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Milestone in Urology

ASYMPTOMATIC INFECTIONS OF THE URINARY TRACT*

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(Introduced by)

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Infections of the urinary tract are second in frequency only to infections of the respiratory tract. Yet, despite their relative frequency, and their apparent association, supported by varying degrees of evidence, with such diverse clinical states as hypertension, malignant nephrosclerosis, toxemias of pregnancy, diabetes mellitus, our knowledge of the incidence and pathogenesis of such infections is incomplete, and methods for their control seriously inadequate.[1,2]

Several observers have found pyelonephritis in 12 to 20 per cent of autopsies; such pyelonephritis had been diagnosed during life in only about one-fifth of these cases.[3,4,5] The discrepancy between the clinical and autopsy findings seems too great to be accounted for on the basis of failure to recognize the generally accepted clinical manifestations of infection of the urinary tract. Alternatively, it may be suggested that there is a high incidence of clinically atypical or inapparent infections of the urinary tract in the population at large. The latter possibility has been investigated.

Initial observations were directed toward the problem of determining by quantitative bacteriologic study whether it is possible to distinguish contamination attendant upon the collection procedure from actual multiplication of bacteria within the urinary tract.

Several considerations suggest that contamination and true bacilluria may be distinguished by counting the number of bacteria in the urine.

When strains of the common pathogens of the urinary tract are cultured *in vitro* in pooled specimens of sterile urine, the bacteria generally grow readily to about 10^8 bacteria per ml. Even without added glucose, urine generally supports multiplication of the usual pathogens of the urinary tract about as well as does nutrient broth, and variations in pH and specific gravity within physiologic ranges exert but slight effects on bacterial multiplication. Occasional pools of urine, acidified to pH 5.0, are inhibitory to bacterial multiplication but the inhibitory effect disappears with dilution. The significance of this indication of the presence of an inhibitor to bacterial multiplication in urine remains to be explored. In general, however, bacteria growing in urine tend to multiply to maximal or near maximal numbers after a sufficient time.

A similar phenomenon probably occurs *in vivo.* When the urines of patients with symptoms generally recognized as those of acute pyelonephritis, namely, chills, fever, flank pain and dysuria, are examined by quantitative methods the numbers of bacteria in the urine are comparable to those found after *in vitro* cultivation. Twenty-five consecutive patients with shaking chills, fever, flank pain and dysuria were studied and all had more than 100,000 bacteria per ml. of their urines; all but one had more than one million bacteria per ml. Thus, the finding of large numbers of bacteria in the urine suggests that bacteria had actually multiplied within the urinary tract.

When the urines of female patients were collected by catheterization, the numbers of bacteria found were distributed in parabolic fashion (Figure 1). Female medical out patients were chosen at random, using no criteria for selection other than that they were not regarded, by those responsible for their care, as having active infections of the urinary tract, and in this sense they, and other patients in this study, are considered to be asymptomatic.

The data presented in Figure 1 indicate that there are two separate but overlapping population groups. One group, with bacterial counts between 0 and 10,000, presumably represents the range of contamination. The second group, with more than 100,000 bacteria, would be expected to encompass those in whom actual multiplication of bacteria had occurred. The two population groups overlap at about 10,000 bacteria per ml. Thus, among 74 patients in whom the diagnosis of pyelonephritis was made or suspected 95 per cent were found to have more than 100,000 bacteria per ml. of urine, and an additional 3 per cent of this group had between 10,000 to 100,000 per ml. Conversely, asymptomatic diabetic women and women who were about to undergo surgery for repair of cystoceles usually had less than 10,000 bacteria per ml. However, in these groups, as might be expected, there were relatively more patients whose urines contained more than 100,000 bacteria than were found in the unselected general group.

It is apparent that the number of bacteria found at either end of the distribution pattern is a function of the population groups under study. Patients with manifest or suspected

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infection add to the numbers with high bacterial counts, and those in whom infection is not considered to be present swell the ranks of those with relatively few bacteria in the specimens to be counted.

The reproducibility of these observations in the same patients is shown in Figure 2. Sixty-seven of the asymptomatic women were catheterized a second time 1 to 12 months after the first observation had been made, and the two sets of counts were compared. Those patients with high numbers of bacteria in their urines in the first count had high numbers the second time with but one, as yet unexplained, exception. Those with low numbers of bacteria in the first count had second counts that fell in random fashion over the entire low-count range. Two of the patients with 10^5 or more bacteria developed symptoms between the two examinations and are not included in this chart. Only two of 14 specimens from patients whose urinary counts were initially between 100 and 100,000 had more than 10^5 bacteria in their urines on second examination.[6] It is noteworthy that frank dysuria and true bacilluria occurred after a single catheterization in about 2 per cent of the female patients studied.

For survey purposes, a count of 10^5 bacteria or more per ml. of urine has been designated arbitrarily as the dividing line between true bacilluria and contamination. Obviously, for individual clinical purposes a reinvestigation of counts higher than 100 may at times be useful, but only occasionally, as has been shown, will patients whose urines are found to contain less than 100,000 bacteria give higher counts on repeated study, and it is not yet clear that the higher counts are unrelated to the catheterization necessary to collect the specimens. High counts show little tendency to become low counts without treatment.

The identification of the bacteria found in urines in relation to bacterial numbers is of interest. In low count specimens, coliform organisms are uncommon, and rarely occur in predominance or as single species in pure culture. Conversely, high count specimens seldom contain diphtheroids, saprophytic Neisseriæ, Sarcinæ and the other common contaminants found in the urethra. Instead, high counts are usually associated with the presence of the common pathogens of the urinary tract which are present in large numbers and are most often found in pure culture.

Urines may be stored at room temperature for one hour, or at refrigerator temperature for 48 hours without significant changes in the bacterial population. Storage at room temperature for two hours or longer leads to distinct increases in bacterial numbers. Therefore, urines should be studied within the hour after they are obtained, unless they are refrigerated immediately.

Using 100,000 bacteria per ml. as the dividing line between contamination and infection, it has been found (Table 1) that the incidence of asymptomatic bacilluria in the medical outpatient department of the Boston City Hospital is about 6 per cent, the incidence in diabetic women is 18 per cent, in women with cystocele 23 per cent, in pregnant women at term 11 per cent. Asymptomatic bacilluria occurs in 4 per cent of males in the medical outpatient department and in 5 per cent of males in the diabetic clinic. Ninety-five per cent of patients with inlying catheters will have developed bacilluria within 96 hours, most of them within the first 24 hours. The prophylactic use of antibiotics has not prevented such infections.

Although pyuria is often relied upon as an index of the presence of infection of the urinary tract, it is difficult to get any group of clinicians to agree on the number of white cells that shall be called pyuria. Pyuria has been arbitrarily defined as the presence of five or more white blood cells per high-power field, using a centrifuged specimen of urine. Pyuria, defined in this way, occurs in one-third to one-half of patients with true bacilluria, depending upon the group, but occurs in only 2 per cent of those with less than 100,000 bacteria per ml. of urine (Table 2). Even if the criterion of pyuria is lowered to three white cells per high power field, the incidence in those with true bacilluria rises by but 10 per cent. It is evident that pyuria is of value diagnostically only when it is clearly present. Its absence from any single specimen cannot be taken as evidence of the absence of bacilluria.

The Gram stain has long been a useful clinical guide to the presence of infection and was subjected to quantitative evaluation. The Gram-stained smears of uncentrifugated urines were positive in 80 per cent of counts of 100,000 and in 20 per cent of counts between 100 and 100,000 (Table 3). Clinicians have long depended upon the Gram stain as a screening device to distinguish infection from contamination, and its use is amply justified in these observations. The intrinsic error in the procedure is about 20 per cent.

Details of the clinical analysis of the patients with and without asymptomatic bacilluria can be summarized briefly. The incidence of hypertension is but slightly higher in those with bacilluria than in those without. Parity and age are not significantly different in the two groups. A history of inlying catheterization, instrumentation, previ-

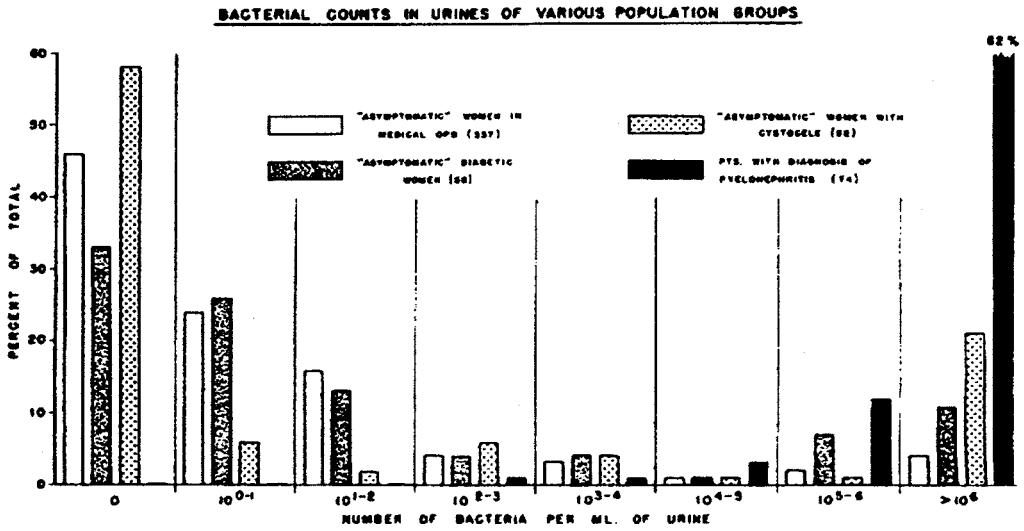

FIG. 1

ous infection, etc., is found in about one-half of those with asymptomatic bacilluria and in less than 10 per cent of those without true bacilluria.

Direct evidence to indicate that asymptomatic bacilluria is associated with pyelonephritis is as yet not available. Several considerations suggest that such an association is not unlikely. First, it is common clinical observation that inlying catheterization and instrumentation may be followed by frank pyelonephritis, indicating that bacteria can, at times, progress from the bladder to the kidney and cause symptoms, regardless of the specific route by which they do so. Secondly, we have observed patients in whom asymptomatic bacilluria was demonstrated in this study, who suddenly, and without obvious predisposing incident, weeks or months later developed fever, dysuria and flank pain.

It may be suggested, then, that bacteria may also reach the kidney in the course of asymptomatic bacilluria without causing marked symptoms. The infected kidney would be expected to discharge bacteria into the urine, and a cycle would be established which could persist for long periods of time. Such an hypothesis may explain some puzzling aspects of the problem of pyelonephritis. It could account, for example, for the pathogenesis of chronic pyelonephritis, and could account for the efficacy in cases of acute pyelonephritis, of drugs such as mandelic acid, and nitrofurantoin, which have negligible activity at tissue levels, but are strongly bactericidal in urine under proper conditions.

In certain instances, the bacterial count of the urine may fall below the range that is characteristic of infections, and these instances may be cited briefly:

(*a*) If a bacteriostatic agent is present in the urine;

(*b*) If the rate of urine flow is rapid, the numbers of bacteria discharged from the kidney small, and pooling of urine in the bladder for a time sufficient to permit multiplication of bacteria to maximal numbers has not occurred;

(*c*) If the micro-organism involved is fastidious in its growth requirements and grows poorly in urine (this has been a rare occurrence, and thus far has been limited to organisms not commonly found in the urinary tract);

(*d*) If there is obstruction of the ureter, thus interfering with the discharge of bacteria into the bladder;

(*e*) If the infection is limited to areas of the kidney not directly accessible to renal tubules.

In summary, contamination may be distinguished from true bacilluria by quantitation of the numbers of bacteria in the urine. Asymptomatic infections of the urinary tract occur frequently in the outpatient department of a municipal general hospital. Instrumentation and catheterization

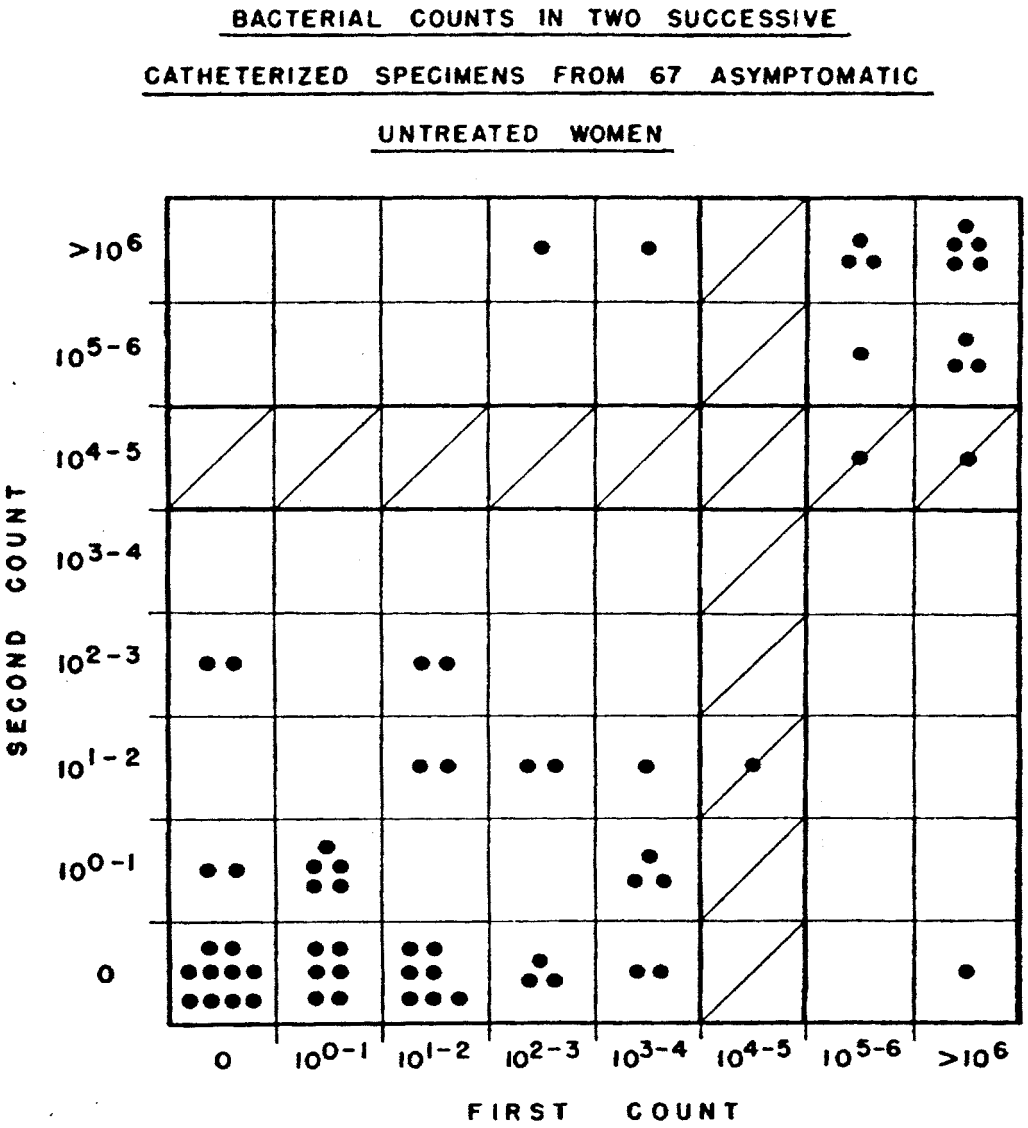

FIG. 2

TABLE 1.—OCCURRENCE OF URINARY COUNTS > 10^5 IN "ASYMPTOMATIC" OUTPATIENT DEPARTMENT POPULATION

1. 6% of 337 females in Medical Outpatient Department
2. 18% of 54 diabetic females
3. 23% of 52 females with cystocele
4. 11% of 152 pregnant females at term
5. 4% of 102 males in Medical Outpatient Department
6. 5% of 37 diabetic males
7. 95% of 22 patients with inlying catheters for 96 hours

TABLE 2.—INCIDENCE OF PYURIA (>5 WBC/HPF) IN ASYMPTOMATIC FEMALE PATIENTS

Number of Bacteria	*Number of Patients*	*Number with >5 wbc/hpf*	*Per Cent "Pyuria"*
0	120	4	3
10^{-1}	60	0	0
10^{1-2}	38	0	0
10^{2-1}	14	1*	7
10^{3-1}	7	0	0
10^{4-5}	5	0	0
10^{5-6}	5	2	40
$>10^6$	12	4	33
Total	261	11	

* On subsequent count this patient had > 10^6 bacteria.

TABLE 3.—GRAM STAIN AND COUNTS IN CONTROL URINES

Count	*Total No.*	*Positive Gram Stain*	
		No.	*Per Cent*
0	200	1	0.5
10^{6-2}	83	4	5
10^{2-4}	25	5	20
$10^{5->6}$	32	25	80

play an important predisposing role in these infections. There are as yet no distinguishing features that permit clinical recognition of the presence of asymptomatic bacilluria; only bacteriologic study has proved adequate for this purpose.

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DISCUSSION

DR. LOWELL A. RANTZ: I would like to compliment Dr. Kass for reundertaking study of a field of the greatest clinical importance.

We too have been interested in this subject for many years and can amply confirm the observations that asymptomatic infections of the urinary tract, particularly in women, are exceedingly common. The use of quantitative methods for the study of organisms in the urine is extremely important. What Dr. Kass has said about multiplication of organisms in the urine is quite correct. If you simply compare the number of organisms per ml. in urine obtained by ureteral catheterization with that obtained simultaneously from the bladder, it will be apparent that there is a many-fold increase during the period of retention in the bladder.

A study we did some years ago casts some light on the significance of the bacteriuria described here. If the discovery of large numbers of bacteria in the urine in the bladder of asymptomatic females is followed by subsequent ureteral catheterization, between one and two per cent will have many microorganisms and pus coming from one or both ureters. This indicates that there is a fairly high incidence at all times of asymptomatic pyelonephritis among women. Even if it is as low as one per cent, it is apparent that there are a truly enormous number of cases of this disease and the whole matter deserves a very great deal of consideration and investigation.

DR. EDWARD H. KASS: I just want to thank Dr. Rantz for his comments. He has promised to send me a reprint of this fine study.

We have made a few similar observations which completely confirm the findings of Dr. Rantz. Incidentally, as an interesting clinical sidelight, when the material obtained from the ureteral catheter has very high counts of bacteria in it, the large numbers are usually due to the presence of hydronephrosis. One can make a diagnosis of hydronephrosis long before the results of the radiologic study are available.

DR. WILLIAM S. TILLETT: I am reminded of an observation that the late Dr. Longcope made about infection of the urinary tract, which I think he never published, but it is an interesting one and we, on our service, have confirmed it. That is that he could clear up infections of the urinary tract by the administration of non-absorbable sulfonamide drugs given by mouth.

As I say, we have confirmed this many times and I think it throws some light on the pathogenesis of some urinary infections. I have always thought that it invited further study in that it suggests that infections in the pelvis of the kidney might be primarily derived from the intestinal tract. Since Dr. Kass has manifested interest in the subject I mention it because he might be interested in pursuing this lead which might add information to the mechanism of urinary infection.

DR. J. P. SANFORD: I would like to congratulate Dr. Kass on his excellent study. As some of you may recall we have carried out similar studies and have come to much the same conclusions.

However, our quantitative figures differ slightly from his in that we have felt that contamination occurred at lower numbers. In other words, we felt that numbers of bacteria somewhere around 10,000 were significant for infection.

Actually, I think, on further study, his figures come closer. The number is somewhere between 10,000 and 100,000 rather than between 1,000 and 10,000, as we have felt earlier.