregnancy have been correlated statistically with the presence of urinary tract infection. The most notable of these are anemia and decreased birth weight of the fetus. After a period of skepticism about the relationship of these abnormalities to infection, recent studies have confirmed their association.<sup>9</sup> As mentioned ear-

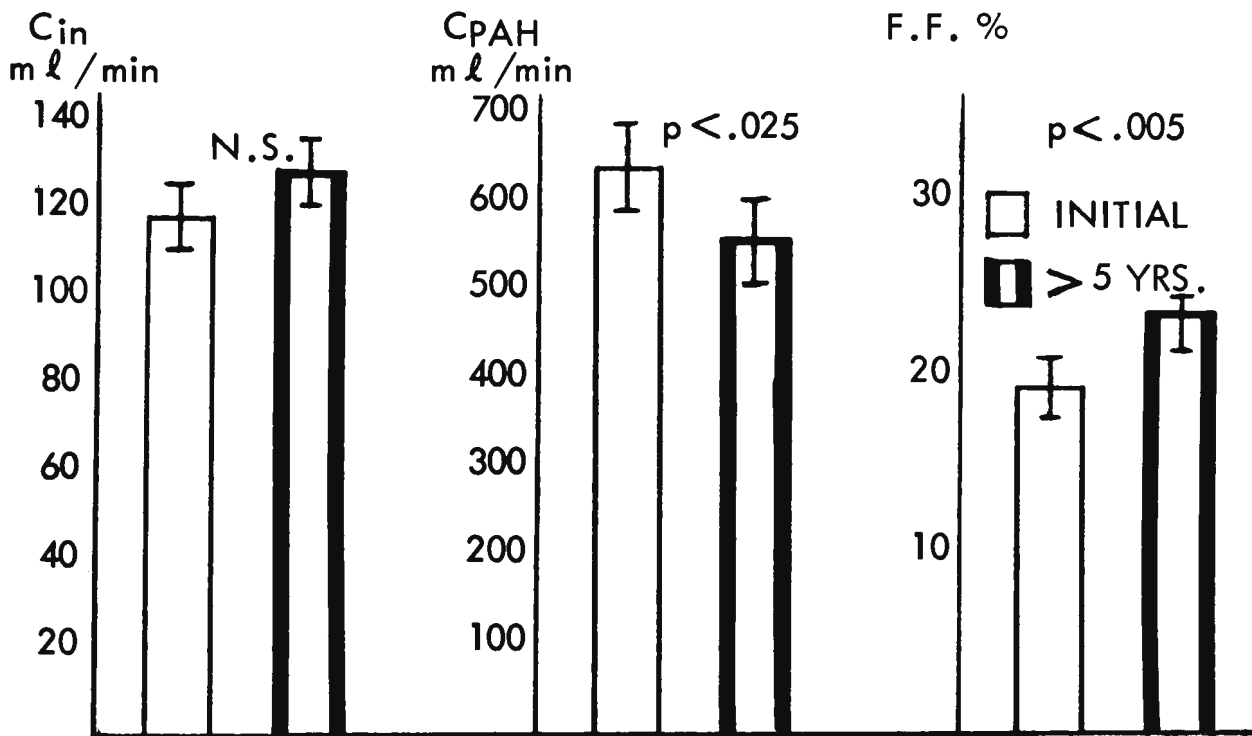


Fig 6—Comparison of mean  $\pm$  SEM values for  $C_{in}$ ,  $C_{PAH}$ , and FF between initial measurements early after injury and similar determinations after more than five years in 18 patients with spinal cord injuries and persistent bacilluria.

lier, there is a high incidence of acute pyelonephritis in pregnant females with bacilluria, and this condition, clearly, should be treated.<sup>9</sup>

For years pyelonephritis was considered to be a major cause of end-stage renal disease. Careful evaluation of patients entering dialysis and transplant programs, however, has indicated that this is not the case.<sup>14</sup> It is likely that many of the cases of interstitial nephritis which were thought to be caused by infection were in actuality the end result of one of the other causes of interstitial disease mentioned earlier. Present estimates would suggest that no more than 15% of the patients reaching end-stage disease have infection as the primary cause of renal failure and virtually all of these are complicated by the presence of stones, reflux, or other anatomic disturbance.

Information about the natural history of urinary tract infection in man is still incomplete. As noted above, end-stage renal disease in the absence of an anatomic or neurologic defect in the urinary tract is rare despite the frequency of culture-proven bacilluria. We have recently attempted to define more clearly the association of chronic bacilluria and dete-

rioration in renal function by a prospective analysis of the changes in inulin clearance ( $C_{in}$ ) and PAH clearance ( $C_{PAH}$ ) in a group of patients with persistent bacilluria (spinal cord injury patients).  $C_{in}$  is an accurate measure of the glomerular filtration rate and  $C_{PAH}$  indicates the renal plasma flow.

Figure 6 demonstrates that at a mean period of five years after the initial determinations, a statistically significant reduction in mean  $C_{PAH}$  from an initial value of 643 ml/min shortly after injury to 556 ml/min at the time of study had occurred in 18 study patients. Over the same period, there was no significant change in  $C_{in}$ ; there was also a significant reduction in the filtration fraction (FF). This index reflects the ratio of  $C_{in}/C_{PAH}$  and is an indicator of the state of perfusion in the kidney. Diseases which produce renal ischemia may be associated with a low FF. Each of the study patients had a neurogenic bladder and persistent bacilluria. A number had experienced one or more severe complications such as renal stones, reflux, or sepsis. Yet, at the time of study, all had adequate urinary drainage. These data suggest that there may be insidious damage occurring to the

kidneys of these patients; however, barring superimposition of some other insult, renal failure is unlikely to be the cause of their death.

There will always be differences of opinion about the work-up and therapy of patients with urinary tract infection. Outlined below are some principles which are generally applicable to these issues:

1. A quantitative culture, colony count, and antibiotic sensitivity determination should be performed in all pregnant women and in all individuals suspected of having a urinary tract infection.
2. A patient with the typical clinical picture of acute pyelonephritis or gram-negative sepsis should be treated with a bactericidal antibiotic to which the organism is sensitive for at least 10 days.
3. Radiographic studies including an intravenous pyelogram and voiding cystourethrogram should be done after the first episode of acute pyelonephritis in the adult male and in all children. Similar studies should be done in any female with recurrent infection or an elevated serum creatinine. Further urologic evaluation should be done in all patients in whom these studies identify a structural abnormality. Surgical correction of obstruction and severe reflux should be undertaken. Mild reflux in children may be observed during a period of antibiotic therapy and can be expected to disappear in 50% of cases by age 6 years and in 65% by age 14 years.<sup>8</sup>
4. The clinical picture of cystitis and asymptomatic bacteriuria may be treated with bacteriostatic agents. If recurrence occurs, the above-mentioned radiologic studies should be done. If these are negative, prophylactic or suppressive therapy may be tried. In the future, tests for antibody coating of bacteria may be helpful in differentiating upper tract infection with renal parenchymal involvement from lower tract infection.<sup>15</sup>
5. Reculture should be done after the completion of therapy for a urinary tract infection and on several occasions over the next two years to determine the presence of recurrence or reinfection.

In summary, current thoughts about the pathogenesis, natural history, complications, and management of pyelonephritis have been reviewed. It is now clear that chronic urinary tract infection in the absence of some anatomical disturbance or complica-

tion seldom leads to renal failure. Efforts should therefore be directed toward discovering and correcting derangements in the anatomical integrity of the urinary tract at an early stage of infection.

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