Medical Progress

Urinary Infections: A Selective Review and Some Observations

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IF, AS HAS BEEN ESTIMATED, one-half of the world's scientific literature has been written by people still alive today, the task of reviewing the literature of even the past 15 years on urinary infections would require Herculean effort. We apologize at the beginning to those authors whose significant contributions have passed unmentioned or have been misinterpreted.

Because the risk of asymptomatic bacteriuria, at least in terms of ultimate renal failure, is unknown, and probably not serious, we decided to divide urinary infections into several well-recognized clinical groups, some of which clearly impose a definite risk to the patient. Those at least risk include (1) nonpregnant women with asymptomatic bacteriuria, (2) pregnant women with bacteriuria, and (3) men with recurrent bacteriuria from chronic bacterial prostatitis. Those at greater risk include (1) children with bacteriuria, especially in the presence of reflux, (2) urinary infections in patients with obstructive urologic disease, and (3) infections in patients with neurologic disease, particularly paraplegia. In addition to reviewing each group separately, we close by presenting a few principles which should govern the treatment of any patient.

Bacteriuria and the Diagnosis of Urinary Infection

If a patient has chills, fever, dysuria and frequency, and if the urine contains many bacilli and leukocytes (with clumps) per high power field of the microscope, few would argue against the diagnosis of urinary infection. Difficulties arise, however, if the patient forces fluids or if he is inadequately treated with an antimicrobial agent; although his symptoms may subside and the leukocytes diminish, bacteriuria can persist. More importantly, many patients with repeated urinary infections come to have no symptoms with recurrences.

Two simple observations form the basis for diagnosing urinary infections. First, there is no evidence that bladder urine intermittently contains bacteria. While transient bacteriemia may be common events in everyday life, the glomeruli do not readily filter these bacteria into the urine. For example, if an anesthetized dog is infused intravenously with billions of bacteria, ureteral urines remain sterile for hours even though thousands of bacteria are perfusing the kidney per minute (Chart 1). Thus, in the absence of any evidence to the contrary, we believe the bladder urine is normally sterile, and the presence of any bacteria in bladder urine is an abnormal circumstance. Second, if bacteria are inoculated into normal urine, the organisms double about every 45 minutes,[1] soon approaching 10^8 bacteria per ml of urine. Most patients with urinary infections contain 10^8 bacteria per ml,[2] especially in a nonhydrated or first voided AM urine.

If the physician accepts the data that pyuria,* depending upon the population studied, occurs in only 50 percent of asymptomatic female patients with bacteriuria,[3] that pyuria occurs commonly in the absence of bladder bacteriuria,[4] and that Gram stain has an intrinsic error of about 20 per-

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*Arbitrarily defined as the presence of 5 or more white blood cells per high power field in the centrifuged specimen.

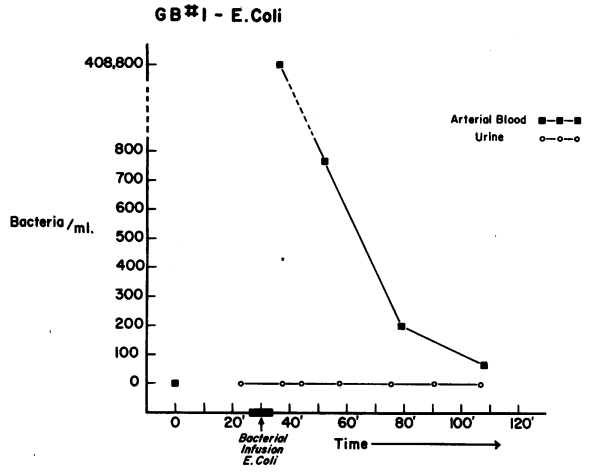

Chart 1.—Ureteral urine and arterial blood specimens from a dog were cultured after a rapid intravenous infusion of 500 ml of saline solution containing 10^5 E. coli per ml. Despite thousands of E. coli perfusing the kidney per minute, the ureteral urine specimens remained sterile; a Goldblatt clamp, placed several weeks before this study, partially occluded the left renal artery.

cent,[3] there is no choice other than to count bacteria in the urine. Under these circumstances, the difference between bacteriuria and nonbacteriuria is clearly a statistical consideration in which methodologic factors are of critical importance. Failure to appreciate this point has caused considerable controversy.

Although Marple at Stanford in 1940,[4] Barr and Rantz of the same university in 1948,[5] and Sanford and his colleagues at Harvard in 1956,[6] made the initial observations in quantitating bacterial counts in catheterized urine, it remained for Kass and his co-workers at Boston City Hospital to establish the quantitative basis for diagnosing bacteriuria.[3,7] Initial studies on the frequency distribution of bacterial counts in asymptomatic women from the Boston City Hospital were obtained by catheterization in the clinics under random circumstances (that is, they were not first morning specimens).[7] Approximately 46 percent of the specimens were sterile, 22 percent contained from 1 to 10 bacteria per ml, 6 percent had more than 10^5 bacteria per ml, and the remainder of the counts fell into the frequency distribution observed in Figure 2. Because the specimens with less than 10^5 bacteria per ml were distributed in frequency toward zero (85 percent contained less than 100 bacteria per ml), because the bacteria in these low counts were frequently staphylococci, enterococci, diphtheroids and lactobacilli, and because repeat catheterizations often showed a different flora as well as low numbers inconsistent with the expected growth in urine (more than 10^5 per ml), these bacterial counts of less than 10^5 per ml were considered to be urethral contaminants. The method of catheterization is not stated in these papers, but the size of the catheter, the type of catheter, the preparation and position of the patient, the attendant doing the catheterization, and most importantly, the volume of urine that flushes the catheter before collection of the culture, all influence contamination of the catheter with urethral bacteria.

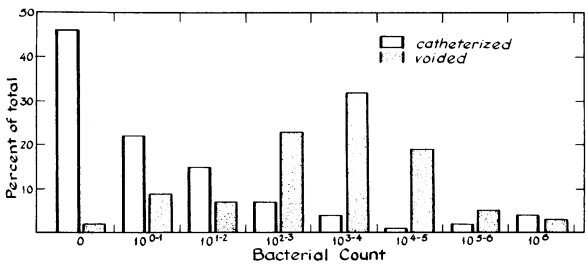

Chart 2.—The bacterial colony counts in catheterized and whole voided urine specimens obtained from several hundred asymptomatic women, taken at random from an outpatient medical clinic. Modified from Kass, E.H.[7]

Undoubtedly, with a more detailed technique of catheterization—such as the one used by Marple[4]—the frequency distribution as to the upper limits of contamination in Chart 2 could be pushed sharply to the left—that is, a higher frequency of sterile specimens and even smaller numbers of contaminating bacteria. For example, in Marple's study of 100 female patients in the hospital, 69 were sterile, 24 had more than 10^5 bacteria per ml, and only seven patients had small numbers of bacteria (all less than 100 per ml). Regardless of the technique of catheterization, however, some sterile bladder urines will be contaminated by urethral bacteria; the consideration of a sterile urine, therefore, even with catheterization, must remain on a statistical basis. The catheter cannot offer a categorical delineation between the presence of bacteria or no bacteria.

Only by direct suprapubic needle aspiration of the bladder[8-10] can sterility be defined in terms approaching 99 percent or more of confidence limits. The data in Charts 3 and 4 are from bladder aspirations in two groups of patients with recurrent urinary infections.[10] One group had received no antimicrobial therapy in their recent past history (Chart 3), while the second group was receiving therapy at the time of aspiration

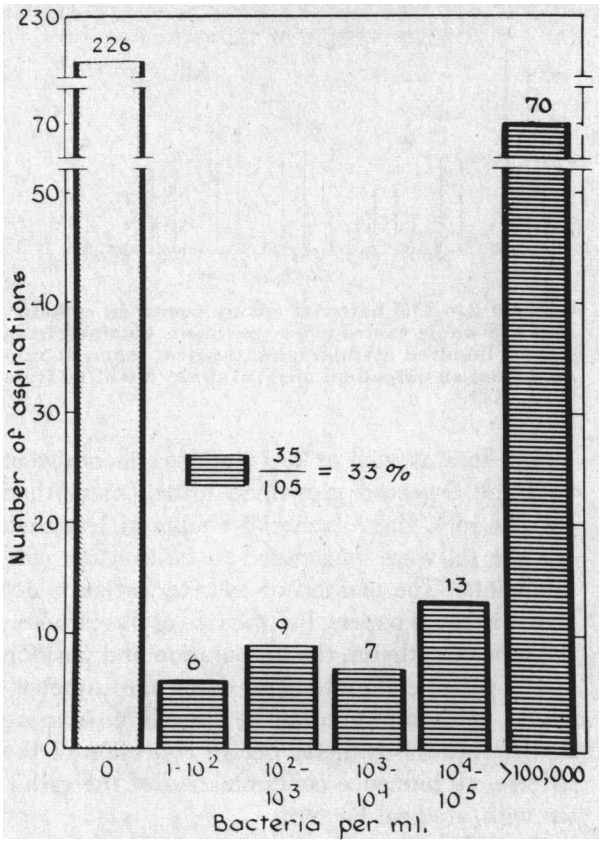

Chart 3.—The bacterial colony counts in urine specimens obtained by direct suprapubic needle aspiration of the bladder. These 331 aspirations were from patients seen in a clinic for urinary infections; none of the patients was receiving antimicrobial therapy.

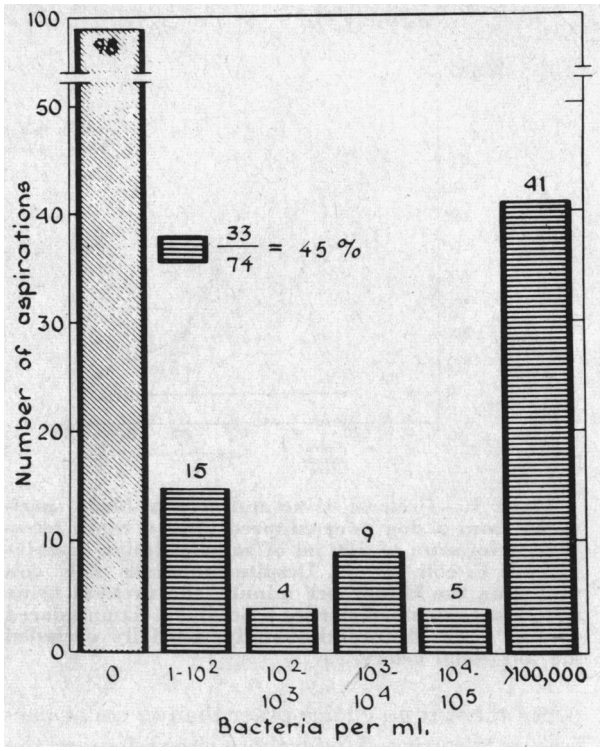

Chart 4.—The bacterial colony counts in urine specimens obtained by direct suprapubic needle aspiration of the bladder; these 172 aspirations were from patients receiving antimicrobial therapy at the time of aspiration.

(Chart 4). In Chart 3, only 35 of the 331 aspirated specimens (approximately 10 percent) contained between 1 and 10^5 bacteria per ml, but of the 105 patients with bladder bacteriuria the 35 low counts (less than 10^5 per ml) represented 33 percent of the total infected patients. As expected (Chart 4), the error in accepting 10^5 bacteria per ml becomes unacceptable in patients receiving antimicrobial therapy; 20 percent of the total aspirated specimens contained less than 10^5 bacteria per ml, representing 45 percent of those infected. It is important to point out that these were hydrated patients. Similar data have been obtained by others.[11]

The real difficulty (and much of the controversy, scientific and emotional) lies not in the interpretation of the catheterized urine in the female, but in the voided urine. As seen in Chart 2, when cultures were made of voided urine from asymptomatic women all at the same clinic at Boston City Hospital, sterile specimens and specimens containing less than 1000 bacteria per ml became relatively rare. The average specimen, thought to be uninfected, cultured $10^{3\text{ to }4}$ bacteria per ml. We obtained a similar distribution curve (Chart 5) when midstream voided specimens* were cultured in 54 women who had sterile bladder urine on suprapubic aspiration.[10] The bacteriologic method used by the Boston group was published in detail in 1967.[2] It is worth emphasizing that (1) the total voided urine is collected (not midstream specimens), that (2) the perineum is washed with four separate 4″ x 4″ sterile gauze sponges soaked with green soap, that (3) the soap is not removed before voiding, and that (4) the quantitative culture is not performed until the following day after overnight refrigeration of the urine (while awaiting results of the qualitative, screening culture). With this method, Kass and his co-workers established that a single culture of the whole voided urine, containing 10^5 or more bacteria per ml, has an 80 percent chance of representing a bladder bacteriuria[7] (in their hands, a single *catheterized* specimen of similar

*The perineum was not cleaned in these studies.

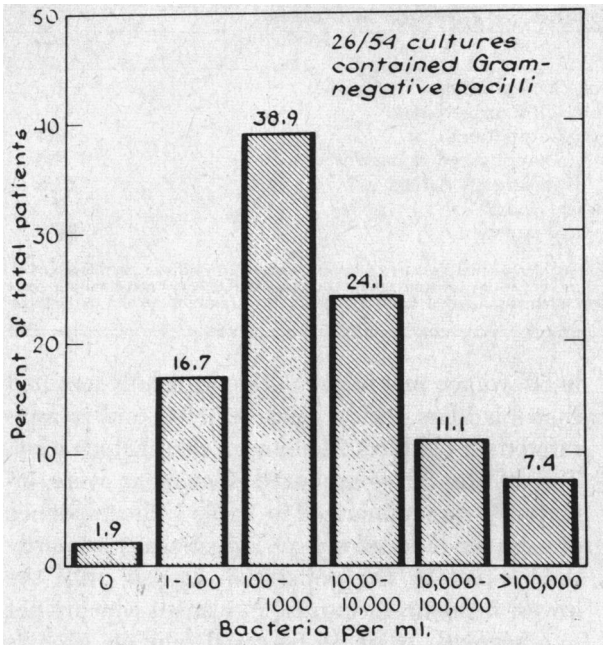

Chart 5.—Bacterial colony counts in 54 midstream voided specimens from patients who had sterile bladder urine by direct needle aspiration. From *Medicine* 44:1-36, 1965, by permission of the publishers, Williams & Wilkins Co., Baltimore.

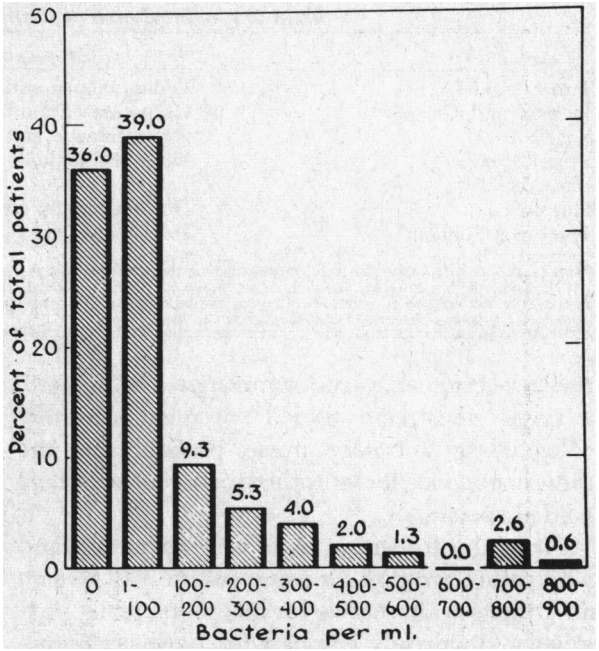

Chart 6.—Bacterial colony counts in midstream specimens collected by a trained nurse as the patient voided from a cystoscopy table; all patients had a sterile bladder urine, proven by direct needle aspiration, immediately before voiding. From *Medicine* 44:1-36, 1965, by permission of the publishers, Williams & Wilkins Co., Baltimore.

count has a 95 percent confidence level); two consecutive whole voided specimens containing 10^5 or more bacteria per ml has 91 percent confidence limits and three specimens with more than 10^5 bacteria per ml approaches the same confidence level as a single catheterized specimen (95 percent).[2]

By this method, Kass and his group have published a remarkable series of epidemiologic studies on the incidence of bacteriuria in different population groups,[7] and on the relationship of bacteriuria to diabetes,[12] pyelonephritis of pregnancy,[2] prematurity,[2] and hypertension.[13]

These same criteria, however, applied to the individual patient in the physician's office, or in the hospital, present some serious problems. Neither the practicing physician nor the patient can afford three consecutive whole voided cultures for a 95 percent reliability. And since one voided culture of 10^5 or greater, using Kass's technique, has one chance in five of not representing an infection,[7] the risk and expense of unwarranted antimicrobial therapy based on a single culture becomes a serious consideration.

What can be done to avoid three consecutive cultures that still have one chance in 20 of not representing an infection even if each culture grows 10^5 bacteria or more per ml? In order of decreasing complexity, (1) the bladder urine can be directly aspirated, providing the highest degree of reliability,[10] (2) the female patient can be placed on a table in the lithotomy position, the perineum cleansed with soap, and the nurse collect a midstream specimen (Chart 6),[10] and finally, (3) the specimen can be obtained by catheter. Bladder aspiration, while neither painful nor dangerous, is not pleasant for the patient. Highly useful in newborn infants,[14] and in patients with paraplegia,[15] bladder puncture should be used freely when the diagnosis remains in doubt in any woman in whom there is persistent questionable culture. Aspiration has the dual advantage of deciding with a single culture the bacteriologic status of the bladder urine, and it does not introduce urethral bacteria to initiate a new infection. Despite these advantages, it will probably never be widely used.

The second method (Chart 6) we have described in detail,[10] and continue to use in both the office and hospital, but most physicians will find this too involved to warrant the effort. But, where possible, the nurse should clean the perineum carefully with detergent, remove the detergent, and collect the patient's midstream specimen herself. As will be discussed in the section on Bacte-

TABLE 1.—*Incidence of Catheter-Induced Infection in Women*

Reported by	*Population*	*Incidence (Percent)*
Turck, et al[17]	Young women without medical illness	1
Jackson and Grieble[16]	Outpatients attending Hypertensive Clinic	2
Kass[3]	Asymptomatic, untreated outpatients	2.4
Brumfitt, et al[18]	Maternity patients — Uncomplicated deliveries*	4.4
Kaye, et al[19]	Non-forceps deliveries*	13.5
Marple[4]	Hospitalized on a medical ward**	9
Thiel and Spühler[20]	Hospitalized on a medical ward	20

*Incidence due to catheter obtained by subtracting the control, uncatheterized incidence from the rate of infection observed following catheterization.
**Nine percent is a minimal incidence; six of the 69 patients with sterile urine on initial catheterization became acutely symptomatic within three days and were found to be infected on repeat catheterization. The rate of asymptomatic induced infection would have required second catheterizations in all patients three to seven days after the first.

riuria in Pregnancy and summarized in Table 2, a single midstream voided specimen, carefully collected by a trained nurse, probably has the same confidence limits as three consecutive, whole voided specimens.

From the foregoing, it is easy to understand why catheterization for urine culture will remain an attractive alternative for many practicing physicians. As already emphasized, however, catheterization—regardless of the technique and care—will not prevent a statistical interpretation of how many bacteria represent urethral contamination. With careful technique (using Marple's method), the presence of 10^4 or even 10^3 bacteria per ml or more should mean, with virtual certainty, the presence of a urinary infection. The objection to the catheter, however, is that it introduces bladder bacteriuria in some patients who have sterile urine.

The incidence of infection varies with the type of patient catheterized. For example, Jackson and Grieble, in an outpatient clinic for hypertensive women, caused bladder bacteriuria in only 2 percent of single catheterizations;[16] Turck et al catheterized 100 nonhospitalized young women, infecting one patient.[17] The incidence of catheter-induced infections increases in patients with diseased urinary tracts. Brumfitt et al found that the rate of urinary infection in catheterized maternity patients at the time of delivery was twice that of noncatheterized women,[18] while Kaye et al observed that a single catheterization tripled the incidence of infection.[19]

When the catheter is used in patients in hospital, the rate of induced bladder bacteriuria becomes prohibitive. Even Marple, using an aseptic technique unlikely to be duplicated by the best of urologists, infected at least 9 percent of the 69 women in hospital who had initially sterile urine. In a most convincing study, Thiel and Spühler proved sterility of urine by suprapubic aspiration in 50 women in a hospital, then carefully emptied their bladders with a glass catheter, and re-aspirated their bladders 24 hours after catheterization. Ten of the 50 re-aspirated specimens were infected.[20] As summarized in Table 1, the incidence of catheter-induced urinary infections is primarily determined by the population at risk, with the lowest incidence occurring in women who are not in a hospital. If an antibacterial solution, such as neomycin and polymyxin, were always left in the bladder after catheterization, the risk might be reduced. Studies on this point would be useful; if catheter-induced infections could be reduced to less than 1 percent for all population groups, it is at least debatable whether better medicine might be practiced (in populations not in hospital) by the correct interpretation of a single catheterized culture than by false interpretation of a single, whole voided culture. Clinical investigations, on the other hand, are immediately rendered suspect if catheterized specimens are used, because the incidence of spontaneous infections (2 to 6 percent) is about the same as that from the catheter.

The data in Chart 2 are based on random specimens from patients expected to have a low incidence of infection. The main emphasis has been on the confidence limits that can be placed on the repetition of bacterial counts of 10^5 per ml or more. There are few data on how often urinary infections can be present with less than 10^5 bacteria per ml.[10,11] Kass clearly stated the major factors that can reduce a bacterial infection in the bladder to numbers less than 10^5 per ml.[3,7] In descending order of importance, these are (1) antimicrobial therapy, (2) hydration,[11,21] (3) frequent voiding, (4) fastidious organisms, and lastly (5) the presence of cleansing detergent washed from the perineum into the culture bottle.[21] This latter factor may have reduced some of the 10^5 counts in the Boston studies, thereby

increasing the number of consecutive cultures (three) required to achieve 95 percent confidence.* The presence of contaminating detergent may be particularly important when the urine is refrigerated overnight before quantitative counts are performed.[2]

Bacteriuria in Nonpregnant Women

Urinary infections in nonpregnant women are common, varying both with the age of the patient and the population under study. In house to house population surveys in Wales and Jamaica, about 2 percent of adult women were found to be bacteriuric in the 15 to 24-year-old age group, increasing 1 or 2 percent per decade to a prevalence rate of 10 percent in the 55 to 64 year decade.[22] Thus, about 4 to 6 percent of women in the child-bearing age will be bacteriuric at any one survey. Because the turnover is substantial, with cure of bacteriuria in some and new infections in others, it is estimated that 10 to 20 percent of women experience a urinary infection in their lifetime.[22] Kunin and McCormack,[23] however, recently reported that the frequency of bacteriuria in nuns is strikingly less (0.4 to 1.6 percent in the four decades 15 to 54 years), clearly suggesting that child-bearing or sexual intercourse or both play a significant role in urinary infections.

Women in general medical units of hospitals, as originally shown by Marple,[4] have a much higher rate of infection (24 percent); Kass reported 30 percent of 76 female patients in the medical wards at Boston City Hospital had bacteriuria.[7]

These studies, and many others, establish that bacteriuria is the most common bacterial infection in women. Since the presence of bacteriuria can be detected, and presumably treated, it is important to decide whether an asymptomatic woman with bacteriuria is at risk or not. What do we mean by "at risk"? If one means recurrent episodes of symptoms, discomfort, multiple courses of antibacterial therapy, many visits to the physician's office, even cystoscopic examination and intravenous urograms—not to mention urethral dilatations, bladder instillations, and more radical approaches such as operations on the urethra—then this disease is expensive, time-consuming for patient and physician, and represents major morbidity for thousands of patients. But if "at risk" means morbidity in terms of a crippling or life-shortening disease, the evidence for this must rest on progressive renal deterioration; there is no clinical reason to believe that chronic bacteriuria permanently damages the bladder or urethra.

A number of investigators have tried to assess renal damage in the presence of bacteriuria. These assessments, in general, are based on (1) histologic evidence for pyelonephritis from biopsy, (2) bacteriologic localization studies to the kidneys, as distinct from the bladder, (3) diminished urinary concentrating ability and (4) serologic antibody titers. The evidence for each of these is briefly discussed.

Histologic evidence for pyelonephritis. Little would be gained in this review by a detailed consideration of the histologic difficulties involved in correctly diagnosing chronic pyelonephritis. The interested reader is directed to chapter 14 (Robert Heptinstall) and chapter 15 (Paul Beeson) in the 1968 edition of D. A. K. Black's book, *Renal Disease*,[24,53] and to the 1961 and 1964 papers of Paul Kimmelstiel.[25,26] Beeson, in his careful and searching analysis of the histologic and clinical data, has this to say: "The suggestion being offered here is that true chronic pyelonephritis may be far less common than most autopsy data suggest, and that the figures based on autopsy findings are misleading because they result from inclusion of a heterogeneous group of disorders with similar morphologic features under the single heading of chronic pyelonephritis."[53] A somewhat similar, if less serious, quotation once was evoked from Dr. Heptinstall when, in reply to a question as to whether he would prefer a needle or open wedge biopsy of a kidney in order to make the diagnosis of pyelonephritis, said, on a national panel, that he "would prefer the whole kidney and a bloody good history."

Bacteriologic localization studies. Bacteriuria only confirms the presence of bacteria in bladder urine; the kidneys may not be infected. Both Rantz[5] and Sanford[6] recognized the importance of establishing the bacteriologic status of renal pelvic urine in patients with bacteriuria; they observed that ureteral specimens of urine collected at cystoscopy often contained much smaller numbers of bacteria than the bladder urine. The ureteral catheters, however, had to pass through an infected bladder, making it difficult to interpret the significance of single ureteral cultures, especially with low counts.

*Dr. Kass assures me (T.A.S., personal communication) that green soap, Sapo Mollis, U.S.P. (10 percent) contains no detergent and does not reduce the bacterial counts during overnight refrigeration.

About 1960, we developed a technique at cystoscopy (based on extensive washing of the bladder, a control culture of the ureteral catheters before entering the ureteral orifices, and multiple serial cultures from each kidney) that distinguished between bladder and ureteral bacteriuria.[27] In 1965, we published further localization studies on 95 women who had bacteriuria proved by suprapubic needle aspiration of the bladder.[10] In 40 percent, the infection was limited to the bladder, 28 percent had unilateral ureteral bacteriuria, and 32 percent had bilateral upper tract infection. Most of these 95 patients had intravenous urograms that were "nonsurgical," that is, only rarely was there obstruction, stones, or gross loss of renal cortex. Reflux was rare in those patients who had cystograms. Since 1965, many more patients have had localization studies. The data remain about the same: *any adult woman with recurrent bladder bacteriuria, studied at one point in time, has about 50 percent chance of the bacteria being present in either one or both renal pelvic urines.* These studies have been confirmed by other investigators.[28,29] We called these upper tract localizations "pyelonephritis,"[10] but is this the correct term? Why not "pyelitis"? Or better still, pelvic bacteriuria. If progressive destruction of renal tissue by bacteria is an acceptable definition, then most of these patients did not have pyelonephritis.

Effect of bacteriuria on renal concentrating mechanisms. A defect in concentrating ability has long been recognized in pyelonephritis.[30,31] Since upper tract bacteriuria in women is as often unilateral as it is bilateral, effects on the renal concentrating mechanism are best studied at the time of bacteriologic localization with ureteral catheters. Recently, in an excellent study, Ronald, Cutler and Turck[32] showed that patients with renal bacteriuria concentrated less well than those whose infection was limited to the bladder, and that the noninfected side in patients with unilateral bacteriuria concentrated better than the contralateral infected kidney. All patients had serum creatinines of less than 1.5 mg per 100 ml. Thus, the presence of renal pelvic bacteriuria is accompanied by a functional defect in renal concentrating ability. But does this mean pyelonephritis? Why not pyelitis? Minimal edema at the papillary tip, well within the renal pelvis, could influence greatly the counter-current concentrating mechanism. There is a tendency in the current literature, especially in pregnancy studies, to equate a decreased concentrating ability with "pyelonephritis" in patients with bacteriuria; nevertheless, impaired concentration may mean nothing more than the presence of pelvic bacteriuria.

Serologic antibody titers as an indicator of renal disease. Siede and Luz were the first to use immune responses to differentiate patients with pyelonephritis from those with cystitis.[33] In 1955, Needell, and his associates introduced the more sensitive method of hemagglutination to study antibody response in patients with urinary infections.[34] Williamson et al[35] and Percival and Brumfitt[36] published early studies in adults, while Winberg and associates measured antibodies in children.[37] In general, patients with acute urinary infections associated with chills, fever, and flank pain, have high serologic titers; patients with classic cystitis have low titers. The major difficulty, at this writing, is that the grey zone is enormous, as emphasized by Sanford and Barnett.[38] For example, Ehrenkranz and Carter found a fourfold rise in antibody titers in 13 of 18 patients with acute lower urinary tract infections.[39] Indeed, the characterization of 0-specific antibodies in serum and urine,[40] and other secretory body fluids,[41] is advancing at so rapid a rate that the interested student and clinician should withhold judgement on the clinical application of these immune responses. Moreover, Sanford's group has recently shown that both the kidney[42] and bladder[43] are immunologically competent organs in producing γ-G immunoglobulin at the local level. Without doubt, however, the ultimate chapter on the relationship of the immunoglobulins and urinary infections will be a significant contribution to our understanding, and perhaps control, of urinary infections. At present, to consider serologic titers as firm evidence of pyelonephritis is highly speculative.

If histology, bacterial localization, urinary concentration, and serologic titers all fail as adequate criteria for chronic pyelonephritis, what measures should the clinician use as evidence for chronic, progressive disease? We believe the intravenous urogram. In the absence of stones, obstruction, and tuberculosis, and with the single exception of analgesic nephritis with papillary necrosis—readily excluded by history—pyelonephritis is virtually the only disease that will produce a localized scar over a deformed calyx; in advanced pyelonephritis, calyceal distortion and irregularity, together

with cortical scars, completes the picture. Unfortunately, most intravenous urograms are grossly inadequate for showing the relationship of calyces to the cortical outline; for this reason, the clinician should insist upon either an early nephrogram phase (60 seconds after the start of intravenous injection) or tomographic films with every intravenous urogram in patients investigated for urinary infections.* C. J. Hodson, in a remarkable review of some 12,000 pyelographic examinations, clearly defined gross cortical scars as well as the case for the rarity of such scars developing in adults.[44] As Hodson pointed out, renal infarction (an extremely rare condition) may closely resemble pyelonephritic scars, but the renal pyramid remains in renal infarction in contradistinction to pyelonephritis.

With this background, how does the clinical investigator or physician decide if adult women with recurrent bacteriuria are at serious risk? One of the real limitations has been that most epidemiologic studies on the 4 to 6 percent of adult women with bacteriuria have included such demographic factors as age, blood pressure, concentrating ability, serologic titers and proteinuria, but have never answered two critical questions: What do the kidneys look like? What is the history of these patients in relation to their bacteriuria?

Fortunately, Asscher, Sussman and their colleagues at Cardiff, Wales, have recently answered these questions with regard to a group of nonpregnant women with asymptomatic bacteriuria between ages 20 and 65.[45,46] They screened 3,578 asymptomatic hospital visitors for significant bacteriuria, defined as two consecutive *midstream* specimens of more than 10^5 bacteria per ml of the *same serotype*. The perineum was cleaned three times with green soap. One hundred and seven subjects (3 percent) were found to have bacteriuria; they were matched with 100 nonbacteriuric women of the same age, parity, and marital status who served as controls. All 107 of the bacteriuric subjects and 88 of the nonbacteriuric controls consented to a detailed history by a medical epidemiologist who was not aware of the culture results. Sixty-nine percent of the bacteriuric subjects gave a history of urinary symptoms within the year preceding the detection of bacteriuria, but only 18 percent of the controls gave a similar story. Asymptomatic bacteriuria, then, in epidemiologic surveys is not actually asymptomatic.

Ninety-three of the 107 bacteriuric subjects (87 percent) and 50 of the 88 controls (57 percent) consented to an excretory urogram (surely a tribute to the persistence of the Welsh). The excretory urograms were read independently by two radiologists. One of us (T.A.S.) also had the unique opportunity to review all of these urograms in the spring of 1968. Every patient had more than an adequate amount of renal cortex. Abnormalities were found in 34 percent of bacteriuric subjects and in 12 percent of controls.[45] There were occasional scars, but most were minor and rarely involved more than a single calyx. Eight patients had small stones, four of them in the same kidneys that had scars. The hydroureter and hydronephrosis reported[45] in nine patients was definitely "nonsurgical" (T.A.S.); it seemed to be more calyceal and pelvic atonicity than actual obstructive disease. The remainder of the abnormalities were congenital, such as kidney rotation and cysts. In short, I did not see one excretory urogram from a patient who seemed in serious trouble from loss of renal cortex, and half the bacteriuric women were over 45 years old. Of equal importance was the comparative delicacy and lack of collecting system abnormalities observed in the 50 urograms from nonbacteriuric women. In summary, the collecting systems were more atonic and contained more stones and scars in the bacteriuric women; it was easy to believe half of these women had pelvic bacteriuria to accompany their bladder infection. It was not easy to believe they had chronic, progressive pyelonephritis.

From these considerations, it is difficult to believe that the nonpregnant woman who has recurrent bacteriuria in the absence of stones and *in the presence of a nonobstructive intravenous urogram* is at serious risk from bacteriuria.

If she is not at serious risk from renal failure, what about the secondary consequences of renal involvement such as hypertension or anemia? The hematocrits of bacteriuric and nonbacteriuric women are essentially the same.[45] Differences in blood pressure, while statistically higher in bac-

*Tomographic films are almost unique in defining cortical outlines, but the primary reason for poor urograms is inadequate preparation. The routine in the Department of Radiology at Stanford, based on the principle of using a cathartic on the small and large intestine (magnesium citrate)—thereby filling the colon with fluid—and followed by colonic mucosal stimulation (bisacodyl), is as follows: At lunch and supper the day before the intravenous urogram, food is limited to bouillon soup, plain Jello, (plain chicken or turkey sandwich at lunch) and apple or grape juice. Water must be encouraged during the day and evening. 11 ounces of magnesium citrate (in adults) is taken at 8:00 p.m. and three Ducolax tablets (bisacodyl) at 10:00 pm. Nothing is taken by mouth after midnight. At 7:00 a.m., the day of the examination, a Ducolax rectal suppository is inserted (for direct stimulation of the rectosigmoid) and retained for 20 minutes to 1 hour. This regimen for preparing the patient produces nearly perfect films.

TABLE 2.—*The Prevalence of Bacteriuria, Acute Pyelonephritis,*

Reported by	*Methods*	*Number of Pregnant Patients Screened*	*% Bacteriurics*	*% Incidence of Acute Clinical Bacteriurics*	
				Treated	*Untreated*
Savage WE, Hajj SM, Kass EH[2] (1967)	3 whole voided specimens $>10^5$ bacteria after preparation and collection by patient. No rinse of soap with water. Pregnancy less than 32 weeks.	6202	4.0	0	26.4
Condie AP, Williams JD, Reeves DS, et al[60] (1968)	2 "clean-catch" (probably midstream) specimens $>10^5$ bacteria after preparation and probably collected by nurse. Rinse of soap with water.	4590	4.6	10.3	23.3
Eykyn SJ, McFadyen IR[61] (1968)	2 specimens obtained by suprapubic aspiration of bladder.	1000	5.9	...	...
Kincaid-Smith P, Bullen M[54] (1965)	1 midstream specimen $>10^5$ bacteria without preparation plus 1 midstream $>10^5$ after preparation and collection by nurse. No rinse of soap with water. Pregnancy less than 26 weeks.	4000	4.0	2.8-3.3	28.7-36.6
Little PJ[57] (1966)	2 midstream specimens $>10^5$ after preparation and collection by nurse. Rinse of detergent with water. Pregnancy less than 14 weeks.	5000	5.3	3.2	24.8
Whalley PJ[55, 58, 63] (1965)	2 "clean whole voided" specimens $>10^5$ after preparation and collection by patient. No rinse of soap with water. Pregnancy less than 28 weeks.	4357	6.9	...	25.7
Brumfitt W, Grüneberg RN, Leigh DA[56] (1966)	1 midstream specimen $>10^5$ bacteria after preparation and collection by nurse.	8907	4.4	2.8	...
Wilson MG, Hewitt WL, Monzon OT[59] (1966)	2 midstream specimens $>10^5$ bacteria after preparation and collection, probably by patient. Rinse of soap with water. Pregnancy less than 32 weeks.	6048	6.5	...	...

*These patients who developed acute pyelonephritis after being screened initially as a nonbacteriuric were either missed because of infections with less than 10^5 bacteria per ml, or became infected after the initial cultures.

teriuric women,[47,48] are simply not impressive enough to believe that urinary infections constitute a major, preventable cause of hypertension.

We cannot leave the problem of urinary infections in the nonpregnant women without calling attention to the important general practice studies of the past five years. From the studies of Gallagher, Montgomerie and North in 1965,[49] of Mond et al,[50] Mestitz et al [51] and MacNaughtan et al[52] we know that about half of the women who present with symptoms of urinary infection actually have sterile bladder urine. Yet as Gallagher et al are careful to point out, the symptoms, relief of discomfort with antimicrobial agents, past history of documented urinary infections, and future episodes of true bacteriuria in the infected and noninfected symptomatic women are surprisingly similar. As will be discussed at the end of this review, these patients with the "urethral syndrome" cannot be excluded from the final consideration of the pathogenesis of urinary infections. Indeed, they may hold the clue to the portal of entry for urinary infections in females.

Bacteriuria in Pregnancy

Several investigators have studied the prevalence of bacteriuria in pregnant women (Table 2). Interest increased in bacteriuria of pregnancy when (1) Kass showed that symptomatic episodes of acute pyelonephritis in later stages of preg-

Prematurity and Radiological Abnormalities in Pregnancy

*Pyelonephritis Nonbacteriurics**	*Nonbacteriurics*	*% Prematurity Bacteriurics*	*Bacteriurics*		*% Radiological Abnormalities On IVP After Delivery*			*Treatment*
			Treated	*Untreated*				
1.4	11.5	...	7.5	15.3	...			Long-term (single or multiple) up to delivery
2	5	12.8	...	...	...			Short-term
...	...	...	...	...	...			Short-term
...	5	...	12.5-14.8	17.8-21.5	51.4			Long-term up to delivery
0.4	7.6	...	8.1	9.2	18			Long-term up to delivery
0	11.9	14.8	...	...	47			No treatment except in symptomatic infections
...	5.5	...	7.2	...	37			Short-term
					Responded to one course of therapy 23	*Responded to repeated therapy* 35	*Did not respond to repeated therapy* 65	
...	...	...	...	...	...			Short-term only when symptomatic

nancy could be prevented by detecting and treating asymptomatic bacteriuria in the early stages of gestation,[2] (2) when he suggested that the incidence of prematurity in bacteriurics could be reduced by early treatment,[2] and (3) when Kincaid-Smith[54] and Whalley[55] reported a strikingly high incidence of radiologic abnormalities in bacteriuric women evaluated after delivery. At this writing, only the prevention of acute episodes of pyelonephritis by early treatment has been amply confirmed (Table 2). Some of these differences may depend on population selection, on relative differences in rigidly defining the bacteriuric population at risk, and on interpretation of radiologic abnormalities. As was pointed out in the first section of this review, confidence limits in interpreting voided cultures vary considerably with the method of collecting the specimen; these limits, of course, determine the number of cultures required to admit a pregnant woman as truly bacteriuric. Since the actual number of women with 10^5 or more bacteria per ml in any pregnant population is only about 4 percent (Table 2), a relatively few who did not have bacteriuria but mistakenly admitted as having infection could readily lead to false conclusions. Some investigators used midstream specimens collected by trained nurses;[54,56,57] others used the whole voided specimen collected by the patients themselves,[2,58] In some studies,[57,59,60] sterile water was used to

rinse off the detergent after cleansing of the introitus, but in others this was not done.[2,58] Of interest is the 4 percent prevalence of bacteriuria (as determined by three consecutive whole voided specimens collected by the patient) in Savage's studies,[2] which is similar to the prevalence found by Brumfitt using one midstream specimen collected by the nurse.[56] This suggests that one midstream specimen collected by a nurse has about the same confidence factor as three whole voided specimens collected by the patient. In Eykyn's study of 1000 consecutive pregnancies,[61] urine obtained by bladder puncture indicated a greater incidence—5.9 percent. Her figures may serve as further evidence that confidence limits based on more than 10^5 bacteria per ml do not allow detection of the total bacteriuric population (that is, patients with less than 10^5 bacteria per ml).

As shown in Table 2, the prevalence of bacteriuria in these different investigations varied from 4 to 6.9 percent, and the incidence of acute pyelonephritis in pregnant women can be reduced, from about 25 to 35 percent in untreated bacteriuric women to less than 10 percent in treated women.

Whereas the incidence of prematurity in Table 2 seems to be higher in bacteriuric than in nonbacteriuric pregnant women (which does not mean the bacteriuria causes the prematurity), most investigators failed to show a reduction in the rate of prematurity by treating the bacteriuria;[54,57] even the rigidly defined studies of Kass and his associates showed a reduction in prematurity that was only suggestive (probability greater than 0.1).[2] Wilson et al concluded that prematurity was more often associated with obstetrical abnormalities than bacteriuria in either symptomatic or asymptomatic pregnant women.[59]

The question of underlying renal disease associated with bacteriuria of pregnancy remains somewhat controversial (Table 2). Whalley found a 47 percent incidence of radiologic abnormalities,[55] a figure similar to that of Kincaid-Smith,[54] but Gower[62] reported only 18 percent incidence of radiologic changes that seem of rather minor order compared with those of Kincaid-Smith. Brumfitt's observations may be relevant:[56] He showed that the incidence of radiologic abnormalities in bacteriuria of pregnancy is proportional to the difficulty in curing the infection. Patients easily cured of their bacteriuria by a single course of therapy had a 23 percent incidence of radiologic abnormalities, but in those who remained bacteriuric despite repeated therapeutic efforts the incidence was 65 percent.

Since the prevalence of bacteriuria is already established at the first prenatal visit of the pregnant woman, and since the incidence of 4 to 6 percent is about the same as in the nonpregnant female population of the same age, it is reasonable to believe that most women carry their infections into pregnancy. From the point of view of simply preventing clinical episodes of pyelonephritis in late pregnancy, it seems justifiable to detect these bacteriuric women and treat them. Data are insufficient to judge the advantage of long-term therapy up to term[2,54,57] or short-term therapy,[60] but with long-term therapy the incidence of acute pyelonephritis in treated bacteriuric pregnant women varied from 0 to 3.3 percent, whereas the rate was 10.3 percent for a similar group receiving short-term therapy. Brumfitt's early report of 2.8 percent incidence of acute pyelonephritis in one group of short-term treated bacteriuric patients[56] compared with a later publication of 10.3 percent[60] is confusing to us. We would prefer short-term therapy with close follow-up, then a complete urologic investigation, after delivery, for patients who proved resistant to therapy. Whalley[55] thought that more patients were bacteriuric after delivery if untreated during the pregnancy, which seems reasonable; but Gower[62] could detect no difference in incidence of postpartum bacteriuria between treated and untreated bacteriurics.

Urinary Infections in Males with Chronic Bacterial Prostatitis

In epidemiologic surveys, asymptomatic urinary infections in males are rare. Freedman,[48] in a study of 1,234 males in Hiroshima, Japan, found no positive cultures in persons under the age of 49, but 0.6 percent had bacteriuria between ages 50 and 59, 1.5 percent in the next decade, and 3.6 percent above age 70. Miall et al,[13] in Jamaican population studies, found only 3 of 700 men had bacteriuria. Two of these had recently undergone prostatectomy. Kunin[64] did culture studies on 7,731 boys and young men (1,116 were university students, ages 15-29). Only two cases of infection were found, both in boys, one 13 and the other 14 years old; and both had normal intravenous urograms.

Thus, infections are rare in younger age groups. Because urinary infections in males, at least in the absence of surgical manipulation such as prostatectomy or indwelling catheters, tend to be very symptomatic and require specific therapy, it is probable that population surveys underestimate the prevalence of this disease. Moreover, it is too easy to assign all urinary infections in the male to instrumentation of the urinary tract. Any practicing physician who cultures the urine, and takes a history, recognizes the spontaneous appearance of documented urinary infections in males.

In an attempt to determine the site of infection in male patients with recurrent episodes of bacteriuria, we established bacteriologic techniques which allow the physician to distinguish between the prostate and the urethra as the cause of recurrent bladder or kidney infections.[65] These studies show that while the urethra is occasionally at fault, especially in children and the very elderly, relapses in most men are caused by the persistence of small numbers of bacteria in prostatic fluid. The relapse time from the prostate to the bladder, after discontinuing antimicrobial therapy, varies from 48 hours to as long as six months.[65] Because antimicrobial therapy with high serum levels failed to clear the prostate of sensitive bacteria, we realized that antimicrobial agents were not reaching the prostatic fluid. This clinical observation led to studies in dogs that confirmed the failure of antibiotics to cross from plasma to prostatic fluid, and defined the pharmacologic characteristics required for diffusion into prostatic fluid.[66,67]

The technique of culturing the voided urine by segmenting the stream into urethral, midstream, and prostatic components must be carefully performed; the bacteriologic method must be capable of quantitating small numbers of bacteria. Although time-consuming for the physician, and expensive for the patient if office bacteriology is not available, there is no other way to diagnose chronic bacterial prostatitis.

The difficulty with previous bacteriologic investigations of the prostate, whether by needle biopsy,[68] analysis of surgical specimens at open operation,[69] or attempted correlations between bacterial culture and leukocytes in expressed prostatic fluid,[70] has been the almost uniform failure to distinguish between urethral and prostatic bacteria. Bourne and Frishette not only recognized that their positive operative cultures, in men undergoing transurethral resection for prostatic obstruction, were urethral in origin, but they showed no correlation between the histologic presence of inflammation and the preoperative number of leukocytes in prostatic fluid.[71]

The problem in diagnosis is further compounded by an unknown but common inflammatory condition of the prostate which is also characterized by leukocytes and oval fat bodies (macrophages) in the expressed prostatic fluid. Although symptoms of perineal discomfort, low back pain, and varying but mild urinary complaints may suggest urinary infection, patients with these symptoms never have recurrent bladder or kidney infections and do not have culturable pathogenic bacteria in their prostates. Unfortunately, this condition is also called "prostatitis"; whether the causal agent is a virus, mycoplasma, obligate anaerobe, or even an autoimmune reaction, is unknown. Fortunately, the disease is self-limiting. It must not be confused with chronic bacterial prostatitis.

Urinary Infection in Children

The epidemiologic studies of Kunin and his associates in Charlottesville, Virginia,[64,72-75] and the clinical investigations of Winberg and his group in Göteberg, Sweden,[76-80] together represent a remarkable series of papers. Kunin screened thousands of asymptomatic school children for bacteriuria and, along with the late Albert Paquin, Professor of Urology at Charlottesville, evaluated the urologic status of those children found to be infected. Winberg's subjects, by contrast, were referred to a university hospital that served as the only referral center for children in a large city; thus, patients were often seen with first or second infections, early in the course of their disease. Both groups obtained intravenous urograms and voiding cystourethrograms on bacteriuric patients, and their treatment regimens were surprisingly similar. The duration of therapy was short (about ten days); both groups insisted on obtaining a sterile urine before discontinuing therapy.

Kunin found the same frequency of infection, about 1 percent, in school girls 5 to 9, 10 to 14, 15 to 19, and 20 to 24 years of age.[64,74] Winberg's statistics, [80] also confirmed by Stansfeld,[81] show that the greatest number of urinary infections in children requiring medical attention occur in the

first year of life, and that, in the newborn, boys outnumber girls.

In the Virginia school girls, who were studied six times over a period of seven years after entering school, new infections occurred at the rate of 0.32 percent per year;[75] thus, the cumulative rate of bacteriuria over the first seven years of school was 2.9 percent although 1 percent only were bacteriuric at any single survey. Of considerable interest is Kunin's conclusion that, since the 0.32 percent rate of emergence of new cases of bacteriuria is linear with time, all girls between age 6 and 13 are at equal risk for acquiring bacteriuria.[75]

In Kunin's series, 107 of the 122 girls with bacteriuria had intravenous urograms and voiding cystograms.[74] Caliectasis was present in 13 percent, reflux in 19 percent. Pyuria, past history, and symptoms were of no help in predicting the presence of positive findings on urographic studies. Of five girls operated upon for gross lesions (reflux), all but one had recurrent infection. Govan and Palmer,[82] in a large series of antireflux operations in girls with recurrent infection, corrected the reflux in 84 percent of their patients. They suggested that the subsequent development of clinical episodes of acute pyelonephritis was drastically reduced, but the number of recurrent infections in a careful bacteriologic follow-up was the same as before correction of the reflux. Twenty-three of Kunin's cases had repeat urologic studies 13 to 26 months after medical treatment; reflux had disappeared in four of six children, and caliectasis in two of seven. Smellie reported disappearance or decided reduction of reflux, except in the severest instances (grade 4), with continuous chemotherapy.[83]

Of greatest importance are the observations by both Kunin and Winberg's group that over 90 percent of recurrent infections are re-infections with different serotypes of E. coli rather than relapses with the same organisms.[74,79] Indeed, the Göteborg studies demonstrated that six out of eight recurrent infections occurring within 60 hours of completing a ten-day course of therapy were actually due to different bacteria and not relapse.[80] The presence of urologic abnormalities did not influence the rate of recurrence,[74] and re-infection (rather than relapse) was just as common in children with reflux as in those without.[79] Recurrent infections are more apt to occur early than late after the first bacteriuria is treated;[74,80] 60 percent in Kunin's series recurred within one year. With repeated recurrent infections, the distribution of bacterial species in Kunin's investigations, as reported by others,[84] showed a small increase in B. proteus, Pseudomonas, enterococcus, and staphylococcus, but E. coli remained the most common species.[74]

Bergström et al demonstrated that 60 days of proper antimicrobial therapy is no better than ten days in preventing recurrent infections. In fact, 60 days of sulfonamide therapy simply made more of the recurrences asymptomatic (and the organism resistant to sulfonamide) than did ten days of treatment.[80]

The role of reflux in girls with recurrent urinary infections remains controversial, as does the time-honored technique of urethral dilatation. Both subjects are beyond the scope of this review, largely because of the lack of bacteriologic evidence to support the views of the various proponents. There is no doubt that infection in the presence of reflux increases the likelihood of renal damage, but in the absence of evidence that sterile reflux in girls causes renal scarring, it is reasonable to believe that the infection presents the primary threat, not the reflux. As already noted, Govan and Palmer show that correction of reflux aborts clinical episodes of pyelonephritis but does not prevent the recurrence of urinary infections.[82] In adult women, the evidence is clear that radiologic evidence of reflux and infection are rarely related events. Heidrick, Mattingly, and Amberg[85] found nine instances of ureteral reflux in 321 normal pregnant females (2.8 percent) and 20 cases of bacteriuria (6.2 percent); only one of the nine women with reflux was infected. In those with reflux, there was "conspicuous absence of radiographic changes consistent with chronic pyelonephritis." Of six refluxing women restudied six months following delivery, only one continued to demonstrate reflux—indicating the often transient nature of the condition.

Köllermann and Ludwig,[86] finding that 30 percent of 102 urologically normal children had reflux on voiding cystograms, consider ureteral reflux a normal phenomenon in infants and children (boys and girls) up to 3 years of age.

Two aspects of urinary infections in school girls perhaps deserve a final comment. Kunin found the same frequency of infection (1 percent) at all ages between 5 and 24 years,[64,74] but this is contrary to any practicing physician's ex-

perience of which we are aware. Our clinics at Stanford are filled with girls who have urinary infections up to puberty (10 to 12 years old); very few are seen with infection between 13 and 17 years of age. Puberty is surely associated with some biologic change that either prevents recurrent urinary infections or else it reduces the clinical severity of the infections. In view of the acute symptomatic nature of "honeymoon cystitis," occurring a short time later in life, we find it difficult to accept the latter explanation.

The second aspect, related to the first, is the question of whether childhood infections serve as the reservoir for premenopausal urinary infections in adult women. Although the incidence of urinary infections is high in children, and recurrence after treatment is frequent, we believe there is no evidence to support a direct relationship between infections in children and adults. Our clinical experience, admittedly based only on detailed histories from intelligent patients, leads us to believe that most infections in adult women have their genesis in adult years, not in childhood. To be sure, an occasional adult does date her urinary infection back to childhood; and it is worthy of note that in these cases the intravenous urogram often shows serious renal scarring, and reflux is likely to be present. But this continuous history is rare, representing a small fraction of the adult population with urinary infections. Thus, it seems reasonable to us that although urinary infections in children are common and, in the presence of severe reflux, can cause serious renal morbidity, most childhood infections cease around puberty.* Except for the occasional infection in girls that persists into later years, we believe most adult infections are caused by a biologic change in perineal bacteriologic factors that occurs during adulthood. These latter observations will be discussed more fully later in this paper.

Urinary Infection in the Presence Of Obstructive Urologic Abnormalities

As to urinary infection in the presence of obstructive urologic abnormalities, only two questions will be considered: Does the presence of residual urine predispose to urinary infections? When infection is present, what is the importance of urologic abnormalities?

*Dr. J. Winberg has just called our attention to a recent paper that presents important evidence to the contrary: Lindblad BS, Ekengren K: The long-term prognosis of non-obstructive urinary tract infection in infancy and childhood after the advent of sulphonamides. Acta Paediat Scand 58:25-32, 1969

The Question of Residual Urine

Although there is widespread belief, especially among urologists, that residual urine predisposes to urinary infection, there is little evidence to support it. The view that patients with residual urine are more likely to become infected than those without is easy to understand: Most patients with residual urine are eventually examined by a method involving insertion of an instrument and hence are often secondarily infected; moreover, once the infection is present, eradication can be difficult, although it is by no means impossible. But these are circumstantial points; they have little to do with the basic question of whether the presence of residual urine *per se* makes a person more likely to become infected in the absence of instrumentation.

Both the clinical and experimental data suggests that residual urine does not predispose to urinary infection. Guze and Beeson showed that the affected kidneys in rabbits and rats with chronic, unilateral hydronephrosis were barely more susceptible to hematogenous pyelonephritis than were the contralateral, nonobstructed kidneys,[87] whereas total ureteral occulsion always caused severe pyelonephritis.[88] Vivaldi, in 1959, found in experiments with rats that if he ligated one ureter before inducing a bladder infection, the obstructed kidney remained sterile while pyelonephritis developed in the contralateral, unobstructed kidney.[89]

Because much of the clinical impression of the relationship between infection and residual urine is derived from experience with patients who have prostatic obstruction, the studies of Hasner are interesting.[90] In 221 patients with prostatic obstruction who needed prostatectomy and who had 50 ml or more of residual urine, he found a spontaneous infection rate (in the absence of instrumentation) of only 8.6 percent. Of the 19 patients who presented with obstruction and infection, seven were 60 to 69 years old and twelve were 71 to 85 years old. Nine of the 19 patients had the severest form of obstruction in his classification—azotemia with pronounced electrolyte and water disorders—and all 19 had had prolonged illness (average, 3.1 years) before seeking consultation. These data are suggestive that most, although not all, of the infection in patients with obstruction is, iatrogenic. Clearly then, the practice of determining residual urine—as an indication for prostatectomy—is not only hard to jus-

tify, but hazardous and unnecessary in patients who have sterile urine and no ureteral abnormality on intravenous urography.

The question can be reversed by asking how many patients with bacteriuria have residual urine. Williams et al determined the residual urine in 100 women, four to six months after delivery, who had been treated for asymptomatic bacteriuria during pregnancy.[91] When the 32 patients in whom bacteriuria persisted were compared with the 64 who had sterile urine, residual urine was the same in both groups.

Ureteral reflux is a form of residual urine. We reviewed in the preceding section the evidence that the correction of reflux does not change the incidence of urinary infections.[82]

And finally, although firm statistics are not available, in the vast majority of patients with ureteropelvic junction obstruction, the urine is sterile and there is no history of urinary infections.

The Importance of Urologic Abnormalities

When the large group of cases of reinfection in children and premenopausal adult women are excluded, we are surprised at how often a chronic urinary infection is due to a specific urologic abnormality; if the abnormality is recognized and corrected, the patient is usually cured of the infection. The urologic abnormalities that have caused chronic urinary infections in our patients at Stanford are listed in Table 3. Because these patients can be cured, and because the underlying abnormality is rarely obvious, Table 3 should serve as a deliberate check list in the investigation of any patient with chronic infection. Infection stones (predominantly in women), infected unilateral atrophic kidneys (also mainly in women), and chronic bacterial prostatitis are by far the most common; infected pericalyceal diverticulae (sometimes nonfunctioning), infected ureteral stumps, vesical fistulae, and infected urachal cysts are must less frequent.*

All of the abnormalities in Table 3 have one thing in common—the persistence of bacteria in a site that communicates directly with the urinary tract. Infection stones - soft, struvite calculi caused by urea-splitting bacteria—contain viable organisms (usually Proteus mirabilis) within the depths of the stone even when the urine has been made sterile by antimicrobial therapy.[92] These

TABLE 3.—*Correctable Urologic Abnormalities Causing Chronic Urinary Infections*

Infection stones.
Unilateral, infected atrophic kidneys.
Infected ureteral stumps following nephrectomy.
Infected pericalyceal diverticulae.
Vesico-vaginal, vesico-ileal, and vesico-rectal fistulae.
Infected urachal cysts.
Chronic bacterial prostatitis.

infection stones, often difficult to see on x-ray because of their soft, putty-like character, are important to detect; once the stone is removed or dissolved, the patient can be returned to society without antibiotics and free of infection.[92]

Several of our most gratifying cures have occurred in patients with unilateral, atrophic kidneys in whom the contralateral kidney has remained sterile despite years of continuous bladder infection. When antimicrobial therapy, especially serum level bactericidal therapy, has failed to cure these patients, nephrectomy can offer them a lifetime free of chronic infection, chills and fever. A detailed report on one such patient with pseudomonas pyelonephritis (and small pericalyceal calcifications) was published in 1963.[27] In the eight years since nephrectomy, she has had one episode of E. coli cystitis.

In our experience transurethral resection of the prostate corrects chronic bacterial prostatitis in only one-third of patients.[65] Most of these patients, however, are in their forties or early fifties, without signs or symptoms of prostatic obstruction; they prefer the alternative of chronic antimicrobial therapy over prostatectomy.[67]

Many observers have commented upon the high failure rate of antibacterial therapy in the presence of urologic abnormalities.[93,94] But these general statistics are not really helpful because either the diagnosis of the presence of infection was inadequate (before 1956),[93] or the specific urinary tract abnormalities were not indicated in the analysis of failures.[94] A few patients with infection stones and a few others with chronic bacterial prostatitis can make any series of chemotherapeutic attempts look dismal. And yet, these patients can be sorted out satisfactorily. Table 3 is presented because these abnormalities *cause* infections to persist and become chronic;

*Again we emphasize that most of these urologic abnormalities are not obvious. Recently, a 36-year-old woman was seen because of a three-year history of chronic urinary infection; because the same bacteria were found in her bladder as in the deep vaginal canal, and because the bladder had been entered five years before at the time of a hysterectomy for endometriosis, she was investigated for and found to have a minute vesicovaginal fistula. Except for a few days after hysterectomy, she had never observed vaginal leakage of urine. Repair of the fistula cured the infection.

TABLE 4.—*Bacterial Species Isolated from Bacteriuric Subjects*

	Paraplegics[15]	*School Girls*[74]	*Adult Females*[103]
Total Isolates	724	122	107
E. Coli	67	102	90
P. mirabilis	126	1	9
Klebsiella-Aerobacter	126	12	2
Pseudomonas	222	1	0
Others	183	6	6

with simple bacteriologic techniques, the site of these abnormalities can be accurately localized and the patients then cured of their infections by appropriate surgical procedure.

A final word of precaution: When acute urinary obstruction, usually from an infection stone or sometimes ureteral instrumentation, occurs in the presence of a chronic urinary infection, the obstruction must be relieved immediately. Failure to act decisively usually leads to renal abscesses, wedge-shaped areas of tubular destruction, and ultimately, renal atrophy. With good radiology now available to all physicians, every adult patient, with the possible exception of pregnant women, who presents with high fever, chills, and flank pain should have an emergency intravenous urogram to exclude acute renal obstruction. The price of procrastination, so often observed on even good medical services, is one of our modern medical tragedies.

Urinary Infections in Patients With Neurologic Disease

Of all patients who have urinary infections, no group compares in severity and morbidity to those with spinal cord injury. Nearly all require catheterization because of spasticity, or flaccidity of the bladder, and in a significant proportion ureterectasis, hydronephrosis, reflux, or renal calculi develops.

Severe pathologic changes in the bladder and pelvic musculature require frequent instrumentation of the urinary tract; the bacterial species cultured from the urine of paraplegic patients reflects the consequences of the need for repeated catheterization. In Table 4, the organisms found on bladder puncture by Govan et al in 724 positive cultures from patients with neurogenic bladder dysfunction[15] are compared to the species distribution reported by Kunin[74] and Sussman et al[45] in nonhospitalized general populations. In paraplegic patients, pseudomonas, Klebsiella, and P. mirabilis replace E. coli as the most common strains.

Bacteriuria occurs in at least 80 percent of patients with spinal cord injury,[95] renal calculi in 12 percent within the first three years of injury (almost all due to proteus),[95] and reflux in about 18 percent in long-term follow-ups.[96] Stovall et al studied the incidence of renal bacteriuria in paraplegic patients who had had indwelling catheters for three months to 15 years;[97] they reported that 83 percent of the ureteral urine specimens were sterile, but their bacteriologic technique could not have detected small numbers of bacteria (for example, all of their bladder cultures after washing with 2000 ml of sterile water were sterile). Nevertheless, Govan et al reported a similar figure—sterile ureteral urine in 42 of 55 patients with "neurogenic bladder dysfunction"[15] (76 percent). These studies suggest that the kidneys are relatively well protected in many paraplegic patients with chronic bacteriuria, but these differences may be due to a greater resistance of the male to upper tract bacteriuria, an observation suggested in our early localization studies in 1965.[10] Future studies of patients with spinal cord injuries would be more useful if females were distinguished from males and the spinal cord level of paralysis and the duration of the disease was noted. For example, Jacobson and Bors noted more hydronephrosis associated with lower motor neuron than with upper motor lesions,[95] but reflux is more common with upper motor neuron lesions.[96]

The major advance in the bacteriuria of spinal cord injuries is undoubtedly Guttmann's introduction of intermittent catheterization in 1954.[98] Catheterization, done only by physicians using a "non-touch" technique, was performed two or three times every 24 hours until spontaneous bladder function returned. Antibiotics were used if cultures became positive. Guttmann and Frankel reported their ten-year experience on 476 patients in 1966,[99] a paper that must have startled rehabilitation centers around the world. Of the 476 patients admitted within 14 days of injury (most within 48 hours), 77 percent had sterile urine on admission and 62 percent on discharge; only a further 7 percent drop occurred in sterility during subsequent follow-up. Most importantly, hydronephrosis was reduced to 7.4 percent, ureteral reflux to 4.4 percent, and renal calculi to 1.7 percent. Moreover, there were no urethral

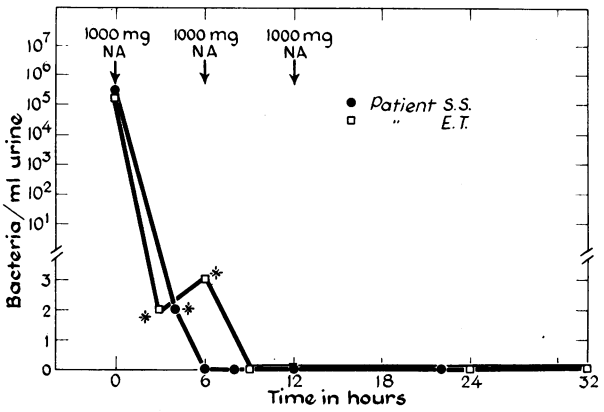

Chart 7.—Urine cultures, performed at about 3, 6, 9, 12, 24, and 32 hours after beginning nalidixic acid (N.A.), 1000 mg every 6 hours, in two patients with E. coli urinary infections. The cultures at 3, 4, and 6 hours (*) were actually sterile by the standard method of streaking 0.1 ml of urine on appropriate agar. When 5 ml of urine was Millipore-filtered, washed with 20 ml of saline solution, and the filter disc cultured, 2 to 3 E. coli per ml of urine were recovered in these three specimens. All later cultures were sterile by both methods. The minimal inhibitory concentration of N.A. for these E. coli was 25 μg per ml, as determined by tube dilution studies.

fistulae or diverticulae from periurethral abscesses, whereas this difficult complication develops in 25 to 30 percent of paraplegics with indwelling catheters.[100] If these data are confirmed, as Bors's initial study indicates,[100] public health money in this country might be better spent by adopting Guttmann's technique of managing spinal cord injuries than by screening our asymptomatic bacteriuric populations.

The Treatment of Urinary Tract Infections

This review is not the place for a detailed consideration of therapeutic regimens, but we would like to emphasize a few important concepts.

¶ Successful antimicrobial cure of a urinary tract infection is always accompanied by sterilization of the urine within a few hours of beginning therapy.[10] For example, in Chart 7 we plotted the bacterial counts in successive urine cultures from two patients following the start of oral nalidixic acid therapy. Usually within six to nine hours, and nearly always by 24 hours, the urine is sterile if treatment is going to be successful. This principle has at least two practical implications. First, if the physician performs his own urine cultures in the office in an inexpensive way,[101] better medicine is practiced, at less expense to the patient, if a culture is repeated 48 to 72 hours after starting therapy than if a useless antimicrobial agent is continued for ten days in the face of ineffective therapy. Unfortunately, the patient's symptomatic response is a poor guide to successful therapy; alleviation of symptoms commonly occurs with minimal suppression of bacteria. Second, rapid sterilization of the urine following oral antimicrobial therapy explains the occasional dilemma of the physician who admits a patient to the hospital with an overt urinary infection only to find the urine culture sterile. The mistake of ordering both a urine culture and antimicrobial therapy simultaneously in the nurse's order book is apparent: the patient receives the medication, cannot void, and the urine culture is obtained three or four hours after the start of therapy. We have observed three patients whose urinary infections were actually cured by a single oral dosage of the proper antimicrobial agent.

Urine cultures obtained during therapy must not contain any—not even one organism—of the original bacterial strain; that is, treatment is inadequate, and relapse will occur, if the colony count is reduced from 10^8 bacteria per ml to 10^2 per ml.

¶ A high correlation exists between immediate urinary sterilization and *in vitro* antibiotic sensitivities.[10] The reason infections with bacteria that are resistant *in vitro* are often cured with an antimicrobial agent thought to be ineffective from sensitivity studies is due to the low antibiotic content of some discs. Many discs, like penicillin-G and tetracycline, reflect the concentrations of drug that can be obtained in the serum, not in the urine. A real need exists for a second set of antibiotic discs, for urinary infections only, that will represent more closely the minimal urinary concentration.[10]

The reason that 80 to 88 percent of uncomplicated infections,[94] including bacteriuria of pregnancy,[102] respond to almost any form of antimicrobial therapy—sulfonamides, nitrofurantoins, antibiotics—is precisely that the bacteria are sensitive at urinary concentrations to the drug on *in vitro* studies. We have commented previously on the almost uniform correlation between *in vitro* tube dilution sensitivity studies and *in vivo* results.[10]

¶ Sterile urine, which must be achieved to cure a urinary infection, does not insure freedom from recurrence once the antibacterial agent is

discontinued. But, as was clearly documented by Bergström et al[79] and Kunin,[74] 80 percent to 90 percent of recurrent infections—even in the presence of reflux to the kidneys—are new infections, not relapse from persistence of bacteria in a focus unaffected by the antimicrobial agent. McGeachie, observing 49 adults through 108 recurrent infections with E. coli, found that 84 percent were reinfections with different strains of E. coli.[103] Winberg's observation that six of eight recurrent infections, occurring within 60 hours after completion of a ten-day course of therapy, were new infections[80] casts some doubt on the usual distinction between relapse and reinfection —that is, that relapses tend to occur early and reinfections later.

The major problem, then, in curing urinary infections is not failure of antimicrobial therapy after initial sterilization of the urine, but the prevention of the next infection. In fact, the major causes we recognize at Stanford for relapse or persistence of the same bacteria following initial sterilization of the urine are either azotemia, where bactericidal urinary levels of antimicrobial agents are difficult to achieve, or the list of correctable urologic abnormalities presented in Table 3. Thus, we do not recognize persistence of bacteria in the kidney as a cause of relapse in the absence of stones, severe obstruction, or renal failure.

¶ In the valuable review by Kleeman, Hewitt, and Guze in 1960,[84] these investigators pointed out that the results of long-term therapy for urinary infections were difficult to evaluate and not clearly superior, in terms of bacteriological cure, to the more usual course of seven to fourteen days. Although the same statement can be made ten years later, there are a few instances where continuous antimicrobial treatment is advantageous: (1) In male patients, where the bacteria persist in prostatic fluid, continuous therapy at much reduced dosage keeps the bladder urine sterile, and the patient well, without clearing the bacteria from the prostate.[65,67] (2) In children who have established a repeated pattern of recurrent infections at frequent intervals, maintenance therapy can be most useful. This is especially true with the methenamine salts,[104] where free formaldehyde, if liberated in adequate concentrations, should kill most pathogens that reach the bladder. (3) In some women where sexual intercourse is clearly the initiating event in recurrent infections, control can be achieved by a single tablet of an oral antimicrobial agent following sexual intercourse.[10] Oral penicillin-G, 250 or 500 mg, is effective, but other urinary level broad-spectrum drugs are also useful.

¶ The argument over the importance of serum versus urinary concentrations of antimicrobial agents in determining cure of urinary infections still goes on. Despite numerous emotional statements, there are only two groups, to our knowledge, that have tried to investigate the problem.[10,105] McCabe and Jackson treated 252 patients with "pyelonephritis";[105] they concluded that antimicrobial activity in the serum did not separate the cures from the failures, but that inhibitory activity in the urine related directly to cure of bacteriuria. Our group at Stanford first localized urinary infections to the kidneys and then used either oral penicillin-G or nitrofurantoin for treatment.[10] Since neither agent is active in serum against Gram-negative bacteria, the resulting cures were attributed to the urinary levels.

The question of serum versus urinary levels, unfortunately, is a practical one because the policy of sensitivity testing antibacterial agents at concentrations obtainable in serum prevents the physician from using effective drugs at the urinary levels—for example, oral penicillin-G (as a broad spectrum antibiotic) for E. coli and Proteus mirabilis, or oxytetracycline for Pseudomonas.[10] Until the Food and Drug Administration allows the manufacture of antimicrobial discs for urinary sensitivity testing, the practicing physician is excluded from an intelligent selection of these useful drugs for his patient.

¶ The observation of Asscher[46] that 36 percent of untreated bacteriuric women had spontaneous remission within 12 months is disconcerting. Kass reported a 25 percent rate in bacteriuric adults in Jamaica,[22] and Freedman observed a 50 percent spontaneous cure rate.[48] These spontaneous cures are disconcerting because one rarely sees them in an outpatient practice. How many of these cures occurred secondary to antimicrobial therapy for upper respiratory infections or other disorders unrelated to the urinary tract? The use of antibiotics is clearly widespread in our modern society. Kunin,[74] in an effort to assess this factor in his studies, interviewed and checked the records in a random survey of 125 school girls. Forty-four of them had received antibiotics for other causes than urinary infections.

Concluding Remarks

Bacteriuria is a common problem in our society. Although much of the research in urinary infections since 1956 has concentrated on the kidneys, three good reasons exist for investigating the more fundamental question of how bacteria reach the bladder from the bowel: First, most recurrent urinary infections, except those listed in Table 3, are reinfections: they are not due to relapse or persistence with the same organism.[74,79,103] Second, any unselected group of women with symptoms of acute urinary infection (dysuria, frequency, and suprapubic cramping) will have sterile bladder urine 50 percent of the time.[49] Third, in males the majority of recurrent urinary infections, lower or upper tracts, are caused by persistence of bacteria in the prostate or urethra.[65] These three observations suggest that the key to the portal of entry of pathogenic bacteria into the urinary tract lies below the internal vesical neck. The study of defense mechanisms in this area, such as the antibacterial substance in prostatic fluid,[106] may be helpful but we also need to know how bacteria from the colon become established in the prostate. Do they ascend up the urethra or cross from the colon via lymphatic channels? In females, as we have commented previously, the vaginal-urethral flora of the patient with recurrent bladder bacteriuria, between episodes of bladder infection, is frequently pathologic, consisting of thousands of E. coli or other Gram-negative bacteria per square centimeter of mucosal surface.[107] We have just completed studies on seven female patients who were observed through two consecutive episodes of bladder bacteriuria. In each instance, the specific serotype of E. coli that became established on the perineum, between bladder infections, was responsible for the succeeding bacteriuria. These observations of an altered bacterial flora on the perineum of women with recurrent urinary infection are in sharp contrast to the absence of pathologic bacteria on the vaginal vestibule of women who never have urinary infections.[108]

The time has now come to turn our attention from the kidney and bladder to those basic biologic changes that allow a pathologic flora to become established in the prostate and urethra of males and in the vagina and urethra of females. In this way, we may one day prevent infections of the bladder, and thereby of the kidney.

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