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## Elusive enemy : pyelonephritis

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THE ELUSIVE ENEMY: PYELONEPHRITIS

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INTRODUCTION. Pyelonephritis may be defined as interstitial inflammation of the kidney parenchyma and renal pelvis which, if not eradicated or controlled, may progressively lead to hypertension, renal failure, uremia, and death. The disease represents a major problem which has proved to be diagnostically and therapeutically frustrating in all fields of medicine.

Among infections in the general population, the incidence of urinary tract infection is second only to the incidence of upper respiratory tract infection. (11, 26, 45, 55) Kass, at Boston City Hospital, reports that pyelonephritis is the most common renal lesion found at autopsy and occurs in 15-20% of autopsies performed at large general hospitals. (44) Kass reports that the disease is diagnosed clinically in about one-fifth of the cases which are found at autopsy. In about one-third of the cases of pyelonephritis found at autopsy the lesion is of major importance in the cause of death. (44) MacDonald (56) at Boston City Hospital found active or healed pyelonephritis in 33% of 1000 consecutive autopsies; and, in less than one-third of these was the diagnosis suspected. Brod (15) at the Institute of Cardiovascular Research, Prague, Czechoslovakia, reports as high as 67% of cases of pyelonephritis found at autopsy escape clinical recognition.

The failure of clinical diagnosis is not due to the inability to recognize the classic symptoms and signs of the disease, but due to the paucity of clinical manifestations

of pyelonephritis in many patients. There is no clear method of identifying pyelonephritis in the presence of lower urinary tract infection or when its symptoms and signs are not obvious. (11, 15, 39, 45, 56, 59, 73, 74) This may be one reason why the relationship between pyelonephritis, uremia, and death has not diminished since the advent of the antibiotic era. (37)

The disease is not particularly prevalent for any one race (83); and, prior to the first year of life, the incidence is approximately equal in either sex. Between the ages of one and sixty years the disease becomes nine times more frequent in females than in males. (30, 55) Past sixty years of age, the incidence becomes more prevalent in men due to the greater incidence of benign prostatic hypertrophy. (32)

Infections of the upper urinary tract are common in early life, especially in girls under three years (6), and constitute 1-2% of all pediatric age hospital cases. (83)

The incidence of pyelonephritis complicating pregnancy is about 2%, the frequency of antepartum and postpartum varieties being about the same. (6) Finnerty, at Georgetown School of Medicine, reports 73 of 1130 pregnancy patients with toxemia had pyelonephritis (25); and Peters reports 11 of 25 patients who died of toxemia actually suffered from pyelonephritis masquerading as toxemia of pregnancy. (65)

The internist states that pyelonephritis is responsible for 36% of all cases of uremia (15, 17) and that it is the

commonest cause of renal death. (15) Brod (15) has reported that 38% of patients with pyelonephritis and normal renal function have hypertension. Pyelonephritis is present in at least 20% of all patients with hypertension (83), either benign (15, 6, 43, 61) or malignant. (73, 82) Pyelonephritis also continues to be listed as a common complication of the Nephrotic Syndrome. (74)

It is the purpose of this paper to point out the elusiveness of this disease with regard to diagnosis.

ETIOLOGY. In the normal state, the urinary tract appears highly resistant to infection; therefore, pathogenic bacteria most commonly associated with pyelonephritis may pass through it without producing disease. This has been shown experimentally by placing these organisms into the cavities of the bladder or kidneys, either directly by retrograde technique or indirectly through the bloodstream. (32) If, however, a condition is created to allow stasis and pooling of urine, or if renal tissue is damaged, such as experimental procedure produces infection in a high percentage of cases. (6) It should be noted here that coagulase positive, *Staphylococcus aureus* is one of the few organisms possessing the ability to invade apparently normal kidneys. (32, 70) Based on this evidence, we may state that there are two prerequisites to establishment of any urinary tract infection: (1) There must be bacteria present capable of establishing a urinary

tract infection, and (2) there must be an accessory factor present to lower the resistance of the tissue to bacterial invasion.

BACTERIA. The most common pathogens associated with pyelonephritis and found in urine culture are the coliform bacteria with *Escherichia coli* predominating. The other members of the group are *Aerobacter aerogenes* and the paracolons.

The coliform bacteria are gram negative rods which are common inhabitants of the gastrointestinal tract, perineal skin, and anterior urethra. (18, 33, 75) These organisms have low virulence and limited ability to invade healthy renal tissue. (24) They are disease producers only when an accessory factor allows them to become invasive. (24) When they do invade, they apparently produce poor immunity because the general population does not have significant antibody titers to these bacteria. (24)

*Pseudomonas* and *Proteus* appear to be more closely related to pyelonephritis in chronic obstructive disease or following catheterization and instrumentation than the coliforms. (53) Because of the ability of *Proteus* to split urea with the formation of alkaline urine, this organism has also been associated with the formation of phosphate stones. (64)

Staphylococci are more frequently associated with cortical or perinephritic abscesses, and bladder or prostatic infections; but coagulase positive, *Staphylococcus aureus*

pyelonephritis may arise from one of these foci in the genito-urinary tract or from a distant focus elsewhere in the body. (12, 74) The coagulase negative staphylococci, usually *Staphylococcus epidermidis*, rarely cause urinary tract infection. Consequently, the coagulase test is of great help in differentiating between pathogenic and nonpathogenic staphylococci. (64)

Enterococci are frequent inhabitants of the anterior urethra, though their status as a cause of pyelonephritis is not clear. There are reports, however, that show a few cases in which this was undoubtedly the organism involved. (68)

ACCESSORY FACTORS. The following are the most common disorders associated with pyelonephritis:

1. Decreased general resistance. Such conditions as hypogammaglobulinemia (60), agranulocytosis, or the excessive use of steroids may interfere with phagocytosis of bacteria in the blood by leukocytes. Tissue invasion by urinary pathogens is normally controlled by the mucous barrier and lysozyme of the gastrointestinal tract and by the keratin layer and fatty acids of the skin. Bacteria which do invade are promptly picked up by phagocytes and, because of their low virulence, are soon destroyed; although they may circulate briefly inside of leukocytes while the destructive process is in progress. This type of sepsis is well controlled unless something interferes with the leukocyte system to remove these cells, as in agranulocytosis, or to inhibit



their function, as in the excessive use of glucocorticoids. In both cases, the resident microflora of the skin and bowel may become invasive and establish focal infections in remote visceral locations such as the kidney. (24)

2. Diabetes mellitus. Upper urinary tract infections are 2-4 times more common in diabetics than in other persons of comparable age. (32) In uncontrolled diabetes, these infections tend to be more severe and protracted; and necrotizing papillitis, a fulminating form of pyelonephritis, is likely to occur. (6) The reasons for the high incidence of upper urinary tract infection in diabetics are not clear.

Several hypotheses have been made (53) in this regard:

(A) It represents part of the generalized susceptibility to infection commonly ascribed to diabetics. Leukocytes of diabetic patients exhibit diminished glycolysis and lactic acid production in vitro. The inability to produce lactic acid normally may be an index of diminished resistance to infection. (B) The occurrence of glycosuria may provide a more favorable culture medium for bacteria which might gain access to the urinary tract. (C) Relatively greater frequency of bladder catheterization is used for diagnostic purposes in diabetics. (D) Diabetic neuropathy is occasionally associated with disturbances of bladder function.

3. Pregnancy. Pyelonephritis most frequently occurs in the last trimester. (6) Significant bacteriuria was found

by Kass at Boston City Hospital to occur in 67% of pregnant women, and this led to clinically apparent pyelonephritis later in 40%. (49) The bacteriuria was found to be acquired before pregnancy or in the first two months of pregnancy. Kass pointed out that if before pregnancy or at the beginning this bacteriuria was eliminated, the disease would not develop. (49) Pyelonephritis of pregnancy is thought by some to be caused by dilatation of the ureters and renal pelves, acting as an obstructive phenomenon which predisposes the kidney to infection. (24, 30)

Recently accumulated data, however, suggest that this hypothesis must be re-evaluated. (48) It has been noted that the incidence of bacteriuria in gravid patients, 6%, is similar to that of nonpregnant females examined at the same hospital. When the incidence of bacteriuria is studied in relation to duration of pregnancy, it appears that most, if not all, instances of bacteriuria are acquired before the second month of pregnancy. This is at a time prior to marked demonstrable changes in the urinary tract. In addition, as the ureteral dilatation and obstruction of urine flow increases with duration of pregnancy, the incidence of bacteriuria does not increase. These facts, plus the observation that there appears to be no difference in volume of residual urine in bacteriuric and non-bacteriuric patients at comparable periods of pregnancy, indicate that anatomic changes in the urinary

tract associated with pregnancy do not account for the appearance of bacteriuria. (6 )

4. Trauma or previous urinary tract infection. Trauma or previous urinary tract infection lead to scarring and distortion of the renal pelvis with subsequent pooling of urine, tubular obstruction, and intrarenal hydronephrosis. (30, 64, 70) Clinically, this manifests itself as an increased susceptibility to re-infection. Experimental confirmation of this was obtained by De Navasquez (20) who noted the occurrence of gram negative bacillary infection in rabbits which had survived preceding staphylococcus infection with resultant areas of healed renal scarring. In these experiments, the active infections were confined to the dilated tubular segments immediately adjacent to the healed scar.

5. Congenital lesions. Congenital anomalies of the genitourinary tract are more common than malformations in any other body system. (30) According to Campbell (16), more than 10% of all human beings are born with some urogenital anomaly, and they represent 40% of all maldevelopments. Therefore, a search for urinary outflow disorders should be made in all cases of recurrent urinary tract infection in children.

Common congenital anomalies (30, 55) may be classified as follows: (A) Agenesis and aplasia, which are often associated with pyelonephritis of the contralateral kidney. (23)

Also included in this group are primitive tubules, rudimentary glomeruli, excessive interstitial tissue, medullary dysplasia, and common vascular anomalies; (B) Cystic disorders of the kidney, the most common of which is polycystic disease (19); (C) Anomalies of position such as malrotation, horseshoe kidney, crossed renal ectopias, and other ectopic kidneys, many of which have drainage difficulties; (D) Hereditary interstitial pyelonephritis, which is a familial type in males, that progresses to uremia and death; (E) Intrinsic strictures at the ureteropelvic and ureterovesical junctions, diverticuli of the ureter, and congenital megaloureter; (F) Bladder anomalies such as congenital diverticula, anomalous ureteral meatuses, congenital dilatation of the vesical neck in girls and congenital obstruction of the vesical neck from fibrosis and urethral valves; and (G) Congenital meatal stenosis.

6. Acquired lesions. Acquired obstructing factors include: Tumors in any part of the urinary tract; calculi; obstruction of the vesical neck from benign prostatic hypertrophy, chronic fibrous prostatitis, prostatic carcinoma; congenital valves in the male infant; urethral strictures, urethral and vesical diverticula both in males and females; hypertrophy of the vesical neck in neurogenic bladder lesions; previous urinary tract infection; idiopathic periureteral fibrosis; and toxic lesions from drugs. (30)

7. Disturbance of bladder innervation. Many disorders

of the nervous system are associated with disturbances in bladder function and with urinary tract infection. Important examples are multiple sclerosis, poliomyelitis, diabetic neuropathy, tabes dorsalis, and spinal cord injury. (6)

8. Instrumentation or catheterization. It is well documented in the literature that in the absence of infection the urethra may harbor staphylococci, streptococci, coliform bacteria, proteus, and pseudomonas. (6, 18, 33, 34, 36, 38, 75) Thus, the dangers of catheterization and instrumentation of the urethra are apparent, since such procedures may push these bacteria into the bladder. Indwelling catheters in particular are dangerous (45, 56) because they also allow entry into the urinary tract via fluid that forms around the catheter. (50) It should be noted that these bacteria have been grown from catheter tips placed 3-5 cm. proximal to the urethral meatus, well out of reach of the commonly used antiseptics. (18, 33, 36) It is said that cystitis develops in 5% of all people following catheterization and in 95% of all people following an indwelling catheter. (15, 25, 26, 37, 39, 44, 45, 56, 59, 64, 65, 73, 74)

9. No apparent causes. A reasonable large number of patients with pyelonephritis have no demonstrable abnormalities of the urinary tract. (44, 80)

It may be seen that the majority of the above factors cause stasis and pooling of urine, which is regarded by some

authors to be one of the main causes of pyelonephritis. (10, 55) Bell found that obstructive pyelonephritis was 12 times more frequent than the nonobstructive type. He found that 60-70% of boys with chronic, recurrent, resistant pyelonephritis had evidence of obstructive uropathy; but this was not true of girls. (10, 30) There have been several mechanisms suggested to explain how urinary obstruction produces an altered resistance to infection: Increased interstitial pressure, urine stasis, diminished renal blood or lymph flow, impaired phagocytosis, and metabolic alterations within various renal cells. (32) None of these theories have advanced beyond the stage of speculation.

SOURCE OF BACTERIA. While it is probable that the source of infecting bacteria may be the gastrointestinal tract (41, 77) urethra (6, 18, 33, 34, 36, 38, 75), or a focus of infection elsewhere in the body (74), there is considerable disagreement regarding the route by which microorganisms reach the kidneys. In general, there are three main theories to explain how the organisms reach the upper urinary tract.

1. Ascending theory. In this theory the urinary tract is pictured as a continuous anatomical unit with a common channel lined by epithelium. Hence, inflammatory diseases for all organs of the tract are closely allied. The ascending route of infection may be seen in patients undergoing catheterization or instrumentation, since either procedure

may carry part of the natural bacterial flora of the urethra into the bladder. (11, 32) Vesicoureteral reflux has been shown to occur in humans (27) and experimental animals (31); and this permits introduction of bacteria into the renal pelvis with minimal, if any, trauma. Kleeman (53) points out that once there is infection in the bladder, it may pass upward through an incompetent vesicoureteral valve, through the ureter, and into the renal pelvis by increased pressure in the bladder from overdistension, coughing, micturition, or straining. (2, 53) It should be noted that vesicoureteral reflux may occur despite normal-appearing voiding cystourethrograms, because the amount of refluxing material may be too small to visualize on the x-ray film. (6)

Vivaldi, Zangwell, Eaton, and Kass (81), who produced retrograde infection of the rat kidney following the initiation of infection in the bladder, showed that unilateral ureteral ligation protected one kidney, thus documenting the role of the ureter as an important route of infection. Carbon particles have also been traced from the bladder to the kidney via the ureter. (24)

Final proof lies in the fact that if pyelonephritis is initiated by retrograde technique, a pyelitis is the first demonstrable lesion to occur; whereas, if a pyelonephritis is initiated by the hematogenous route, the first demonstrable lesion occurs in the cortex. (2, 24)

This theory explains the far greater frequency of spontaneously occurring infections in females, since the short urethra and its nearness to the anus should provide more opportunity for fecal bacteria to reach the bladder cavity. It would explain the high incidence of pyelonephritis in children between 6 months and 2 years of age, especially in girls, on the basis of fecal soiling of diapers and contamination of the urethral meatus.

Michie (63) placed ten girls less than 10 years of age into a bath with dyed water and found that all had dye in their bladders after they sat down and stood up 20 times in 6 inches of water.

2. Hematogenous theory. Although there is little doubt the hematogenous route plays an important role in the pathogenesis of pyelonephritis (6), it should be noted that the majority of cases are caused by gram negative organisms which rarely cause bacteremia. (13) Bacteremia may be due to instrumentation of the urethra (3, 6) or to a primary source of infection in the body, such as conjunctivitis, sinusitis, otitis media, appendicitis; or more commonly to chronic prostatitis, tonsillitis, or abscesses. (6, 12, 74) With the hematogenous route, the cortex of the kidney is first involved, and the infection descends by way of the tubules to infect the pelvis within 48 hours. (24)

In recent studies on small animals, it has been shown



that 10,000 coliforms infused intravenously are capable of establishing infection in the kidney. (24) It has however, been difficult to produce infection by this method unless the kidney had been previously injured by urinary obstruction (54), infectious scarring (20), massage (14), or cauterization (8). It has been suggested that the pre-existing injury appears to promote recurrent chronic pyelonephritis from coliform bacteria by local slowing of circulation and allowing production of local infection from the circulating bacteria. (70)

3. Lymphatic theory. There are only limited clinical observations on the role of lymphatics in the pathogenesis of pyelonephritis, and these do not permit conclusive definition. To a lesser extent, similar comment may be made concerning experimental approaches to this problem. (6, 51)

A. Lymphatic communication from the intestine directly to the kidney: Franke (28), in 1910, demonstrated lymphatic connections between the appendix, cecum, and right kidney. The passage of *E. coli* has been demonstrated from various portions of the large bowel, which is often sluggish or atonic during pregnancy, through lymphatics to those of the right kidney region. (24) These facts have been cited repeatedly as a possible explanation for the greater frequency of right-sided upper urinary tract infection. However, it should be noted that Franke searched for, but failed to find, any

similar lymphatic connection between the left kidney and the colon to explain left-sided pyelonephritis.

B. Direct lymphatic communication between the lower and upper urinary tracts: It has been suggested that the course of events is: First, cystitis; second, migration of bacteria into the rich lymphatic network of the lower urinary tract; and third, transport by peri-ureteral lymphatic vessels to the kidneys. The weak point in this hypothesis lies in the fact that direct lymphatic communication between the lower and upper urinary tracts has not been demonstrated convincingly. (6, 22, 79, 84)

Sweet and Stewart (79) and Eisendrath and Kahn (22) believed that they had shown its existence in animals, but their principal evidence was lymphocytic infiltration in the outer coats of the ureters following inoculations of bacterial cultures into the bladder. As pointed out by Bell (9) these changes may simply be due to ureteritis. Eisendrath and Kahn made the unwarranted assumption that the possibility of blood stream transfer of bacteria from bladder to kidney was ruled out by the fact that the heart's blood culture was negative at the time of sacrifice of the animal.

Winsbury-White (84), in an unconvincing but frequently quoted piece of work, claimed that he had demonstrated passage of India ink particles from the lower to the upper urinary tract via lymphatic vessels in animals. He gave so few de-

tails that one cannot now evaluate the possible loopholes or soundness of his work.

As pointed out by Beeson (6), it seems anatomically unlikely that there are direct lymphatic communications between lower and upper urinary tracts because there are no parallel channels of blood supply. The general rule is that lymphatic drainage of a region follows its blood supply and venous drainage. The arteries and veins of the urinary tract are segmentally distributed, even at different levels of the ureters. It would be surprising then to find that the lymphatics run upwards from the bladder to the kidneys around the ureters. The spermatic and ovarian veins are in separate fascial sheaths, having no close connection with the urethra or bladder.

The excellent study by MacKenzie and Wallace (57) shows that dye particles injected into the uterine cervix, bladder wall, and ureter of a rabbit travel not toward the kidney, but into the common iliac glands, then upward along the aorta to the thoracic duct. This is in opposition to the findings mentioned previously by Winsbury-White.

MANIFESTATIONS OF PYELONEPHRITIS. Few physicians overlook the classical picture of pyelonephritis suggested by chills, fever, malaise, costovertebral angle tenderness and bladder-type symptomatology. However, pyelonephritis is many times overlooked because: (1) The disease is often a

complication accompanying some other disease process and is not the primary reason for the patient's visit; (2) up to 50% of cases are asymptomatic (53, 64); and (3) the atypical cases far outnumber the typical cases. (15, 40, 42) It may be that constitutional symptoms such as chronic fever, tiredness, anemia, weakness, anorexia, and weight loss, without genitourinary symptoms, may be all that are present. (64)

In children, few diseases display such a variety of symptoms as does pyelonephritis. Fever, in the majority of cases, is only slightly elevated, lasting 1-2 days, and is usually spiking. Fever may be entirely absent in the newborn or may be markedly elevated and prolonged in severe cases of all ages. Chills are common in older children, but are rarely seen in infants. Pallor is often striking at onset in severe cases, and gastrointestinal and central nervous system symptoms may appear to such an extent that urinary tract symptoms may not be regarded as primary. Anorexia, vomiting, and diarrhea may lead to severe dehydration in infants. Meningismus, convulsions, prostration, stupor, and delirium are often marked at onset but rarely persist. Abdominal tenderness and bladder symptoms are rare in infants and constipation is less frequent in children than in adults. (83)

In older children and adults, the symptoms of acute pyelonephritis generally develop rapidly within a period

of a few hours to one or two days. Fever may be high (103°-105°) and associated with shaking chills and dull aching pain in one or both lumbar areas. Nausea, vomiting, diarrhea, and occasional constipation are seen. There may be frequency, straining, tenesmus, dysuria, and a constant desire to urinate. There may be pain, tenderness, and guarding in the costo-vertebral angle or lumbar areas produced by deep palpation or bimanual examination. In some cases, pain may be poorly localized; and the condition may be confused with appendicitis, pelvic inflammatory disease, or intrauterine infection. Duration of acute attacks is variable; even without antibiotic therapy, constitutional complaints rarely last longer than a week. (7, 83) Recurrences may occur weeks, months, or years after the acute attack, and may represent flare-ups of chronic latent infection or a decreased resistance of the urinary tract predisposing it to repeated new infections. (83)

In perhaps no other disease of the kidneys can fluctuations in renal function be so marked and so frequent. During acute infections or episodes of dehydration, renal decompensation may progress to the stage of advanced uremia; yet the patient may be able to recover and carry on with adequate, though impaired, renal function for years. As the disease slowly progresses, the glomerular filtration rate and renal blood flow decline together proportionally. There is usually more disparity between the function of the right

and the left kidneys than in diffuse renal disease, such as glomerulonephritis, and maximum concentrating ability tends to become impaired earlier. Occasionally, patients with advanced azotemia may excrete urine hypotonic to plasma even when they are dehydrated. Many patients are unable to conserve sodium on a low salt diet even when only mild azotemia is present, and polyuria and nocturia are prominent in such cases. Hyperchloremic acidosis, as a result of impaired renal excretion of acid and reabsorption of bicarbonate, is seen in late chronic pyelonephritis. Proteinuria is usually less than 2 gm. per day but may reach 4-5 gms. per day in final stages. (83)

DIAGNOSTIC PROCEDURES. Two of the most important diagnostic procedures for any urinary tract infection are :

(1) Microscopic examination of the urine sediment, and (2) the quantitative colony count. It is preferable to collect a morning urine specimen at a time after the bladder has been emptied of overnight urine. A number of lysed casts and white blood cells, multiplied bacteria, and much debris may be present in urine that has been in the bladder overnight (64), thus making microscopic examination difficult.

1. Urine sediment. It is to be remembered that in acute pyelonephritis it is primarily the polymorphonuclear leukocyte that moves out of the inflamed area, into the tubules, and into the sediment of the urine. Numerous leuko-

cytes will be seen singly or in clumps. (83) White blood cell casts are highly suggestive of parenchymal inflammation (41) but are not commonly seen. (83) Bacteria can usually be demonstrated in large numbers by suitable stains. (83) In chronic infection of low grade activity, the diagnosis of pyelonephritis may become very difficult on the basis of urine sediment. In chronic indolent pyelonephritis, the renal inflammation becomes lymphocytic in character and no cells may appear in the urine. (14) Further, scar tissue cannot produce an inflammatory exudate; and both pyuria and bacteriuria may occur intermittently and be detected only by repeated urinalysis. It has been shown that pyelonephritis may exist without diagnostic alterations of the urine both clinically (15, 17, 25, 33, 37, 39, 65) and experimentally (21, 53).

A. Pyuria: Pyuria is defined as greater than 5 white blood cells per high power field of centrifuged urine. (11) Alone, it is difficult to evaluate since it may arise from kidneys, ureters, bladder, prostate, or urethra. The relation of preoperative urinary findings to the pathological conditions revealed at the operation was studied by Jackson and others (40) in 71 patients who underwent unilateral nephrectomy. Pyelonephritis was present in 42 of these kidneys. They found that 22% of the removed pyelonephritic kidneys had less than 10 white blood cells per high power field, and that 33% of those without pyelonephritis had

more than 10 white blood cells per high power field. Sanford (72) has shown that the absence of pyuria in single or multiple urine specimens did not negate the diagnosis of urinary tract infection, nor did the presence of pyuria imply that a pyogenic urinary tract infection was always present.

B. Red blood cells: In contrast to the occurrence of pyuria, the occurrence of hematuria with pyelonephritis should be looked upon with suspicion. It suggests the desirability for further investigation of the patient for tumors, congenital anomalies, tuberculosis, urinary tract concretion, embolism, trauma, or glomerulonephritis; all of which can be complicated by pyelonephritis. (39) Although large and equal increases of red and white blood cells point against pyelonephritis, it does not rule out advanced chronic cases, since erosion of medullary arteries may occur in this stage. (6)

C. Glitter cells: Much discussion has been centered around the glitter cell phenomenon as a diagnostic feature of chronic advanced pyelonephritis. These are polymorphonuclear leukocytes, which stain pale blue, and contain granules in the cytoplasm which show Brownian movement. (67, 76) It is now thought that the glitter cell phenomenon depends upon the hypotonicity of urine and is not specific for pyelonephritis, since normal leukocytes produce this phenomenon when placed in hypotonic saline. (11, 78)

At the present time the best approach to quantitative



estimation of the urine sediment is the Addis count. (1, 11) Normally, in the adult, about 1,000 hyaline casts, 70,000 red blood cells, and 300,000 leukocytes are found in a 12-hour urine specimen. More than 9,000 casts, 1,000,000 red blood cells, and 3,000,000 leukocytes are definitely abnormal. In children, different normal limits are allowed: 10,000 casts, 2,000,000 leukocytes, and 600,000 red blood cells. If evidence of overt infection of the lower urinary tract is lacking, and the Addis count shows more than 3,000,000 leukocytes, less than 1,000,000 red blood cells, the presence of pus cell casts, proteinuria less than 1 gm. per 12 hours, then one can suspect pyelonephritis.

2. Quantitative colony counts. The problem of what constitutes a significant bacteriuria and the value of catheterized vs. midstream cultures has encompassed a broad area of controversy in the literature. (11) There is now very good evidence in the form of clinical investigation combined with post mortum studies to support the value of quantitative urine cultures (45, 58, 72) and the importance of significant bacteriuria, which is defined as more than 100,000 pathogenic bacteria per ml. of urine. (46, 49, 52, 53)

The principle of the quantitative urine culture technique is that urine is an excellent medium for growth of the common pathogens of the urinary tract. When small numbers of these bacteria are inoculated into urine, they multiply

rapidly in just 8 hours at body temperature to a concentration of a million or more per ml. of urine. (4, 11, 44) Thus, if a small number of bacteria are dislodged from an infected focus in the kidney into the urine, one would expect to find large numbers of bacteria in the bladder urine. (4) More specifically, in acute pyelonephritis, one could find less than 10,000 bacteria per ml. in the kidney pelvis while urine obtained simultaneously from the bladder would contain more than 100,000 bacteria per ml. (11, 44) Exceptions to this principle are:

- (1) Fastidious organisms, such as *Mycobacterium tuberculosis* or fungi, that do not multiply in urine;
- (2) Ureteral obstruction blocking the passage of bacteria into the bladder urine;
- (3) Bacteriostatic agents in the urine;
- (4) High rate of urine flow combined with brief pooling period in the bladder, thus not allowing time for multiplication;
- (5) Kidney infection not draining into the tubules;
- (6) pH below 5.5 or above 8.5.

It should be emphasized that these instances are the exception rather than the rule and are not frequently encountered in practice. (4)

Kass (45) studied 25 consecutive cases of acute pyelonephritis with classical signs and symptoms and found that all had more than 100,000 bacteria per ml., and all but one had more than 1,000,000 bacteria per ml. (47) Kass then

studied individuals not thought to have pyelonephritis and noted that the bacteria counts were 10,000 per ml. or less and frequently less than 1,000 per ml. Hall and Sanford (72) indicate another dividing line between those patients with active infection and urinary contamination. Their patients were of two groups: (1) Those with 1,000 or less bacteria per ml. and (2) those with 10,000 or more bacteria per ml. It is important to note that all studies have shown that only 2-3% of patients with true bacilluria fall between 10,000 and 100,000 bacteria per ml. (4), and most cultures above 10,000 are also above 100,000 bacteria per ml.

A gram stain of the urine should always be done at the time the urine culture is plated. When bacteria can be seen on an uncentrifuged smear, there is an 80% correlation that the bacterial count will be greater than 100,000 per ml. (4, 11, 45, 64, 78) Thus, we have a check on the validity of the culture. When bacteria are seen by gram stain and culture shows a low number of bacteria or no growth, there may be a laboratory error.

Evidence has been cited to indicate that, with meticulous technique (35), a carefully examined midstream specimen in the female gives results comparable to those obtained with a catheterized specimen. It has been shown that both male and female urethras are normally contaminated with bacteria and can never be considered sterile. (5, 11) Thus,

urine flowing through this flora or through a catheter will be contaminated. (5, 11, 31, 63) If the foregoing studies are correct, then the conclusion that contaminated urine will contain less than 100,000 bacteria per ml., whether it is obtained from a catheter or from a carefully collected midstream culture, seems valid (6, 11, 41, 42, 43, 54, 59, 69, 66 ); and that when significant bacteriuria is present, the number of organisms will exceed 100,000 per ml. by either collection method. (5, 17, 40).

Proper interpretation of urine cultures demands seasoned judgment, a sharp focus on the over-all picture presented by the patient, and above all, knowledge of the limitations of culture reports and of the exact technique used to obtain the culture. To expect untrained personnel to collect a valid specimen is wishful thinking. Ideally, all specimens should be obtained by the same personnel, using the same technique, and be in close proximity to the bacteriology laboratory.

3. Pyelography. Retrograde and intravenous pyelograms may reveal asymmetry of ~~size~~ of the two kidneys and distortion of the renal pelves in the pyelonephritic patient. Normal pyelograms, however, do not rule out the diagnosis of pyelonephritis, since abnormal findings occur late. (83)

4. Renal biopsy. Renal biopsy is informative in

only 60% of cases because of the spotty distribution of lesions. The procedure is very difficult to perform on children due to the small target and lack of cooperation. (55)

SUMMARY AND CONCLUSION. Pyelonephritis may be defined as interstitial inflammation of the kidney parenchyma and renal pelvis which, if not eradicated or controlled, may progressively lead to hypertension, renal failure, uremia and death. The disease represents a major medical problem in all fields of medicine because there is no clear method of identifying the disease in the presence of lower urinary tract infection or when its symptoms and signs are not obvious. The disease is many times not diagnosed because: (1) Up to 50% of cases are asymptomatic; (2) The disease is often a complication of some other disease process and is not looked for; (3) Pyelonephritis may present in many ways and the atypical cases far outnumber the typical ones.

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