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FACTORS IN THE PATHOGENESIS OF PYELONEPHRITIS

In 1916 Cabot and Crabtree made the following statement about bacterial infections of the kidney:

> While it is almost literally true that a satisfactory comprehension of the diseases of the genitourinary tract depends upon a clear appreciation of the nature and probable course of renal infection, there is no subject in which there is so little uniformity of opinion and so much confusion. The literature of the subject is stupefying both in quantity and in complexity, and anyone who has attempted to master it will, we think, be convinced of the fact that it is more likely to confound than to enlighten the reader.[18]

In the succeeding forty years some progress has been made, the most important being an appreciation of the long, indolent course which may be taken by this kind of disease. The misleading word "pyelitis" has been replaced by the more accurate "pyelonephritis," and the tendency of the disease to cause serious destruction of the kidney is now well recognized. Furthermore, good evidence has been provided to implicate pyelonephritis in the etiology of some forms of hypertension and some cases of toxemia of pregnancy.

However, there is still much uncertainty and confusion about the pathogenesis of pyelonephritis. Problems which should be susceptible to study by accurate clinical observation or laboratory experiment remain unsettled. An example is the ancient mystery as to whether bacteria reach the kidney by way of the blood stream, the lymphatics, or the urinary passages. Adequate information is lacking on the microbial population at various levels of the normal urinary tract. Although pyelonephritis is known to occur with special frequency in certain age periods and to be a common accompaniment of certain diseases and conditions, the causes of these associations are difficult to define. It is not known whether the pyelonephritis of an infant should be regarded as the same disease as that which may be encountered in a patient with spinal cord transection. We do not know whether the course of pyelonephritis varies depending on the kind of causative micro-organism, or why infection occurs so much more commonly when there is obstruction to urine flow. The risk of upper urinary tract infection following cystitis cannot be stated, and, conversely, it is not known how often cystitis occurs

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as a sequel to kidney infection. It would be important to know how often such procedures as catheterization and cystoscopy lead to upper urinary tract infection, and also why treatment with potent antimicrobial agents only occasionally results in eradication of the infection.

In preparing this article an attempt has been made to bring together and appraise many of the clinical observations and laboratory experiments which bear on questions such as those listed. Here and there the collected evidence seems adequate to permit the forming of a tentative conclusion, but more often the answer is still elusive, partly because no information is available and partly because the "data" are inadequate or undependable. Attention will be called to certain peculiar features of this infectious process. It is hoped that the material as presented here will not also be "stupefying" but will instead help to define some of the problems and provide stimulus for further productive studies of an immensely important disease.

SOME NOTEWORTHY FEATURES OF PYELONEPHRITIS AS AN INFECTIOUS PROCESS

The micro-organisms commonly associated with pyelonephritis (E. coli, staphylococcus, enterococcus, etc.) are pathogens capable of producing acute pyogenic infections in many parts of the body. They are usually looked upon as extracellular parasites susceptible to phagocytosis and lacking any notable tendency to lurk in the tissues for long periods of time. Although at times pyelonephritis exhibits the characteristics of an acute pyogenic infection, its outstanding characteristics are indolence and extreme chronicity, comparable to the usual behavior of pulmonary tuberculosis. It is not uncommon for this infection to proceed to a stage of severe renal damage without any preceding illness or disability which can be identified in retrospect as having been a manifestation of acute pyelonephritis. The histological picture found in an established case is not typical of an acute pyogenic process or of a viral or granulomatous disease; it is compatible, instead, with the indolent clinical course of the disease: some cellular infiltrate, some scarring, but bacteria rarely demonstrable.

Considering the fact that the responsible micro-organisms are usually susceptible *in vivo* to the action of sulfonamides, nitrofurans, or antibiotics, the results of drug therapy in this disease are surprisingly poor. Only about 10 per cent of cases of chronic pyelonephritis respond satisfactorily.[87] Consider, for example, the results in enterococcal infections of the urinary tract. The enterococcus is susceptible to the combined effect of penicillin and streptomycin, these drugs appearing to have a bactericidal action *in vivo* as well as *in vitro*.[54] Nevertheless, enterococcal infections of the urinary tract are eradicated only occasionally by this same supposedly bactericidal com-

bination of antibiotics. Yet the factors responsible for the poor response to chemotherapy are not obvious. Inadequate blood supply does not seem likely since even the "scarred" kidney is not the avascular structure we find in a vegetation of bacterial endocarditis or the wall of a chronic draining sinus. As a surface on which phagocytosis can take place, the kidney does not seem to share the defects noted on serous surfaces or in fluid media.[68] The indolence, chronicity, and resistance to chemotherapy bring up the question whether the causative bacteria may at times lodge in some kind of shelter in the kidney, perhaps establishing a form of intracellular parasitism there. The very indolence of the infection may be partly responsible for the indifferent results of chemotherapy, since these agents are often most effective when the micro-organisms are in a stage of active multiplication.

Undoubtedly one of the important factors in the problem of kidney infections is the matter of frequent or almost continuous seeding of the kidney with fresh supplies of bacteria. All clinicians have experienced the frustration of watching an infection due to one kind of microbe subside, only to be superseded by infection due to another. Even with persisting infection due to, say E. coli, there remains the possibility that fresh strains not differentiable by common bacteriological methods are entering the picture from time to time. It is impossible to determine whether these changing bacterial populations represent *new* infections, or whether they are simply alterations in equilibrium whereby the suppression of one form permits growth of another.

The interrelation between bacteria growing in the urine and bacterial infection in the tissues of the kidney, ureters, and bladder is not understood. The question is often raised whether the aim in chemotherapy is eradication of the bacteria in the tissues or those in the urine. Prevailing opinion seems to emphasize the importance of directing treatment toward bacteria in the tissues, but this may not be correct, since it may be necessary to prevent growth in both areas. Undoubtedly phagocytosis of micro-organisms in urine is not very effective; this may be one of the factors which makes sterilization of the entire system so difficult.

Of central importance is the rôle of obstructive uropathy in contributing to the occurrence and stubborn persistence of kidney infection. This problem will be considered in more detail later, though without satisfying answer.

BACTERIOLOGY OF THE NORMAL URINARY TRACT

The urethra. The meatus, being on the surface of the body, and contiguous with skin heavily populated with bacteria, naturally always has bacteria on its surface. We need more information, however, on the bacterial flora of

the urethral canal. Textbooks of bacteriology usually state that it is normally sterile or may contain a few micrococci, diphtheroids, etc., the scarcity of bacteria being attributed to the acidity of urine and its mechanical flushing effect. Actually, however, the presence of micro-organisms within the urethra is not at all unusual. Helmholz has reported recovery of bacteria at a depth of 5 cm. in the urethras of 50 per cent of normal males.[30] Shackman and Messent report that the normal male urethra may contain "staphylococci, Str. faecalis, diphtheroids, Bact. coli, Str. viridans and bacilli of the Proteus group."[57] Leishman, testing only for E. coli, found it in the urethras of 4 of 25 adult females. Hirshfeld *et al.* found bacteria of some kind in the urethras of about half of 114 normal pregnant women.[31]

One is not justified, then, in assuming that a catheter or other instrument being introduced into the bladder is passing through a bacteria-free passage.

Urine obtained from the bladder and upper urinary passages. There are many reports on cultures of bladder urine and ureteral urine, although most of these deal with patients in whom there had been some reason to suspect presence of urinary tract disease. For obvious reasons the data on normal subjects are insufficient, although several studies have been carried out on normal pregnant women. The techniques of catheterization, of bacteriological procedure have varied considerably, as have the population groups studied. The surprising thing, however, is the frequency with which bacteria have been found. The published reports from various sources appear to indicate that one can expect bacteria in the urine of from 5 to 40 per cent of normal adult people who give no evidence or history of urinary tract disease.[40, 41, 45] According to Schulte[55] the "normal flora" of urine of normal human subjects, arranged in order of frequency is "micrococcus, diphtheroids, strep. faecalis, alpha streptococcus, gamma streptococcus, Staphylococcus albus, E. coli, A. aerogenes and Pseudomonas."

In evaluating these studies the possibility of false positive results due to contamination by organisms introduced into the bladder urine during passage of catheter or cystoscope can never be eliminated positively. Helmholz and Millikin[29] found that even with the most careful technique, including thorough washing of the meatus, they got positive cultures in bladder urine in "one-half to two thirds" of normal infants. They concluded: "Chances of contamination are so great that the presence of organisms in the urine does not prove, without further control, that they have come from the kidney." In a compilation of the results of urine cultures of normal pregnant women the incidence of positive results reported by different investigators varied from 13 to 74 per cent.[46] In a similar study bladder urine was said to be "infected" in 43 of 114 antepartum women.[31]

Hundley *et al.*[38] compared bladder urine cultures of 50 normal women and 50 pregnant women. Positive cultures were obtained from 32 of the former and 22 of the latter group. However, E. coli was encountered in only 9 of the 54 positive cultures, most of the organisms found being of doubtful pathogenicity, i.e., staphylococcus albus, streptococcus viridans, diphtheroids, and yeasts.

Studies such as those quoted would have provided more meaningful information if some rough quantitative test had been made. It is probable that up to 1,000 micro-organisms may be found per ml. in normal urine, due to unavoidable contamination from the surface of the urethra during urination or catheterization. In active infection, however, the number of organisms is likely to be from many thousands to millions per ml. of urine. A simple and practical quantitative bacteriological test is to examine a stained smear of the urine. If bacterial cells can easily be found by this method, it is safe to assume that more than 10,000 per ml. are present. Another useful procedure is to dilute the urine, say 1 to 100 and 1 to 100,000, before inoculating culture media. Growth obtained from the higher dilution would be indication of active infection.

THE SOURCE OF BACTERIA WHICH INFECT THE URINARY TRACT

There cannot be much doubt that the origin of the micro-organisms which cause pyelonephritis is in the flora of the intestinal tract. This can confidently be inferred from the bacteriology of pyelonephritis, since coliform bacilli are responsible for about 80 per cent of early, uncomplicated cases. Staphylococci, enterococci, Proteus, and Pseudomonas may also be found, especially in complicated cases of long standing, but these too probably get to the kidney from the bowel. Story[58] compared Proteus strains from urine with Proteus from the same patients' bowel contents and found most pairs from individual patients to be identical. He concluded that autoinfection from the gut is the most frequent mechanism of Proteus urinary infections. Jensen reported that he could lower the incidence of complicating urinary infection following urological operative procedures by first reducing the bacterial content of the intestinal tract with antibiotic therapy.[35]

CONDITIONS AND DISEASES WHICH ARE ASSOCIATED WITH PYELONEPHRITIS

Pyelonephritis of young children. Although exact figures are not available there seems no question about a high incidence of acute pyelonephritis in children between six months and three years of age. It is generally agreed, too, that the disease is commoner in females than males, perhaps 3 : 1. This occurrence of pyelonephritis during the diaper period, when fecal contami-

nation around the urethral meatus is likely to occur, together with the higher incidence in females, has been thought to indicate that the pathway of infection in these cases is via the urethra. Female children would seem to be more susceptible because of the short length of the urethra and greater chance of soiling its meatus. As will be discussed later, this kind of pyelonephritis is very possibly an example of ascending urinary tract infection.

It is generally believed that the pyelonephritis of infants has the same potentialities for chronicity and serious complications as other forms of the disease.[65, 15, 64]

Pyelonephritis of pregnancy. Acute pyelonephritis occurs in about 2 per cent of pregnant women, usually during the second half of pregnancy. It is not an inconsequential infection, probably being an etiologic factor in some cases of toxemia,[51] and certainly being followed by chronic pyelonephritis, with all of its serious potentialities.[63]

Many opinions have been expressed about the cause of the high incidence of pyelonephritis in pregnancy. The most obvious lead is the dilatation of the kidney pelves and ureters, demonstrable in most women after the third month and generally disappearing a few weeks after parturition. The dilatation is more frequent and of greater extent on the right side. It involves the ureter only to the pelvic brim, that portion lying within the true pelvis maintaining normal caliber.

The cause of ureteral dilatation in pregnancy has been discussed extensively. Some have suggested that it is a matter of obstruction by the pregnant uterus, since similar effects have been seen in patients with other large pelvic tumors.[1] The fact that the right ureter seems to be affected more than the left has been attributed to: (a) dextro-rotation of the uterus, (b) the wider angle at which the right ureter crosses the iliac vessels, and (c) protective cushion of the sigmoid colon overlying the left ureter. Another possible cause of the ureteral dilatation which has been proposed is the great hypertrophy of the longitudinal sheath of muscle bundles at the lower end of the ureter.[32] This, however, would not easily explain the greater involvement of the right ureter or the fact that the dilatation is observed only above the pelvic brim. Another possibility is that the ureteral dilatation is part of the atony that affects several smooth-muscled structures during pregnancy (uterus, colon, gallbladder). In support of this, Traut and McLane have found diminished amplitude of the ureteral peristaltic wave after the third month of pregnancy.[61] A reasonable conclusion, then, would be that atony of pregnancy, plus obstruction by the gravid uterus and the anatomical factors which render the right ureter more susceptible are all involved in the changes which occur during pregnancy.

Why does infection tend to occur in the kidneys under these circumstances? We must not forget that ureteral dilatation occurs nearly always, but pyelonephritis only once in 50 cases. The available information does not show the bladder urine in normal pregnant women to have more bacteria than the bladder urine of nonpregnant women[88]; the vesical irritability so common in pregnancy is not to be regarded as a manifestation of cystitis. There remain these possibilities: (a) It is said, but without any kind of support, that the constipation often present in pregnancy favors transport of enteric organisms from colon to the kidney via lymphatic anastomoses. The reasons for rejecting the likelihood of this pathway will be considered in detail later. (b) Barksdale[4] reported that he could demonstrate vesicoureteral reflux in some pregnant dogs, but not in normal or post-partum animals. This might facilitate passage of bacteria from the lower to the upper urinary tract. (c) A dormant infection in the kidney may be activated in pregnancy, possibly because of unidentified factors associated with pregnancy, comparable to the higher incidence of poliomyelitis, or possibly because of low-grade obstruction to the drainage of urine. That there is increased hydrostatic pressure in the atonic dilated ureter is indicated by the work of Hundley *et al.*[33] who found that the ureteral and pelvic dilatation could be reduced by allowing an ureteral catheter to remain in place for 48-72 hours. (d) Bacteria which happen to escape from the bowel may be carried to the kidney in the blood, and there find conditions suitable for growth and establishment of a new infection, as outlined under (c).

Diabetes mellitus. Urinary tract infection is commoner in diabetics than in nondiabetics, although precise data on this are lacking. Harrison and Bailey searched for bacilluria and pyuria in 50 patients with diabetes mellitus and in 50 control individuals of comparable age groups. They found a higher incidence of both in the diabetic group.[28] Baldwin and Root discussed 86 cases of upper urinary tract infection in patients with diabetes mellitus observed in one clinic over a 5-year period, 37 of which had terminated in death. They were of the opinion that urinary tract infections in diabetics are more frequent, more protracted, and more serious in nature. They quote statistics based on autopsy examination indicating that 20 per cent of the diabetic individuals show evidence of bacterial infection of the kidney, as compared with 4 per cent of nondiabetic persons.[3]

Necrotizing papillitis, a severe and fulminating form of pyelonephritis is much more likely to occur in the diabetic than the nondiabetic patient. Edmondson *et al.*[18] reported on 50 cases of necrotizing papillitis found in 32,000 autopsies at the Los Angeles County Hospital. Twenty-nine of the 50 were encountered among 859 known cases of diabetes mellitus in this

series, whereas only 21 examples were found among the remainder, 1,023 of whom had pyelonephritis. It is generally believed that vascular disease associated with diabetes is an important factor contributing to the greater frequency of renal papillary necrosis in diabetic subjects.

Why should pyelonephritis be more likely to occur in the patient with diabetes mellitus? Possibilities which suggest themselves are: (a) Patients with diabetes are generally believed to be more susceptible to infections, e.g., carbuncles, tuberculosis, mucormycosis, moniliasis. They may have a similar increased susceptibility to kidney infection. (b) Glycosuria may favor the growth of bacteria in the urine. (c) Catheterization is performed frequently in patients with diabetes, in the course of routine work-up and especially in management of patients in severe acidosis.

Obstructive lesions of the urinary tract. The most obvious and probably most important factor in the etiology of pyelonephritis is obstruction to the free flow of urine anywhere between the kidney pelvis and the urethral outlet. The kind of obstructing lesion varies with the age group: congenital anomalies in children, stone, inflammatory edema or stricture in all age groups, and tumors after middle age.

The statistics on the relation between obstructive uropathy and infection are impressive. Campbell[14] estimates that chronic urinary tract infection is 20 times as frequent in children with anomalous urinary tracts as in normal children. Bell's autopsy findings were that the obstructive type of pyelonephritis is about 12 times as frequent as the nonobstructive type.[7] Bell's data also indicate an apparent difference in incidence of infection depending on whether the obstruction is in the ureter (23 to 46 per cent) or in the bladder or urethra (61 to 83 per cent). He suggested that the difference in frequency of infection might be due to the fact that in low obstruction the bladder becomes distended and that this would tend to cause reflux of urine from bladder into ureter. There is, however, another and perhaps better, explanation, namely, that indwelling catheters and cystoscopic treatments are more frequently employed in patients with low obstruction. These therapeutic procedures may themselves be responsible for introducing the infection.

The terms "stagnation" and "stasis" enjoy great favor when the relationship between obstruction and infection is being discussed. The analogy of the "stagnant millpond and the swiftly-running brook" has been drawn, the implication being that growth of bacteria in an inadequately draining reservoir of urine provides a constant source of re-infection to the adjacent tissues of the urinary system. The concept of the evil influence of urinary stagnation is undoubtedly responsible for the common practice of "forcing

fluids" in urinary tract infection. No evidence could be found, however, that this is of curative value, although of course it may have some virtue in reducing dysuria and retarding stone formation. On the other hand, we all have seen many instances where large daily flow of urine has been obtained in patients with incomplete obstruction, without affecting the existing infection, and conversely have seen infections subside quickly after relief of obstruction whether fluids were "forced" or no.

Campbell states that there is some evidence that in the presence of urinary tract obstruction there is perceptible reduction in the phagocytic activity of endothelial cells of renal capillaries.[14] It has not been possible to locate a detailed description of the work on which this statement was based.

It is easy to demonstrate that ureteral obstruction increases susceptibility of the kidney to infection by bacteria which are injected intravenously. The obstructed kidney usually becomes massively infected and progressively destroyed by pyogenic infection whereas the opposite kidney shows no evidence of infection. The best description of this phenomenon is that of Mallory, Crane, and Edwards.[44] These authors noted also that *the progress of the acute infection could be halted simply by removing the ligature from the ureter.*

The relation between urinary obstruction and susceptibility to infection may be only another example of a general phenomenon, that tissues under increased hydrostatic pressure exhibit diminished resistance to pyogenic infection. For example, pyogenic infection is more common in any organ whose excretory duct is obstructed (gallbladder, salivary gland, pilonidal cyst, lacrimal sac, para-nasal sinus, etc.). Several possibilities might be suggested: alteration in blood flow, alteration in lymph flow, diapedesis of leukocytes, efficiency of phagocytosis.

Disturbances in bladder innervation. Many disorders of the nervous system are associated with disturbance in bladder function and urinary tract infection, important examples being multiple sclerosis, poliomyelitis, diabetic neuropathy, tabes dorsalis, and spinal cord injury.

The best information about the sequence of anatomical and functional changes comes from studies of war veterans who sustained spinal cord injury and paraplegia. In special hospitals set up for the care of groups of such patients some helpful observations have been made, although there seem to be no good data on how soon after injury the first sign of kidney infection makes its appearance. Talbot and Bunts[60] report on pyelographic and cystographic studies. In a group of 331 patients with paraplegia, 16 were found to have developed significant hydronephrosis. Cystograms were done on 15 of the 16, and 10 of those were found to have vesico-ureteral

reflux. Thirteen of the 16 patients living at the time of their report had studies of renal function, and 8 of the 13 showed "serious renal impairment." In a later report from the same center[84] Hutch and Bunts discuss the time relationships between spinal cord injury and the appearance of radiographic evidence of uropathy. They found that hydro-ureter and calyectasis increased steadily during the first two years. Functional damage (judged by excretory urography) is not marked for the first three years, but is likely to increase rapidly after that time. Vesico-ureteral reflux also appears and increases after three years, paralleling the loss of renal function. At another center 56 of 238 (23%) paraplegic patients were found to have developed vesico-ureteral reflux.[8]

The foregoing observations seem to make a strong case for the importance of ascending infection in the pyelonephritis complicating neurogenic uropathy, the sequence of events being: retention—catheterization—cystitis—vesico-ureteral reflux—pyelonephritis.

Iatrogenic urinary tract infection. One of the most important questions that must be asked is how frequently some therapeutic or diagnostic procedure such as catheterization or cystoscopy causes urinary tract infection? Catheterization is one of the commonest procedures in medical practice today. Obstetricians, gynecologists, and urologists unhesitatingly do it as a routine practice before a variety of procedures. It is carried out one or more times in a considerable proportion of postoperative patients. Indwelling catheters are often employed routinely in the management of unconscious patients. Clinical investigators leave catheters in the bladder during certain kinds of renal function test.

Opinions vary greatly on the danger of catheterization. The fact that no one would use an unsterile catheter or fail to make some gesture toward antisepsis in cleaning the area around the meatus proves that some risk is acknowledged, still the very frequency with which the procedure is done indicates that many clinicians believe the danger to be small. At the other extreme there are experienced clinicians who regard the danger of catheterization sufficient to require stringent indications for it. Certainly cystitis developing as a result of one or two postoperative catheterizations is no great rarity. Marple's study furnishes some information on this point.[45] He catheterized 100 female patients on a medical ward service, employing strict aseptic and antiseptic technique, but observed that four of his patients developed urinary infections one to three days later.

In considering this subject we should differentiate between simple catheterization and the indwelling catheter. When the latter is used, the urethra is distended by a foreign body for days or weeks. The response to

this is production of a sheath of mucopurulent exudate around the catheter, providing a splendid medium for growth of micro-organisms. *Infection of the bladder cavity is almost inevitable* under these circumstances,[57] and is not prevented by irrigations or by "prophylactic" antibiotic therapy. As emphasized by Kass,[37] prophylactic antibiotic therapy in such circumstances only serves to ensure that the infection will be caused by organisms not easily affected by available antimicrobial agents.

Simple catheterization does not seem to have all of the dangers associated with the indwelling catheter but, as has already been discussed, it does carry some risk of introducing bacteria into the bladder, either from errors in aseptic and antiseptic techniques or from contamination by bacteria lying in inaccessible parts of the urethra. Garrod *et al.* have some data which they interpret as indicating that catheterization increases the likelihood of enterococcal infection in patients with pre-existing infection.[21]

Scandinavian workers have laid special stress on the danger of catheterization, cystoscopy, etc. Ørskov, by typing Klebsiella strains isolated from urinary infections of patients in one hospital, obtained convincing evidence that cross-infection was a common occurrence.[48] She suspected, but did not prove, that inadequate sterilization of catheters and other urologic instruments was responsible. This view was endorsed by Lindau and Ouchterlony in discussing Ørskov's findings. In a later report, however, Ørskov suggests that indwelling catheters may become fecally contaminated by the hands of the individual patients.[49] Jensen[35] reports that every one of 14 patients with previously sterile urine had bacteria in the urine within 48 hours "after operation or large instrumental interference." Jonsson and Erlanson stated that "practically all" patients with prostatic disease or bladder tumor, requiring catheterization or indwelling catheter, became infected during their stay in hospital, whereas the incidence of infection in patients with disorders not requiring catheterization, such as malformations and urinary calculi, was comparatively low.[36] Similar opinion is voiced by Halkier *et al.*[27] This is in agreement with Bell's finding,[7] mentioned previously, that pyelonephritis is commoner in patients with obstruction to bladder emptying than in patients with ureteral obstruction.

One further danger of urethral instrumentation is that it may produce a transient bacteremia. Clinicians have known since the last century that the passage of catheters and sounds might be followed by fever. It is now known that the fever is a manifestation of bacteremia, the mechanism doubtless being sudden increase in tension of inflamed tissues around the urethra causing lymph containing bacteria to flow in the direction of the blood stream. Powers summarized the literature on this subject in 1936, including some interesting quotations on "catheter fever" from the older literature.[52]

In view of the possibility that infection of the kidneys may take place via the blood stream, *the bacteremia of urethral instrumentation probably represents one of the ways in which infection is transferred from lower to upper urinary tract.*

Hereditary pyelonephritis. One example of high familial incidence of pyelonephritis has been observed among a kindred in Utah.[50] About 50 members had renal disease similar to the entity described by Weiss and Parker,[68] but progressive insufficiency developed only in the males affected. This observation, although of interest, does not provide additional clues in respect to the problems under consideration here.

SOME QUESTIONABLE ASSOCIATIONS

Acute infectious diseases in children. Statements are occasionally encountered to the effect that children are liable to pyelonephritis following acute respiratory infection, otitis media, etc. There is actually no convincing evidence of any such relationship, and indeed when we consider that children average half a dozen acute respiratory illnesses per year, it would be a practical impossibility to obtain proof that the relationship exists.

Diarrheal disease. Schwartz, in 1918, described an extraordinary frequency of urethral and bladder contamination in infants, with diarrhea, especially in females.[65] Since that time there have been numerous statements about an increased incidence of urinary tract infection following diarrheal disease in children. No conclusive data on this have yet been provided, and the possible relationship seems unproved as of now. It is interesting to note, however, that Leishman[40] found 19 urine cultures positive for E. coli among 36 women with diarrheal disease, and only one positive among 16 men with diarrheal disease. None of those patients had pyuria or symptoms of urinary infection.

Constipation. The impression that constipation favors urinary tract infection seems to have been widely entertained, but a definite correlation has not been demonstrated, indeed, one wonders how it ever could be, in view of the frequency and indefiniteness of constipation as a symptom. A negative correlation was obtained by Leishman, who performed urine cultures on a group of 14 men and 40 women, all with "obstinate constipation." The proportion of positive cultures was almost identical with that in his control groups. It would seem that for the present we should omit constipation from the list of factors in the pathogenesis of pyelonephritis.

Birth trauma. The view that the relaxations which may follow birth trauma predispose to urinary tract infection seems to be only a clinical

impression, almost impossible to substantiate or to disentangle from such factors as catheterization, residuals of pyelonephritis of pregnancy, etc. In Marple's study of 100 female medical patients[45] no evidence of a higher incidence of positive urine cultures associated with birth trauma was observed.

"Honeymoon cystitis and pyelitis." Gynecologists agree that symptoms of cystitis are not rare in women during the first few days of marriage. This is ascribed in some way to the trauma of sexual intercourse. It is not an easily studied entity, and the symptoms are probably not always due to infection. No evidence whatever was found to support the concept of "honeymoon pyelitis," and this term should be abandoned.

THE POSSIBLE PATHWAYS BY WHICH BACTERIA REACH THE KIDNEY

Let us now consider some of the evidence pertaining to the oft-debated problem: by what route do bacteria travel from the intestinal tract to the substance of the kidney? Medical literature contains many strong statements of opinion, but there is still nothing conclusive. Writers often seem to have drawn unwarranted conclusions based upon a set of animal experiments or some clinical observation on one form of pyelonephritis. To cite a recent example: Barnard, Story, and Root[5] state that 51 of 52 patients who were referred to a special clinic for urinary tract infections in diabetics were women. They seem to regard this fact alone as reliable evidence that the initial event in urinary tract infection is urethral contamination. Cabot and Crabtree[18] in their masterful summary of the problem in 1916 came out forcefully in favor of the hematogenous pathway of infection and indulged in some sarcasm regarding other points of view; yet they fell back on the following statement to explain the higher incidence in women: "In the adult female, we think, there can be no doubt that the large intestines are more favorable to the occurrence of bacilluria than in the male. There is as yet no adequate explanation of the greater frequency of these infections in the female child, but we think that existing evidence points to the view that this explanation will be found, not in the anatomical peculiarities of the female urethra, but in the anatomical peculiarities of the female intestine."

Infection of the kidney by way of the lymphatics.

(a) *From the intestine directly to the kidney.* Postulation of the importance of this pathway of infection has been popular since the work of Franke[20] in 1910. He demonstrated lymphatic connections between the appendix and cecum and the right kidney. This fact has 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. While the right kidney is involved somewhat more frequently than the left, anatomical factors already discussed may account for the difference which is noted in pregnancy.

If we assume that bacteria do sometimes pass from the bowel into the intestinal lymphatics, what is the likelihood that they will travel to the kidney in preference to the usual pathway into the para-aortic system and eventually into the thoracic duct and thence to the circulating blood? The mere demonstration that dye injected under pressure exposed channels of communication between the ascending colon and the right kidney does not prove that lymph from the bowel would ordinarily travel by such a pathway, and certainly does not explain left-sided or bilateral disease. Where lymphatic obstruction exists, as in filariasis, chyle may appear in the urine, but this is certainly a rare event.

(b) *From the lower urinary tract.* In many instances there appears to be infection in the bladder, urethra, and para-urethral structures for a variable period of time before there is a spread to the upper urinary tract. Several writers have suggested, therefore, that the course of events is first cystitis, then migration of bacteria into the rich lymphatic network of the lower urinary tract, and 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. Sweet and Stewart[50] and Eisendrath and Kahn[19] believed that they had shown its existence in animals, but their principal evidence was lymphocytic infiltration in the outer coats of the ureters following inoculation of bacterial culture into the bladder. As pointed out by Bell, these changes may simply be due to ureteritis.[7] Eisendrath and Kahn made the wholly unwarranted assumption that the possibility of blood stream transfer of bacteria from bladder to kidney was ruled out by the fact that heart's blood culture was negative at the time of sacrifice of the animal. Winsbury-White[66] in a most 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 some animals. He gave so few details that one cannot now evaluate the possible loopholes or soundness of his work.

On anatomical grounds it seems unlikely that there are direct lymphatic communications between the 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 upward from bladder to 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 of MacKenzie and Wallace[48] shows in fact that in rabbits dye particles injected into the uterine cervix, bladder wall, and ureter travel not toward the kidney but into the common iliac glands, thence upward along the aorta to the thoracic duct. Their findings contradict Winsbury-White's.

It appears unlikely then, that the postulated pathway from lower to upper urinary tract via the lymphatics exists at all.

Hematogenous. The principal points for and against the blood stream as the principal pathway of kidney infection are as follows:

(a) No one questions that coccal infections of the kidney develop as a result of hematogenous dissemination. Oftentimes no other anatomical possibility exists, as, for example, when renal cortical abscess develops subsequent to carbuncle of the neck.

(b) It is usually assumed, although without much factual proof, that enteric bacteria must occasionally escape from the intestinal canal of the human being, and be carried to the blood, via lymphatics. This would provide opportunity for some of them to reach the substance of the kidney, where under favorable circumstances they might be able to establish infection. Actually, coliform bacteria are not common "contaminants" of blood cultures of human beings, and their presence in the blood is seldom noted in the absence of definite coliform infection in the urinary tract or elsewhere. Furthermore, many experiments in animals have shown that only a small proportion of bacteria which are injected into the blood stream are trapped by the kidneys. One might ask why, if enteric organisms are frequently disseminated in the blood, the principal tissues to suffer are the kidneys?

For the concept of infection by the path: normal intestinal tract—lymphatics—blood—kidney—one would like to have a little more evidence that enteric bacteria do in fact get into the blood stream occasionally in healthy human beings.

(c) It can be accepted as proved beyond question that bacteria may reach the blood stream following instrumentation of the urethra. Bacteremia has been found in a significant proportion of cases immediately after the passage of a sound or cystoscope.[6] This having been proved, one is justified in assuming that instrumentation may not always be required, and that bacteremia may occur in the course of a lower urinary tract infection as a result of normal lymphatic drainage and perhaps augmented by such acts as micturition or straining to defecate.

On the whole, then, there can be little question that bacteria sometimes reach the kidney by the path: infected bladder or urethra—lymphatics—blood—kidney.

(d) It has been amply demonstrated that kidney infection can be induced in animals by bacteria injected into the blood stream. In the case of staphylococci[17] and C. renale[42] this occurs in previously normal kidneys. In the case of coliform bacteria, however, in order to obtain kidney infection in a high proportion of experimental animals it is necessary to injure the kidney in some way first. The usual method employed is to obstruct the ureter.[44] The same effect can be obtained, however, by trauma to the kidney before inoculating the bacteria.[9,10]

(e) Some writers have pointed to the cortical distribution of lesions in early pyelonephritis as evidence favoring the hematogenous pathway of infection.[24,65] However, Kennedy, in what appears to be an important contribution,[38] says that it is futile to attempt to decide the portal of entry on the basis of distribution of lesions in the human kidney. He had the opportunity to study the organs of four children who succumbed within a few days after the inception of acute pyelonephritis and found the lesions to be widespread in all of them. He carried out animal experiments in which the bacteria were inoculated intra-ureterally or intravenously and found that by the end of 48-72 hours the lesions in the two groups were indistinguishable.

Ascending infection. Cabot and Crabtree, before detailing a series of objections to it, remarked in 1916 that "the theory that infections reach the kidney by direct extension from the lower urinary passages has acquired the dignity of old age and has been a widely held and attractive theory because of its extreme anatomic simplicity."[18] Despite the arguments presented by these writers the theory is still an attractive one, supported by a variety of clinical and experimental observations.

The main question in connection with the ascending pathway revolves about the possibility of movement of bacteria out of the bladder into the ureters and thence to the kidneys. It is generally accepted that bacteria gain entry to the bladder most frequently by way of the urethra. We should, therefore, consider at this time the evidence on vesico-ureteral and ureteral reflux.

Vesico-ureteral reflux. There is lack of agreement about the frequency with which reflux occurs in normal individuals. Many observers are impressed with the mechanical excellence of the vesico-ureteral valve, and believe that it is rarely if ever incompetent. At autopsy the ureteral orifices are seldom found widely patent even in patients who have had obstruction to bladder emptying for some time. One urologist states that in 722 cysto-

grams reflux was never observed except in the presence of some other uropathy.[14] Another, however, says that he was able to demonstrate reflux in 2 of 43 children without known urologic disease.[22] Another reports that reflux was encountered in 3 of 10 normal children and 1 of an unstated number of normal adults. The various pieces of evidence on this subject up to 1944 were reviewed by Prather.[58]

The employment of the "delayed" cystogram[8, 12] seems to be an improved way of demonstrating reflux when it is present. In this technique the bladder is filled with radio-opaque material, a picture is taken, the patient is allowed to get up and move about; a second exposure is made after 30 to 60 minutes. In some instances the second examination reveals reflux when the one done immediately after filling the bladder had not.

Considering that cystography is our only method of testing for reflux in the human being and that it will only disclose a comparatively gross spilling sufficient to be visible in the x-ray film, it seems reasonable to suspect that escape of small quantities of urine from bladder into ureter may occur more frequently than can be detected, even in persons with normal urinary tracts. For example, greater distension of the bladder can be achieved when it is gradually filled with urine than when fluid is rapidly introduced through the urethra, as is done in cystography. The mechanical effectiveness of the valve undoubtedly depends on the long oblique course which the ureter takes through the bladder wall, but when the bladder becomes greatly distended, the wall thins out, and the ureter must take a nearly perpendicular course.

Reflux into the ureters is a fairly common finding in patients who have chronic urinary tract infection, even when the appearance of the ureteral orifices as seen through the cystoscope is normal. Bumpus reviewed the records of 1,036 patients on whom cystography had been performed.[11] He found that chronic reflux from bladder to ureters was demonstrated in 8 per cent of them. He suggested that reflux probably occurs because the intravesical portion of the ureter is involved in inflammation and changes from its normal easily compressible state to that of a semi-rigid tube. This appears to be a plausible explanation of the high incidence of reflux in chronic urinary tract infection, and is perhaps the mechanism responsible for extension of infection from the bladder to the kidneys in patients with long-standing bladder infection, e.g., in paraplegic individuals with indwelling catheters. One other possibility might conceivably play some part in this relationship between urinary tract infection and vesico-ureteral reflux: individuals who already have incompetent valves may develop upper tract infection because of this defective barrier.

Mention has already been made of the possibility that reflux may occur temporarily in pregnancy. This suggestion, based upon observations in dogs, has not been substantiated in the case of human beings; in fact, in one small series of cases tested for it, reflux was not found.[47]

Studies on animals show that vesico-ureteral reflux does occur when the bladder is greatly distended, and the workers who have made these studies have concluded that this probably occurs in the human being and may be a significant factor in the etiology of pyelonephritis.[23, 26]*

Ureteral reflux. Among the arguments against ascending infection are statements that spread of infection upward via the ureter would be prevented by the effects of gravity and ureteral peristalsis. These arguments are not very convincing. Gravity would not oppose flow toward the kidney when the individual is lying in the recumbent position. A drop of fluid can squirt fast and far through a collapsed tube, as is observed, for example, when the last few drops of urine are expelled through the urethra at the end of micturition, or in the passage of dyes injected into lymphatic vessels. Forces which could provide this propulsion up the ureter might be contraction of the bladder or of the abdominal muscles during movement, coughing and straining. In cystography, once the radio-opaque material gets by the uretero-vesical junction it usually travels up to the renal pelvis in a few seconds.

As for the matter of peristalsis in the ureter, not enough information is available. The excellent acute experiments of Lapides[39] indicate that these structures are more or less autonomous, not affected by a variety of pharmacological agents or the autonomic nervous system. The only stimulus which he found to be effective in stimulating forward peristalsis was the entry of fluid from above. Reverse peristalsis has been observed, however, in the ureters of experimental animals[25]; furthermore, the force of ureteral peristalsis can be overcome if the pressure from the bladder is great enough.[67] Reverse peristalsis or retrograde flow must occur at times in the human ureter. Stones have been observed to move from the lower ureter back up to the kidney pelvis in successive x-ray examinations. Foreign bodies introduced into the bladder have been recovered from the kidney pelvis,[62] and solid fecal material has appeared in the nephrectomy drainage of patients with uretero-colonic anastomoses.[2] The frequency of massive

* Dr. Charles Kleeman has observed what appeared to be instances of this in two healthy young physicians serving as subjects for experiments involving severe diuresis. In attempting to empty the bladder only at specified intervals an uncomfortable overfilling had developed. Both subjects described sudden onset of severe pain in the flank and kidney region, promptly relieved by emptying the bladder. It seems probable these are instances of vesico-ureteral reflux due to overdistension of the bladder.

infection of the kidney in patients with uretero-colonic anastomoses is further proof that infection can easily reach the kidney via the ureter once the safeguard of a normal uretero-vesical valve has been sacrificed.

Let us turn back now to a consideration of the evidence for and against the ascending pathway in the different conditions under which pyelonephritis occurs.

(a) The arguments against ascending infection are all levelled against the likelihood of spread past the vesico-ureteral valves and up the ureters, since it has always been more or less taken for granted that the portal of entry in cystitis is by way of the urethra.

(b) We have already noted the greater frequency of acute pyelonephritis in female children and the opinions that it is related to greater chance of fecal soiling of the urethral meatus during the "diaper" period. The greater frequency of cystitis in adult females has also been noted. A related point is that catheterization is carried out more frequently in females than in males (except possibly in the older age groups). That catheterization carries some risk of cystitis cannot be denied. Yet women are often catheterized "routinely" in obstetrical and gynecological procedures, and much more frequently than males to obtain urine for culture or microscopic examination.

(c) While the manifestations of acute pyelonephritis sometimes come on without preceding symptoms of urinary tract infection, e.g., in pregnancy and in young children, we see many instances where cystitis precedes evidence of kidney infection for a considerable period of time, e.g., in neuropathic bladders and in prostatic disease. Here it is almost certain that *infection spreads from the bladder to the kidney.* From a practical standpoint this is perhaps the most important thing to recognize: that bladder infection, not very serious in itself, is dangerous as a precursor of pyelonephritis. Whether the route from bladder to kidney is via the ureter or the lymphatics-and-blood is less important.

(e) The ascending route appears less obviously the pathway of infection in pyelonephritis of pregnancy and the other instances where signs of acute renal infection appear abruptly in a person who has had no previous urinary disorder and whose urinary tract appears normal. In these cases symptoms and signs of cystitis are absent or minimal, and if present at all, they seem to be secondary to the kidney infection. To explain such cases on the basis of ascending infection one would have to postulate: (i) Entry of bacteria into the bladder, despite the bactericidal action of the urethral mucosa and the mechanical barrier of the bladder sphincter. Admitting that all of the information we have on the bacteriology of "bladder urine" is subject to the error of possible contamination by bacteria picked up from the

lining of the urethra, it must be acknowledged that all workers have reported presence of bacteria in a formidable proportion of normal individuals. Even if we disregard organisms of doubtful pathogenicity it is perhaps significant that the incidence of E. coli in the "bladder urine" of antepartum women is 6 per cent or higher.[40, 88] Yet these are single samples; perhaps repeated examination throughout the course of pregnancy would reveal E. coli in the bladder at one time or another in a much higher proportion of women. (ii) Multiplication of bacteria in the bladder, without pyuria or dysuria. This is not difficult to conceive of, and David's work indicates that it can take place in dogs.[16] He found that instillation of E. coli into the unobstructed, nontraumatized bladder did not cause development of a cellular exudate, but that organisms could be isolated from the bladder urine for as long as a month afterward. (iii) Passage through or around the uretero-vesical valve. Here we cannot fall back on chronic inflammation and stiffening of the intra-vesical portion of the ureter with reflux, or on chronic bladder distension thinning out the valve. Does this happen now and then when due to some circumstance an individual does not empty the bladder until it has been uncomfortably distended for a period of time? Or are there frequent small refluxes, so minute that they could never be detected by cystography? Does the demonstrated abnormality in function and tone of the ureters during pregnancy also include a small proportion of women liable to vesico-ureteral reflux? (iv) Progression up the ureter to the kidney. In a preceding section this subject was discussed, and some reasons were given for stating that ureteral peristalsis and gravity do not appear to be adequate safeguards against this possibility.

Although the passage of bacteria from urethral meatus up to the kidney via the urinary passages is not the matter of "delightful simplicity" it appears to be at first glance, especially in persons without demonstrable disease of the urinary tract, it is certainly within the bounds of reasonable possibility.

SUMMARY AND CONCLUSIONS

Information derived from clinical observations or from animal experiments which may shed light on factors of importance in the pathogenesis of pyelonephritis has been evaluated.

Pyelonephritis has certain peculiarities as an infectious disease. Although the causative bacteria are regarded as extracellular parasites which ordinarily provoke a purulent exudate, they seem capable in the kidney of establishing an infection of extraordinary chronicity. Although most of the causative bacteria are susceptible to one or more potent chemotherapeutic

agents, the results of drug therapy are surprisingly poor, a fact not readily explainable on the basis of such factors as presence of pus, inadequate blood supply, or poor surface for phagocytosis. Lastly there is no good explanation for the well-recognized tendency of urinary obstruction to enhance the infectious process. Further study of these problems is needed.

Evaluation of clinical data on urinary tract infection is hampered by certain sources of error: (i) Lack of quantitative data on urine cultures due to confusion as to the existence of infection or "contamination" by harmless flora of the urethral channel. (ii) There is often no simple and reliable method of differentiating between infection of the lower and upper urinary tracts. (iii) "Bladder urine" obtained by catheter may give a falsely positive culture because it is impossible to sterilize the urethral canal before passing a catheter through it. (iv) The chronicity of pyelonephritis, with remission and exacerbations, renders recognition of the conditions associated with first attacks difficult in many instances.

Acute pyelonephritis occurs with unusual frequency in early childhood and in pregnancy.

Diseases in which there is an unusually high incidence of pyelonephritis include: (i) those with interference with bladder innervation, (ii) those with obstruction to urinary flow, and (iii) diabetes mellitus.

Clinical impressions that it is a complication of respiratory or intestinal inflammation, constipation, or birth trauma lack convincing substantiation.

The part played by catheterization and other instrumentation in causing infection of the urinary tract is discussed. There is substantial evidence that this is one of the major factors in the etiology of urinary tract infection at the present time. There is, however, a regrettable lack of factual information on these problems, e.g., the frequency with which simple catheterization causes cystitis, and, in turn, the frequency with which cystitis leads to pyelonephritis.

The theories offered as to the pathways by which enteric bacteria travel from the bowel to the kidney are discussed. The conclusion is reached that there is little support for the idea that bacteria travel directly from the intestine to the kidney in lymphatic vessels or that they are carried from the lower to the upper urinary tract in lymphatic vessels. It is possible, indeed probable, that they sometimes pass from the bowel or the lower urinary tract into the lymphatic system and thence into the blood stream and to the kidney. Instrumentation of an infected lower tract is known to cause bacteremia.

"Ascending" infection, via the urinary passages, is almost certainly the method by which pyelonephritis occurs in some conditions, notably neuro-

genic bladder disturbances and in diseases such as prostatic hypertrophy, where the bladder is chronically distended.

Evidence on the mechanism and occurrence of vesico-ureteral and ureteral reflux is considered.

Stress is laid on the importance of bacterial contamination of the urinary bladder as a factor leading to the development of pyelonephritis. This appears to be a subject deserving of careful consideration, since it is undoubtedly easier to prevent or to treat than pyelonephritis.

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