Papers and Originals

Asymptomatic Significant Bacteriuria in the Non-pregnant Woman

I. Description of a Population

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Summary: The clinical, laboratory, and radiological findings in a group of 107 non-pregnant bacteriuric women and 88 controls have been compared. A previous history of urinary tract infection was more commonly obtained from the bacteriuric women. The means of the diastolic blood pressures, serum ureas, and erythrocyte sedimentation rates were significantly higher in the bacteriuric group, and acquired renal abnormalities were demonstrated in 18% of the bacteriuric women as compared with 4% of the controls. It is concluded that screening for asymptomatic bacteriuria in the adult non-pregnant female population in many instances fails to detect urinary tract infection at an early and reversible stage.

Introduction

Asymptomatic significant bacteriuria is defined as the presence in the urine of more than 10^5 living bacteria per millilitre in the absence of symptoms referable to the urinary tract (Kass, 1956). When infection is present multiplication of bacteria in the bladder urine produces high viable counts (usually more than 10^5 organisms per ml. of urine), while contaminants which enter the urine during or after voiding occur in much smaller numbers (usually fewer than 10^3 organisms per ml). This distinction between infection and contamination based on viable counts depends for its accuracy on careful cleaning of the perineum and labia (or glans) before collection of a mid-stream specimen of urine. In addition it requires that any organisms present in the urine are prevented from multiplying in the urine by immediate culture or by refrigeration for not more than 24 hours.

Population surveys in South Wales and Jamaica (Kass *et al.*, 1965) and Japan (Freedman *et al.*, 1965) have shown that significant bacteriuria is present in from 3 to 7% of adult women. It has been suggested (Kass *et al.*, 1961, 1965) that asymptomatic significant bacteriuria represents an early stage of the natural history of urinary tract infection and that these subclinical

infections may lead to acute infections, chronic infections, and eventual death from kidney failure. However, the natural history of asymptomatic significant bacteriuria has not so far been sufficiently well documented to substantiate such claims. It is known that in pregnancy asymptomatic significant bacteriuria predisposes to the development of acute pyelonephritis and that treatment of the bacteriuria can markedly reduce the incidence of this complication (Turner, 1961; Kass, 1962; Kincaid-Smith and Bullen, 1965; Little, 1965). However, the fate of the great majority of women with asymptomatic significant bacteriuria—that is, those who are not pregnant—has not so far been studied in detail.

In this report the clinical, laboratory, and radiological findings in a group of adult non-pregnant women with asymptomatic significant bacteriuria are described and compared with those in a group of non-bacteriuric controls matched for age, marital status, and parity. In the following paper (Asscher *et al.*, 1969) the response of the subjects with bacteriuria to antibacterial therapy and their subsequent clinical course is examined.

Material and Methods

Urine Collection.—Mid-stream “clean-catch” urine specimens were obtained from 3,578 women aged 20 to 65 who attended the outpatient and casualty departments of the Cardiff Royal Infirmary between September 1966 and January 1968. The reasons for hospital attendance, marital status, and parity of these subjects were recorded. The majority were visitors to the hospital. Subjects with urinary symptoms at the time of attendance, diabetic patients, and pregnant women were excluded from the screening programme. The urine samples were collected in the outpatient department by the subjects themselves after careful explanation of the procedure by a trained nurse. They were instructed to separate the labia and to clean the perineum three times from front to back with gauze swabs impregnated with green soap solution. Then, while still holding the labia apart, the first part of the stream was voided and part of the remainder was collected in a wide-mouthed sterile polypropylene jar. Each specimen was immediately cooled by placing it in an insulated bag which was lined with “Handy Ice” blocks (Glud and Marstrand, Copenhagen) which had previously been frozen at -10°C . At the end of each three-hour screening period the specimens were transferred to a refrigerator in the laboratory and kept at 4°C . The specimens were cultured on the day of collection.

Bacterial Examination of Urine Specimens.—Initial screening for the presence of bacteriuria was performed by spreading a

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standard loopful of urine on nutrient agar and MacConkey's agar. The plates were incubated overnight at 37° C. Specimens containing more than 10⁵ organisms per ml. were regarded as positive, and colony counts were performed on urine specimens in which there was doubt about the number of viable bacteria present. A second urine specimen was obtained at a home visit from all subjects whose initial specimen had been positive, and was examined in an identical manner. Single colonies were picked from the growth obtained from all urines showing significant bacteriuria and stored. Detailed identification was carried out at a later date. The criteria for admission to the present study were that two consecutive urine specimens contained more than 10⁵ organisms per ml. of urine and that the organisms isolated from the two specimens were identical.

Methods of Bacterial Identification.—Organisms were plated out on fresh blood agar and MacConkey's agar. A single typical colony was then subcultured in nutrient broth and the organisms were identified by the methods of Cowan and Steel (1965). The antibiotic sensitivity of the organisms was determined by means of Oxoid Multodiscs. Identity of strains of *Escherichia coli* in successive urine specimens was assumed if they were of the same O-serotype as determined by slide agglutination. Identity of *Proteus* strains was established by the ability of identical strains of *Proteus* to swarm into each other (Dienes, 1946).

Control Subjects.—For each of the first 100 bacteriuric subjects included in this study, a control matched for age, parity, and marital status was chosen from the non-bacteriuric population. A second specimen of urine was obtained from each of the control subjects before inclusion in the study to confirm the absence of bacteriuria. Where a control subject refused to co-operate no substitute was chosen, since it was considered probable that the very fact of agreeing or refusing to co-operate might select a group of women with special characteristics.

Clinic Procedure.—All confirmed bacteriuric subjects and controls were informed of the results of their urine culture and were asked to attend the outpatient department. They were first seen by a medical epidemiologist who was unaware of the results of urine culture and who took a history, with particular reference to past and present urinary symptoms, method of contraception, and analgesic intake. Blood pressure was measured after the subjects had been seated for at least five minutes, with a standard mercury manometer and a 13 by 25 cm. cuff. Diastolic pressures were taken at the point at which muffling of sounds occurred, and readings were recorded to the nearest 5 mm. Hg. A sample of venous blood was then

obtained for the estimation of serum urea, haemoglobin, and erythrocyte sedimentation rate. The subjects were then seen by a physician who was aware of the results of urine culture and who fully explained the purpose of the study. Arrangements were made for an intravenous pyelogram. Though all the bacteriuric subjects were seen in the clinic, 48 of the controls did not attend. They were seen at their own homes by the medical epidemiologist.

Excretion Urography.—Control radiographs were taken after a 12-hour period of dehydration. Then 50 ml. of Urovison (diatrizoic acid) was injected intravenously and radiographs of the kidneys with and without abdominal compression were taken. Bladder films were taken before and after micturition. The radiographs were interpreted independently by two radiologists who were unaware of the results of urine culture, and the radiological findings were recorded on standard forms. Films which gave rise to disagreement were later resubmitted to the radiologists for a joint report.

Results

Demographic Data

A total of 3,578 women were screened for significant bacteriuria. A single positive culture was obtained from 255 (7.1%) subjects and the second culture was positive in 126 (3.5%). Identity of the organisms in the two urine specimens was observed in 107 subjects (3.0%). The first 100 bacteriuric subjects were matched with non-bacteriuric controls drawn from the total population, and 88 of these co-operated in the study.

The age distribution, civil state, parity, and reasons for hospital attendance of the total bacteriuric and control populations are shown in Table I. The age distribution of the subjects in the total population differed from that of the general female population of Cardiff obtained at the 1966 census. There was a deficiency in the 20–29 and 50–65 age groups, which was balanced by an excess of subjects in the 30–49 age group. There was no significant difference between the age distribution of the bacteriuric population and that of the total population. This suggests that bacteriuria occurred at a similar rate at all ages from 20 to 65. The three populations did not differ significantly with regard to age, civil state, and parity, and bacteriuria did not predominate in any one parity group, though there was a slight but statistically insignificant rise in the group of parity 5 and over. Bacteriuria occurred significantly more often in subjects

TABLE I.—Distribution of Age, Marital Status, Parity, and Reasons for Hospital Attendance in the Total, Bacteriuric, and Control Populations

Age	No.	Civil State			Reason for Attendance				Parity							
		Married	Single	Widow	Visitor	Medical	Surgical	Dermatological	0			1	2	3	4	5 +
									Single	Married	Widow					
20-29	673	515	157	1	533	41	59	40	151	83	—	133	162	95	34	15
30-39	1,140	1,099	30	11	980	50	90	20	31	56	—	101	346	288	176	142
40-49	1,012	926	46	40	829	69	101	13	33	61	2	163	289	217	103	144
50-59	544	457	32	55	429	67	41	7	32	54	10	112	141	86	51	58
60-65	209	132	18	59	167	17	21	4	18	24	9	38	43	32	18	27
Total	3,578	3,129	283	166	2,938	244	312	84	265	278	21	547	981	718	382	386
Bacteriuric Subjects																
20-29	20	16	4	—	16	2	1	1	4	0	—	2	7	5	1	1
30-39	33	33	—	—	31	2	—	—	—	1	—	2	10	10	5	5
40-49	32	28	2	2	27	4	1	—	2	2	—	7	7	5	3	6
50-59	13	10	—	3	8	5	—	—	—	1	1	2	6	2	0	1
60-65	9	8	—	1	8	1	—	—	—	—	—	1	2	—	2	4
Total	107	95	6	6	90	14	2	1	6	4	1	14	32	22	11	17
Control Subjects																
20-29	21	18	3	—	17	3	1	—	3	1	—	2	8	5	1	1
30-39	27	27	—	—	22	3	2	—	—	1	—	1	8	8	5	4
40-49	24	23	1	—	16	7	1	—	1	1	—	6	5	3	2	6
50-59	11	8	—	3	6	4	1	—	—	1	1	2	6	—	—	1
60-65	5	5	—	—	2	3	—	—	—	1	—	—	2	—	2	—
Total	88	81	4	3	63	20	5	0	4	5	1	11	29	16	10	12

who attended medical clinics than in those attending surgical or dermatology clinics. Surprisingly, the controls were also significantly more frequently drawn from subjects who attended for medical reasons than from those attending surgical or dermatology clinics. The explanation for this finding is unknown.

Bacteriological Findings

The organisms isolated from the 107 bacteriuric subjects are shown in Table II. In 90 (84%) the infecting organism was *E. coli*. Other organisms found were *Proteus mirabilis*, which was isolated from 9 individuals (8%), coagulase-negative *Staphylococcus pyogenes*, which was found in 3 cases (3%), and coagulase-positive *Staph. pyogenes* and *Klebsiella aerogenes*, which were each found in 2 cases (2%). Only one subject was infected with *Alcaligenes faecalis* (1%). The most commonly isolated serotypes of *E. coli* were O75 (8%) and O6 (6%). Rough strains of *E. coli* represented 22% of the isolates, and 14%, though smooth, were untypable with available sera.

TABLE II.—Organisms Isolated from the 107 Bacteriuric Subjects

<i>Escherichia coli</i>	90
<i>Proteus mirabilis</i>	9
<i>Staphylococcus pyogenes</i>	3
<i>Klebsiella aerogenes</i>	2
<i>Alcaligenes faecalis</i>	1

Serotypes of <i>E. coli</i>					
Type	No.	Type	No.	Type	No.
O1	1	O23	1	O86	1
O1 × O31	1	O25	1	O86 × O90	1
O2	1	O31	2	O89	1
O2 × O50	1	O39	1	O104	1
O4 × O12 × O108	1	O48	1	O108	1
O6	5	O50	3	O110 × O125	1
O7	2	O51	1	O117	2
O7 × O71	3	O55	2	O120 × O139	1
O10	1	O62	1	O129 × O130	1
O12	1	O71	2	O131	2
O13 × O68	1	O75	7	O133 × O135	1
O18	1	O77	1	Rough	20
O22	1	O81	1	Untypable	13

FIG. 1

FIG. 1.—Distribution of systolic blood pressure in the bacteriuric and control populations. FIG. 2.—Distribution of diastolic blood pressure in the bacteriuric and control populations.

of loin pain with fever had occurred more commonly among the bacteriuric subjects. Ninety-seven of the 107 bacteriuric subjects (91%) gave a past history of urinary symptoms as compared with 55 out of the 88 controls (63%). This difference is highly significant ($P < 0.001$). An even more striking difference between the past histories of the bacteriuric and control subjects was that 74 (69%) of the bacteriuric subjects gave a history of urinary symptoms in the year preceding the detection

TABLE III.—Replies to Standard Questionnaire Obtained from 107 Bacteriuric and 88 Control Subjects

	Bacteriurics		Controls		Significance
	No.	%	No.	%	
Dysuria	97	90.8	55	62.5	$P < 0.001$
Frequency	80	74.8	40	45.5	$P < 0.001$
Nocturia	54	50.5	24	28.4	$0.02 > P > 0.10$
Loin pain with fever	21	19.6	3	3.4	$P < 0.001$
Haematuria	3	2.8	1	1.1	N.S.
Symptoms during last year	74	69.2	16	18.2	$P < 0.001$
No previous history	10	9.3	33	37.5	$P < 0.001$
Excessive analgesic intake	5	4.7	4	4.5	N.S.
Oral contraceptives	24	22.4	11	12.5	N.S.

of the bacteriuria, whereas only 16 (18%) of the controls gave such a history.

Analgesic and Oral Contraceptive Intake.—Excessive analgesic intake was defined as the consumption of one or more analgesic tablets daily for at least one year. On this basis the consumption of analgesics by bacteriuric and control subjects did not differ significantly (Table III). As shown in Table III oral contraceptives were more commonly taken by the bacteriuric subjects than the controls. Although this difference does not reach the conventional level of statistical significance the trend is worthy of note.

Blood Pressure.—The distribution of systolic and diastolic blood pressures in the bacteriuric and control groups is shown in Figs. 1 and 2. The means ($\pm$ S.D.) of the systolic blood pressures in the bacteriuric and control subjects were 138.5 ± 19.0 mm. Hg and 135.5 ± 17.0 mm. Hg respectively. The difference between these means was not significant ($0.3 > P > 0.2$).

FIG. 2

Clinical Findings

Previous History of Urinary Tract Infection.—All of the 107 bacteriuric subjects and 88 of the 100 (88%) controls provided answers to a standard questionnaire about their previous history of symptoms of urinary tract infections, method of contraception, and analgesic intake. The analysis of replies is given in Table III. It will be seen that a history of dysuria, frequency, and nocturia was significantly more common among the bacteriuric than the control subjects. Similarly, attacks

The means ($\pm$ S.D.) of the diastolic blood pressures in the bacteriuric and control subjects were 86.0 ± 10.7 mm. Hg and 83.1 ± 9.0 mm. Hg respectively. This difference was significant ($0.05 > P > 0.02$).

Laboratory Findings

Serum Urea.—The distribution of serum urea in the bacteriuric and control subjects is shown in Fig. 3. The mean ($\pm$ S.D.) was 25.7 ± 7.8 mg./100 ml. in the bacteriuric group

and 23.2 ± 7.7 mg./100 ml. in the control group. The difference between these means was significant ($0.05 > P > 0.02$). It will be seen from Fig. 3 that, although the serum urea in the bacteriuric subjects never exceeded 55 mg./100 ml., 54 of 109 (50%) had a serum urea between 25 and 55 mg./100 ml., whereas only 20 of the 82 (24%) controls had a serum urea in this range.

FIG. 3.—Distribution of serum urea in the bacteriuric and control populations.

Haematological Findings

There was no significant difference between the haemoglobin levels in the bacteriuric and control subjects. The mean ($\pm$ S.D.) haemoglobin value in the bacteriuric group was 13.8 ± 1.4 g./

Radiological Findings

Excretion urograms were obtained from 93 (87%) of the 107 bacteriuric subjects and from 50 (57%) of the 88 controls. Abnormalities were found in 32 (34%) of the bacteriuric sub-

FIG. 4.—Distribution of erythrocyte sedimentation rate in the bacteriuric and control populations.

jects and in 6 (12%) of the controls. This difference was significant ($P<0.001$). The abnormalities which were detected are shown in Fig. 5. Acquired abnormalities (scars, stones, and differences in kidney size of greater than 2 cm.) were found in 17 of the 32 abnormal urograms obtained from the bacteriuric group and in two of the six abnormal urograms obtained from

[illegible]

Abnormalities	Controls						Total
	1	2	3	4	5	6	
Scars	■						1
Stones							0
Hydroureter	■	■					1
Hydronephrosis							0
Duplex pelvis and ureter			■				1
Difference in size (>2cm)				■			1
Calycial cysts							0
Renal cysts							0
Rotation of kidney							0
Horseshoe kidney					■		1
Ureterocele							0
Foetal lobulation							0
Polycystic kidneys					■		1

FIG. 5.—Abnormal findings in the excretion urograms of 93 bacteriuric and 50 control subjects. Note: Each vertical column shows the findings in one of the abnormal pyelograms. Abnormalities were detected in 32 of the bacteriuric women and 6 of the controls.

100 ml. and that of the controls was 14.0 ± 1.2 g./100 ml. ($0.3 > P > 0.2$). The distribution of erythrocyte sedimentation rates in the bacteriuric and control subjects is shown in Fig. 4. The mean ($\pm$ S.D.) of the erythrocyte sedimentation rates in the bacteriuric subjects was 14.6 ± 10.0 mm./hour and that of the control was 12.2 ± 6.8 mm./hour. This difference was of borderline significance ($0.1 > P > 0.05$).

the controls. Multiple abnormalities were confined to the bacteriuric subjects. Thus 8 of the 12 bacteriuric subjects with cortical scars showed multiple abnormalities. Metabolic causes for stone formation and tuberculosis were excluded in the eight subjects with calculi. Only one of these women was infected with *Proteus mirabilis*; in the remainder the infecting organisms were coliforms.

Discussion

This study was the first part of an attempt to determine the value, as a preventive measure, of screening for asymptomatic bacteriuria in an adult non-pregnant female population. The population from which the bacteriuric women described in this study were drawn was not random, as shown by the difference in age distribution from that of the general female population of Cardiff. The present study, therefore, does not add to previous prevalence studies carried out in unselected populations (Kass *et al.*, 1965; Freedman *et al.*, 1965). Nevertheless, the epidemiological results presented above tend, in some respects, to confirm previous work. Thus the prevalence of bacteriuria at 3.0%, though somewhat lower than that observed by Kass *et al.* (1965) in Jamaica and South Wales, was similar to that observed by Freedman *et al.* (1965) in Japan. Kass and his associates found a prevalence of 6.6% and 4.2% respectively in a rural area and mining area in South Wales. The lower incidence found by us in the City of Cardiff is partly due to the introduction of an additional criterion for significant bacteriuria—namely, the requirement for identity of the organisms isolated from the initial urine specimens. The prevalence of bacteriuria in this study was unaffected by age or parity, though, in agreement with Kass *et al.* (1965), there was a suggestion of a greater prevalence among women with five or more children.

The data reported here suggest that in the great majority of women significant bacteriuria does not detect urinary tract infection at an early stage of its natural history. More than 90% of the bacteriuric subjects had experienced symptoms of urinary tract infection in the past. Moreover, significant rises in diastolic blood pressure and serum urea were found among the bacteriuric subjects, and the prevalence of radiological abnormalities in the bacteriuric subjects far exceeded that in the controls. These findings suggest that significant bacteriuria in non-pregnant women is not entirely an indicator of early and reversible disease.

Mean systolic and diastolic blood pressures in the bacteriuric subjects were higher than in the non-bacteriuric controls. This association between bacteriuria and raised blood pressure confirms the findings of Kass *et al.* (1961) in South Wales and Jamaica and those of Freedman *et al.* (1965) in Japan. The significance of the association remains unknown. Although experimental work suggests that hypertension increases the susceptibility of the kidney to infection (Shapiro, 1963), epidemiological evidence would favour the view that bacteriuria contributes to the development of high blood pressure (Kass *et al.*, 1961; Miall *et al.*, 1962).

Oral contraceptives were taken more frequently by bacteriuric subjects than by the controls. Although this difference was not significant, the trend is worthy of note. The association may have resulted from a greater frequency of sexual intercourse in women taking oral contraceptives. This seems unlikely, since the available data indicate that other methods of contraception were not more commonly practised by the bacteriuric subjects. It is possible, therefore, that humoral factors are responsible for the association. Andriole and Cohn (1964) and Corriere and Murphy (1968) have shown that the administration of oestrogens to rats increases their susceptibility to haematogenous as well as ascending infection of the urinary tract and leads to persistent bacteriuria. This effect was associated with the development of bilateral hydronephrosis and hydronephrosis. Since many oral contraceptives contain oestrogens, interference with the dynamics of urine flow may account for the higher prevalence of bacteriuria in subjects taking these drugs.

Radiological abnormalities were found in 32 of the 93 bacteriuric subjects (34%) and in 6 of the 50 controls (13.0%). This difference is highly significant and establishes that radio-

logical abnormalities are found more commonly in bacteriuric subjects than in uninfected controls. Acquired renal disease was found in 17 subjects (18%). In a series of 163 pyelograms, obtained from six months to four years after delivery, from women who had had bacteriuria in pregnancy, acquired renal abnormalities were found in 15% by Gower *et al.* (1968). Although the prevalence of acquired renal disease in the two series is similar there are certain differences of detail. Cortical scars were almost twice as common, and stones were three times as common, in our series as compared with that of Gower *et al.* (1968). The similarity in the prevalence of acquired renal disease in the two series, therefore, is due to the more frequent occurrence of multiple abnormalities in the present series. Our radiological findings as well as those of Gower *et al.* (1968), Leigh *et al.* (1968), and Whalley *et al.* (1965) contrast with the observations of Kincaid-Smith and Bullen (1965) in Australia. The prevalence of acquired renal disease in the Australian series was 45%. Gower *et al.* (1968) suggested that the difference was due to the widespread abuse of analgesics in Australia.

No mention has been made of the age distribution of the subjects included in the above four series of women who had significant bacteriuria during pregnancy. Nearly half of the bacteriuric subjects in the present series were over 45 years of age. It seems likely, therefore, that the present series consisted of bacteriuric women older than those included in the previously reported series, which were restricted to women of child-bearing age. That multiple acquired abnormalities are commoner in the older bacteriuric women reported here may mean that abnormalities acquired in early life are later complicated by stone and scar formation. Continued follow-up of the present series of bacteriurics may provide further information on this important point.

The two basic requirements of a good screening procedure are that it should detect disease at an early stage before irreversible damage has occurred and that the disease so detected can be effectively treated. The association of bacteriuria with past history of urinary tract infection, radiological abnormalities, and significant rises in diastolic blood pressure and serum urea establishes that significant bacteriuria fails to satisfy the first of the requirements of a good screening technique, since in many instances it does not detect urinary tract infection at an early stage of its natural history.

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