

## ORIGINALS

### Bacteriuria in Diabetes Mellitus\* \*\*

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*Summary.* One hundred and four diabetic patients with bacteriuria were followed for a mean period of 44 months. They were divided in two groups "cured" and "persistent" according to the results of treatment. Retinopathy and albuminuria as evidences of microangiopathy were present at the beginning of the study in a greater number of patients and in a greater degree in those with persistent bacteriuria than in those cured. At follow-up the number of patients with and the severity of retinopathy and albuminuria were higher in those with persistent bacteriuria although not statistically different. Microangiopathy usually antedated bacteriuria and may have contributed to its persistence, although the possibility that bacteriuria played a role in the progression of microangiopathy cannot be excluded. No significant deterioration in renal function became apparent in either group, suggesting that persistent bacteriuria had not obviously contributed, to the development of pyelonephritis or progressive renal damage.

#### *La bactériurie dans le diabète sucré*

*Résumé.* Cent-quatre diabétiques atteints de bactériurie ont été suivis durant une période moyenne de 44 mois. Ils étaient divisés en deux groupes: les "guéris" et les "persistants" selon les résultats du traitement. La rétinopathie et l'albuminurie, preuves de la microangiopathie, étaient présentes, au début de l'étude, à un degré plus important et chez un plus grand nombre de "persistants" que de "guéris". Par la suite, le nombre de malades avec rétinopathie et albuminurie était plus grand et la gravité de la maladie plus forte dans le groupe des "persistants", mais cela n'était pas statistiquement significatif. La microangiopathie précédait en général la bactériurie et pouvait avoir contribué à sa tenacité, bien

que l'on ne puisse exclure la possibilité du rôle joué par la bactériurie dans la progression de la microangiopathie. Dans aucun des deux groupes n'est apparue une détérioration très nette du fonctionnement rénal, ce qui suggère que la bactériurie persistante n'a pas contribué de façon évidente au développement de la pyélo-néphrite ou de lésions rénales progressives.

#### *Die Bacteriurie im Diabetes Mellitus*

*Zusammenfassung.* 104 Diabetiker mit Bacteriurie wurden im Durchschnitt 44 Monate beobachtet. Entsprechend dem Ergebnis der Behandlung wurden die Patienten in die beiden Gruppen „Geheilt“ und „Persistierend“ eingeteilt. Retinopathie und Albuminurie, als Anzeichen einer Mikroangiopathie, waren zu Beginn der Untersuchung in einer größeren Anzahl und in einem größeren Ausmaße bei den Patienten mit persistierender Bacteriurie als bei den geheilten vorhanden. Am Ende der Beobachtungszeit war die Zahl der Patienten mit Retinopathie und Albuminurie größer und der Schweregrad noch stärker ausgeprägt in der Gruppe mit persistierender Bacteriurie, aber dies ist nicht statistisch signifikant. Die Mikroangiopathie begann meist vor der Bacteriurie und kann zu ihrer Resistenz beigetragen haben, obgleich die Möglichkeit nicht ausgeschlossen werden kann, daß die Bacteriurie eine Rolle im Fortschreiten der Mikroangiopathie spielte. In beiden Gruppen waren keine bedeutenden Veränderungen der Nierenfunktion ersichtlich. Dies bedeutet, daß die persistierende Bacteriurie offensichtlich nicht zu der Entwicklung einer Pyelonephritis und einer progressiven Nierenzerstörung beigetragen hat.

*Key-words:* Bacteriuria, albuminuria, retinopathia, microangiopathy, diabetes, hyperglycaemia, juvenile diabetes, blood urea nitrogen.

The significance of true bacteriuria (100000 or more colonies/ml) as an expression of occult chronic pyelonephritis leading to renal deterioration, is unsettled. Kass [9] considers bacteriuria highly significant in this respect and, as Kunin [11] expressed it, "bacteriuria, urinary tract infection, pyelonephritis, and significant renal disease are part of a broad continuum,

evolving slowly with time in an often erratic and insidious manner". Kimmelstiel [10] and Petersdorf [13] emphasize that in many patients bacteria in the urine live in symbiosis with the host while producing no detectable disease in terms of symptoms, signs or gross abnormalities in renal function.

Significant, or true, bacteriuria as evidence of urinary tract infection (UTI) has been found more frequently in diabetic patients than in the population at large [18, 5, 1]. However, in recent years, others [19, 7] have questioned this higher prevalence.

The possible role played by bacterial infection in the development or aggravation of microangiopathy in diabetic patients or vice-versa, has received scant attention in studies dealing with bacteriuria. In some

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of these, microvascular disease is mentioned as a finding without conclusions [16, 15], Vejlsgaard [20] has noted a direct relationship between frequency of retinopathy and increasing incidence of urinary infections.

The present study was undertaken to answer two questions, 1) whether true bacteriuria expresses or leads to chronic pyelonephritis, and 2) whether there is a relationship between bacteriuria and microangiopathy.

#### Material and Methods

Between February 1963 and August 1964 one hundred and four Joslin Clinic outpatients had significant bacteriuria (100 000 or more colonies/ml) and represent the material for this study. These patients had a follow-up of their present condition in the later months of 1968 and in January 1969. Physical examination was done by the Clinic's medical staff, and in many cases by one of us (MAB).

Of the 104 patients with positive urine cultures 95 were females. The mean duration of follow-up after the diagnosis of bacteriuria was 44 months. Seventy-four patients were more than 50 years old when bacteriuria was detected with the peak in the sixth decade (Fig. 1).

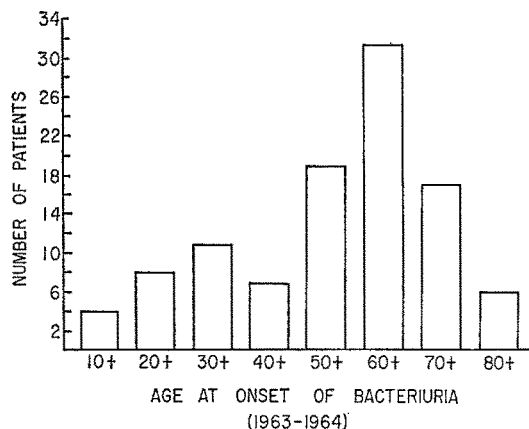


Fig. 1. Age distribution of patients at diagnosis of bacteriuria

In sixty-one patients diabetes developed at an age greater than 40 years, with a mode of 40 to 50 years (45 cases). Of the 43 patients under 40 at diagnosis, 19 had the onset of diabetes before the fifteenth birthday ("juvenile diabetes"). The duration of diabetes in 69 of the 104 patients with bacteriuria was 10 years or longer, and in the remaining 35, diabetes was known for ten years or less.

The urine was obtained for culture from a "mid-stream clean voided" specimen and processed by the laboratory immediately. A count of 100 000 or more colonies per ml was considered significant bacteriuria.

The following examinations were conducted at the beginning of the study in 1963-1964 and at the follow-up period: eyegrounds, blood pressure, protein in the urine, blood urea nitrogen, haemoglobin, electrocardiogram and intravenous pyelogram. The findings were considered abnormal in the presence of a blood pressure of 151/91 or higher, proteinuria 100 mg per 100 ml or higher, a blood urea nitrogen of 26 mg per 100 ml or higher and a haemoglobin level of 12.4 g or less.

Retinopathy was diagnosed as simple (in the presence of microaneurysms, exudates, small haemorrhages) or as proliferative (neovascularization and/or gliosis). Abnormalities in the electrocardiogram were tabulated either as diagnostic of a myocardial infarction or all other changes combined. The findings on intravenous pyelograms considered were those of chronic pyelonephritis or neurogenic bladder. Other abnormalities were disregarded.

The control of diabetes was estimated by averaging all blood glucose determinations done during the follow-up visits of the period of study. Thus a mean blood glucose value for each patient was obtained.

The chi square test, paired and unpaired *t* tests were used for statistical analysis of the observed differences.

#### Results

*E. coli* alone was the causative organism in 54 cases, whereas twenty-two had another single organism, most frequently *Aerobacter* or *Proteus*. A mixed growth was found in 28, in 16 of whom *E. coli* was included. The treatment comprised most of the drugs available and was usually prescribed in accordance with the results of sensitivity studies. Sulphonamides were the drugs most frequently used; other were chloramphenicol, tetracycline, nitrofurantoin and methenamine mandelate. In this material however no chemotherapeutic agent appeared superior to the others in obtaining cure of bacteriuria.

On the basis of the results obtained following therapy, patients with bacteriuria were divided into two groups: "Cured" (34 cases), those patients showing no significant bacteriuria on subsequent urine cultures after a single course of treatment. "Persistent" bacteriuria (70 cases), those who showed more than one positive urine culture taken one month or later after completion of the initial treatment irrespective of whether or not the most recently obtained culture was positive or negative (Table 1).

The frequency of abnormal findings and their subsequent progress, if any, were compared in the two groups. Twenty-five patients died between 1963 and 1969. The causes of death as reported on death certificates were coronary heart disease in 13, renal failure in three, cerebral vascular accidents in three and other causes in six. Seven deaths were in the "cured" group and 18 in those with "persistent" bacteriuria. No

statistical differences were apparent on comparing the groups to indicate that bacteriuria played a role in the number dying or in the cause of death.

Proteinuria was initially found with significantly greater frequency in the group with "persistent" bacteriuria than in the "cured" ( $p < 0.005$ ) (Table 2). The mean level of urinary albumin excretion was 18.7 mg% in the "cured" and 95 mg% in the "persistent" ( $p < 0.02$ ). Five additional patients changed at the end of the follow-up from the category of under 100 mg% proteinuria to over that level. All of them belonged to the "persistent" group.

and most cases had retinopathy at the time of appearance of bacteriuria.

The number of patients with blood glucose levels over 150 mg% and the average blood glucose levels were significantly higher in the "persistent" group than in those "cured" ( $p < 0.02$ ) (Table 4). Haemoglobin levels were significantly higher in those "cured" (13.48 mg%), than in those with "persistent" bacteriuria (12.65 mg%) ( $p < 0.05$ ). Both systolic and diastolic blood pressure remained without significant changes during the follow-up interval and showed no significant differences between the two groups. No

Table 1. *Clinical data on diabetic patients with bacteriuria*

Group of patients	Total patients	Females	Males	Age in 1963-64	Duration of Diabetes	Juvenile Diabetics	Months of Follow-up	No. of Infections	No. of Cultures
Cured	34	30	4	52.1	15.9	7	45	1.0	3.55
Persistent	70	65	5	56.75	14.54	12	44	2.46	5.45

Table 2. *Albuminuria in diabetics with bacteriuria*

Groups of patients	Number of patients with urinary albumin at beginning of the study		Urinary albumin > 100 mg% at follow-up
	< 100 mg%	> 100 mg%	
Cured	33	1	1
Persistent	52	18	23

$p < 0.005$

Table 3. *Diabetic retinopathy in patients with bacteriuria*

Group of patients	Total	Retinopathy at diagnosis of bacteriuria			Retinopathy at follow-up
		Simple	Proliferative	Total	
Cured	34	7	4	11	12
Persistent	70	28	13	41	47

$p < 0.025$

Table 4. *Blood glucose level in diabetic patients with bacteriuria*

Group of patients	Blood glucose level		
	< 150 mg%	> 150 mg%	Mean mg%
Cured	20	14	161.14
Persistent	15	54	184

$p < 0.02$

Retinopathy, simple or proliferative, was present in 52 patients at the diagnosis of bacteriuria. The distribution in the groups showed a greater frequency in the "persistent" than in the "cured" group ( $p < 0.025$ ) (Table 3). It was found in seven additional patients at the follow-up examination, six of them in the "persistent" group. The difference in frequency of development of new cases of retinopathy between the groups during the follow-up was not statistically significant,

significant changes were noted in blood urea nitrogen values before the diagnosis of bacteriuria and at the end of the study (Table 5). Nevertheless, the number of patients in the "cured" group who lacked this information was great, possibly because those cured with the first treatment did not require subsequent renal studies.

Intravenous pyelograms were available in 35 patients. Most of these were done in the patients with persistent bacteriuria, possibly because these were the ones who presented urinary problems. Four out of 4 pyelograms in the cured group were normal whereas 8 out of 31 were normal in those with persistent bacteriuria. Eight in the latter group showed evidence of chronic pyelonephritis, 7 had neurogenic bladder, and another 8 had both.

Abnormalities in the electrocardiograms showed no significant differences between the groups, although again the scant information especially in the "cured" group could bias the results.

The bacteria identified by culture could not be correlated with a number of the above-mentioned clinical parameters (Table 6).

### Discussion

From the results of the present study it is apparent that true bacteriuria in the diabetic is observed almost exclusively in females, whereas the ratio of females to males who attend the Joslin Clinic has been found to be

ences in the two groups suggest that the presence of bacteriuria was not associated with gross renal parenchymal injury, a finding reported also by others [21, 14, 4].

The significantly higher prevalence of retinopathy and proteinuria in the patients with "persistent" bacteriuria than in those "cured" suggests either an important role of bacteriuria in the higher prevalence of these manifestations of microangiopathy, or a predisposing prior role of microangiopathy in producing "persistent" bacteriuria. Although the former possi-

Table 5. Blood urea nitrogen level in diabetic patients at diagnosis of bacteriuria and at follow-up

	Blood urea nitrogen			Mean blood urea nitrogen level mg%	
	same	worse	no inf.	before	after
Cured	14	2	18	16.60	20.00
Persistent	42	11	18	15.50	23.75

Table 6. Clinical data and causative agent in diabetic patients with bacteriuria

Causative Agent	Sex		Age at Onset of Bacteriuria	Age at Onset DM	Duration DM	Type of Mat.	DM Outcome		Final Result	Albuminuria		Total		
	F.	M.					Juv.	Alive		Dead	Cure		Perst.	>100 mg%
<i>E. coli</i>	49	5	55	39	16	45	9	45	9	22	32	8	46	54
Single other than <i>E. coli</i>	20	2	57	43	14	19	3	20	2	5	17	6	16	22
Mixed Bacteria	27	1	52	39	13	20	8	20	8	14	25	5	23	28

almost equal, 52% to 48% respectively. The majority of patients who developed bacteriuria were in the older age groups, in accordance with other studies [21]. The age distribution of patients with bacteriuria by decades was similar in distribution to the data given by Joslin *et al.* [8] for all diabetics, indicating that the present group was representative in age to the general diabetic population. Of the 19 juvenile-onset patients with bacteriuria, only seven were under 15 years of age at the time of this study whereas the rest became bacteriuric after many years of diabetes.

The final result of treatment ("cured" or "persistent") did not bear a relationship to causative agent, age at onset of diabetes, age at onset of bacteriuria, duration of diabetes, sex, type of diabetes or mortality.

The greater number of patients with hyperglycaemia and the higher mean blood glucose levels in patients with "persistent" bacteriuria compared with the "cured", suggest an association of the former group with increasing mean blood glucose. The greater degree of hyperglycaemia could be either the result of bacteriuria or be responsible for its perpetuation.

The fact that blood urea nitrogen levels and blood pressure did not change in this diabetic bacteriuric population during the follow-up interval, and that the intravenous pyelograms showed no significant differ-

bility cannot be excluded from these data, the latter possibility is favoured by the absence of a significantly greater rate of development of retinopathy or albuminuria during the follow-up interval in those with "persistent" bacteriuria. That microangiopathy is more likely to be predisposing is further suggested by the relatively long duration of diabetes in most patients, and in particular in the persistent group. Although 35 patients purportedly had diabetes for less than 10 years, in only six of these could the date of onset be established with certainty. In the remaining 29, diabetes was of the maturity-onset type and thus of uncertain duration. Of these 29 patients, 26 belonged to the persistent group; six of the latter were found to have retinopathy prior to the diagnosis of bacteriuria, which also suggests a longer duration of diabetes.

The frequency of electrocardiographic evidence of a myocardial infarction in the two groups is similar to that shown by others in diabetic population [2].

The frequency of vascular deaths (76%), primarily coronary heart disease, is comparable with the distribution in the diabetic population as a whole [17]. The lack of statistical difference in frequency of electrocardiographic abnormalities and mortality, especially that due to coronary artery disease, between the "cured" and "persistent" cases suggests that bac-

teriuria *per se* plays no significant role in the development or progression of larger vessel disease, at least of the coronaries.

In spite of these negative results in demonstrating an aetiologic role in the progression of microangiopathy or gross renal damage, the importance of diagnosis of bacteriuria in a diabetic should not be underestimated. The risk of perinephritis [14], renal medullary necrosis [12] and a higher foetal mortality [6], necessitates prompt and appropriate treatment of bacteriuria in the diabetic.

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