Our patients had had malignant tumour before renal transplantation, and in such patients subsequent development of the tumour might be facilitated by immunosuppressive therapy.

It could, therefore, be argued that organ transplantation with subsequent immunosuppressive therapy has no place in the treatment of patients with cancer (*Lancet*, 1969). Total hepatectomy for primary tumours and orthotopic liver transplantation has been performed, however, with encouraging success (Starzl *et al.*, 1968; Calne, 1972) though tumour recurrences have been reported (Starzl *et al.*, 1971). In our series of liver transplants two patients who had primary malignant hepatomata were alive and well one year and six months after orthotopic transplantation with no evidence of recurrence. A third patient survived five years and had no evidence of malignant tumour when she died.

There have been very few reports of kidney transplantation in patients with previous neoplasia (Hume and Egdaahl, 1955; Hume *et al.*, 1963; Hume, 1968; Woodruff *et al.*, 1969). Hume's two patients had Wilms's tumours, and both patients did well, but in one case where the time interval between removal of the tumour and transplantation was only six months tumour recurrence occurred two years later. In the other patient where the interval between tumour removal and transplantation was 12 years there was no evidence of recurrence. In the patient of Woodruff *et al.* (1969) with bilateral hypernephromata renal transplantation was performed a few days before the removal of the tumour. There was no evidence of metastases after four years (Woodruff, 1969), but the patient eventually died of recurrent growth seven years after grafting (M. F. A. Woodruff, personal communication).

Two of the patients reported here had malignant tumours of the kidneys, and transplantations were performed about two months after the removal of the tumours. In the two cases with non-renal tumours transplantation was performed two and three years after the removal of the primary tumours. In case 4 no information regarding the removal of the mole was available at the time of transplantation. The prognosis for stage I seminoma of the testis treated by orchidectomy and irradiation of para-aortic nodes approaches 90% survival (Peckham and McElwain, 1974). The decision to proceed with transplantation in case 1 was therefore entirely justified.

Sarcomatous changes in polycystic kidneys are usually considered to be noninvasive and in case 2 they seemed to be confined entirely to the kidneys, but reports of distant metastases from such tumours have been found in the literature (Lowsley and Curtis, 1945; Borski and Kimbrough, 1954; Roberts, 1973). These are rare tumours and though survival for five years after nephrectomy has been reported no information is available in regard to their prognosis.

The prognosis in patients with transitional cell carcinoma of the renal pelvis, even after removal, is poor, and when invasion of the renal substance and extrarenal structures has occurred the five-year survival rate is about 11% (Williams and Mitchell, 1973). The patient in case 3 enjoyed excellent health for eight months, but rapidly deteriorated and died within a few weeks with extensive metastases. It is difficult to assess the effect of renal transplantation and one week's immunosuppressive therapy in case 4. It is highly unlikely that she would have been considered for transplantation had the history of a previous melanotic tumour been known.

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Periurethral Enterobacterial Carriage in Pathogenesis of Recurrent Urinary Infection

W. R. CATTELL, M. A. McSHERRY, A. NORTHEAST, E. POWELL, H. J. L. BROOKS, F. O'GRADY

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Summary

Periurethral carriage rates of enterobacteria have been studied in 20 normal women, 34 patients between episodes of bacteriuria, 34 patients with the "urethral syndrome,"

and 15 asymptomatic abacteriuric patients with a previous history of frequency and dysuria.

Over a six-week period no difference in the *Escherichia coli* carriage rate was shown between these four groups. The carriage of all enterobacteria was slightly but significantly ($P < 0.05$) lower in normal women compared with the patient groups but no difference was observed between the latter. There was no difference in the recovery rate and carriage of individual *E. coli* serotypes between the four groups.

It is concluded that the presence of enterobacteria or *E. coli* on the periurethral area is not the principal determinant factor in the pathogenesis of recurrent urinary tract infection or the urethral syndrome and that definition of carriage status is of little practical value in management.

St. Bartholomew's Hospital, London EC1A 7BE
 W. R. CATTELL, M.D., F.R.C.P., Consultant Nephrologist
 M. A. McSHERRY, S.R.N., Research Assistant
 A. NORTHEAST, S.R.N., Research Assistant
 E. POWELL, F.I.M.L.T., Research Assistant
 H. J. L. BROOKS, B.Sc., Research Assistant
 F. O'GRADY, M.D., F.R.C.PATH., Professor of Bacteriology

Introduction

It is now generally accepted that urinary infection most commonly results from ascending per-urethral invasion of the bladder by potentially pathogenic organisms normally present in the gut. The postulated sequence of events is: initial colonization of the introitus and periurethral area, extension of colonization to the urethra, transfer of bacteria to the bladder during micturition or coitus, and, when bladder defence mechanisms are impaired, the establishment and multiplication of bacteria in bladder urine. To account for recurrent infection it has been suggested that women so afflicted may be distinguished from normal subjects by a special facility for harbouring pathogenic enterobacteria on the introitus or in the urethra. In support of this, Stamey *et al.* (1971) observed striking differences in enterobacterial carriage on the vestibule and in urethral urine between normal and affected women. Most other investigators (Cox, 1966; Cox *et al.*, 1968; O'Grady *et al.*, 1970; Marsh *et al.*, 1972; Bailey *et al.*, 1973) have failed to confirm these observations though O'Grady *et al.* (1970) observed that "recurrent infection was commoner in patients who were persistent carriers of enterobacteria." Marsh *et al.* (1972), studying patients with symptoms of recurrent infection, found little correlation between the level of introital colonization and the incidence of subsequent infections.

Review of these conflicting reports suggests that some of the confusion may relate to differences in the selection of patients and the timing of studies in relation to episodes of urinary infection. To clarify this point, to attempt to establish whether systematic study of periurethral carriage can be used to identify patients at special risk from recurrent infection, and to elucidate further the role of periurethral enterobacterial carriage in the pathogenesis of the "urethral syndrome" a detailed study comprising serial periurethral and urine culture has been carried out on carefully defined groups of normal women and patients presenting with frequency and dysuria.

Subjects and Methods

Normal Subjects (Group A).—Studies were carried out on healthy adult women who had no previous history of urinary tract symptoms or of asymptomatic urinary tract infection. This group was drawn from friends, relatives, and research assistants and did not include any hospital patients.

PATIENTS

All the patients studied had been referred to a specialist urinary infection clinic with a history of recurrent frequency and dysuria. Following initial documentation and investigation they were seen at a minimum of one, three, seven, and 12 months after their first attendance, their symptoms being recorded and a urine specimen for culture being obtained at each visit. Symptomatic or infected patients were seen more often. All patients were required to attend immediately for urine culture if symptoms recurred or were exacerbated. On the basis of this follow-up patients could be divided into the following three groups.

Recurrent Bacteriuria (Group B).—All patients in this group were documented as having recurrent episodes of bacteriuria during follow-up, sometimes over a period of several years.

Symptomatic Abacteriuria (Group C).—This group consisted of patients with persistent symptoms of frequency or dysuria or both who were never shown to have bacteriuria on repeated urine culture. Such patients have also been described as having the "urethral syndrome."

Asymptomatic Abacteriuria (Group D).—These were patients who though presenting with a history of frequency or dysuria or both remained asymptomatic and abacteriuric throughout a 12-month follow-up period.

PLAN OF STUDY

All subjects were studied weekly for six weeks. On each occasion a periurethral swab was obtained followed by a midstream, clean-catch urine sample. A condition of inclusion in the study was that none of the control subjects or patients were bacteriuric or had received any antibacterial therapy in the previous six weeks. Patients with intermittent bacteriuria were studied between episodes of infection, no bacteriuria having been shown within six weeks before, during, or after the study period. None of the patients or controls had any evidence of vaginitis during the study period.

Periurethral swabs were obtained by separating the labia without prior washing and swabbing the area around the external urethral orifice with a sterile tampon. All swabs were immediately plated on MacConkey's medium and incubated aerobically overnight. Any enterobacteria (*Escherichia*, *Aerobacter*, *Klebsiella*, and *Proteus* spp.) isolated were identified by standard methods and the numbers of colonies on the plate were recorded. The presence of micrococci, diphtheroids, streptococci, and other organisms was similarly recorded but they were not further categorized. No attempt was made to isolate slow-growing, fastidious, or anaerobic bacteria or other micro-organisms. *Escherichia* isolated from the periurethral swab were serotyped using a set of 150 O antisera raised in rabbits against the known serotypes (Bettelheim and Taylor, 1969).

Urine Samples.—Bacterial counts were carried out using a standard surface-plating technique. In symptomatic patients with low bacterial counts urine was obtained by suprapubic aspiration to exclude low levels of bladder bacteriuria.

Results

Twenty normal subjects aged 21 to 50 years were studied over six weeks. Thirty-four patients with documented recurrent bacteriuria (group B) entered the study. Six weekly samples were obtained from 28 of these patients but only four or five weekly samples were obtained from the remaining six. Similar numbers of samples were obtained from 34 symptomatic abacteriuric subjects (group C). Six weekly samples were obtained from all 15 patients who were neither symptomatic nor bacteriuric (group D).

For ease of interpretation the bacterial counts were allocated to subdivision of colonies in which either none (0) or 1 to 5, 6 to 50, 51 to 500, or more than 500 were present on the MacConkey plate (tables I and II). The results obtained for all enterobacteria are shown in table I. Though there was no striking difference between the groups there were rather more negative results from the normal subjects and a lower percentage of swabs in the upper ranges compared with the patient groups. When *E. coli* alone was studied (table II) no difference was found between any of the groups. Analysis of the mean figures may, however,

TABLE I—Carriage Rate of Enterobacteria in Each Group

Group	No. of Subjects	No. of Swabs	Percentage of swabs yielding colony counts of:				
			0	1-5	6-50	51-500	>500
A	20	120	40	16	17	16	11
B	34	196	31	6	19	25	19
C	34	198	27	8	22	27	16
D	15	90	28	2	21	23	26

TABLE II—Carriage Rate of *E. coli* in Each Group

Group	No. of Subjects	No. of Swabs	Percentage of swabs yielding colony counts of:				
			0	1-5	6-50	51-500	>500
A	20	120	44	15	18	11	12
B	34	196	53	3	18	14	12
C	34	198	51	8	13	17	11
D	15	90	44	3	21	16	16

conceal differences within the groups—for example, regular high carriage rates in some but not other patients within each group. To exclude this possibility cumulative carriage rates were plotted at levels of ≥ 1 , ≥ 5 , ≥ 50 , and ≥ 500 colonies. The results for enterobacteria and *E. coli* at levels of ≥ 5 and ≥ 500 colonies are shown in figs. 1 and 2. Again a difference was observed with respect to enterobacteria between the control group (A) and the patient groups (B to D), the former showing significantly lower recovery rates throughout. This was observed at all levels of the bacterial count (≥ 1 to ≥ 500). Though variations occurred in cumulative carriage no significant difference could be shown for enterobacteria between groups B to D and no difference between any (A to D) of the groups with respect to *E. coli* at any level (≥ 1 to ≥ 500 colonies).

FIG. 1—Cumulative carriage rates of enterobacteria at levels of ≥ 5 and ≥ 500 colonies in the four groups. Numbers of subjects in each group are shown.

FIG. 2—Cumulative carriage rates of *E. coli* at levels of ≥ 5 and ≥ 500 colonies in the four groups. Numbers of subjects in each group are shown.

Serotyping was carried out on all the *E. coli* organisms isolated. Again there was no difference in the pattern of persistence of particular *E. coli* serotypes in normal subjects compared with patients irrespective of the level of periurethral colonization (fig. 3). Though in some of the group B patients the same *E. coli* serotype was recovered at some stage from the periurethral area as had previously been or was subsequently the cause of infection there was no regular association in most of the patients. With respect to the particular serotypes isolated 38 different O serotypes were represented. Many were single isolates. The serotype pattern for the common serotypes seen in British

FIG. 3—Persistence of same serotype on periurethral area in the four groups of subjects from whom *E. coli* was recovered on three or more occasions.

TABLE III—Recovery Rate of *E. coli* Serotypes (O Antigen) Commonly Encountered in Britain (Gruneberg *et al.*, 1968). Figures are Numbers of Subjects

<i>E. coli</i> Serotype	Subject Groups			
	A	B	C	D
O 1	1	0	2	0
O 2	0	2	0	2
O 4	0	0	1	1
O 6	3	3	1	1
O 7	2	1	1	0
O 11	2	0	0	0
O 17	0	1	0	0
O 18	1	3	2	2
O 25	1	3	0	0
O 39	0	0	0	0
O 75	1	2	4	1

practice (Gruneberg *et al.*, 1968) is shown in table III. No obvious pattern emerges.

Discussion

Recurrent urinary infection in adult women is most often due to repeated reinfection by gut flora. Though notable success has been achieved in the management of such recurrences with the use of long-term, low-dose prophylactic therapy (Cattell *et al.*, 1971) little advance has been made in understanding or correcting the factors predisposing to repeated reinfection. The claim by Stamey *et al.* (1971) that women susceptible to repeated reinfection can be distinguished from normal women by virtue of some biological difference which facilitates the introital carriage of *E. coli* and other urinary pathogens is of importance, for if such is the case research and therapeutic effort must be directed to defining the nature of this difference and, hopefully, altering introital conditions so as to eliminate bacterial carriage.

In contrast to Stamey, however, most workers have failed to show striking differences between normal subjects and women with recurrent infection. Thus Cox (1966) and Cox *et al.* (1968) recovered Gram-negative bacilli from the urethra of 54% of women with recurrent infection and 27% of normal women. We ourselves recovered five or more enterobacteria from periurethral swabs from 23% of healthy women and 28% of women with frequency or dysuria or both in the absence of bacteriuria (O'Grady *et al.*, 1970). More recently Bailey *et al.* (1973) have reported periurethral bacterial carriage (five or more colonies of enterobacteria) in 13% of healthy premenopausal women and 21% of postmenopausal women. The carriage rates increased in women with a previous history of recurrent infection. This latter observation also correlates with our previous finding that recurrent infection appeared to be commoner in patients who were persistent carriers of enterobacteria (O'Grady *et al.*, 1970). That study, however, was not designed to examine the regular periurethral carrier state as measured by serial examination of the individual patient or normal subject.

Several explanations have been proposed to explain these divergent results—failure to define the population being studied; differing, possibly incorrect methods of sample collection; failure to obtain truly “normal” subjects for control purposes, etc. To avoid these various criticisms we have studied a group of normal, asymptomatic women who had not been hospitalized and compared the findings with those in three groups of patients, the pattern of whose illness had been carefully defined by long-term follow-up in a specialist urinary infection clinic. To reduce sampling errors and to define the regular carrier state of these women each was studied weekly for five or six weeks. To exclude the possible influence of recent infection (Marsh *et al.*, 1972) or antibiotic treatment or a changing state before subsequent infection (Stamey *et al.*, 1971) all the patients were known to have had no bacteriuria or antibiotics for six weeks before the study and no bacteriuria during or within six weeks of completion of the study.

The results show no difference in the introital carriage rate of *E. coli* between normal subjects and patients referred with a history of previous urinary infection whether they were subsequently shown to be intermittently bacteriuric, symptomatic and abacteriuric, or asymptomatic and abacteriuric. A small difference in periurethral carriage of enterobacteria in general was observed between normal subjects and the patient groups though there was no difference between the patient groups. Thus it does seem that patients with a previous history of urinary infection may have a slight change in the overall periurethral colonization as compared with normal women but that there is no difference in this respect between those who are subsequently intermittently bacteriuric and those who are persistently abacteriuric. Furthermore, though *E. coli* was the most common cause of bacteriuria in our patients no difference in the periurethral carriage rate was observed between the normal subjects and the three patient groups. There was also no difference in the recovery rate or persistence of particular *E. coli* serotypes.

When these results are compared with other reports it must be noted that slightly differing techniques are used. Thus Stamey *et al.* (1971) studied clean-catch urethral urine samples (labelled VB₁) and samples from the vaginal vestibule, Bailey *et al.* (1973) studied swabs from the external urethral meatus (periurethral swabs) and vaginal vestibule, and Cox *et al.* (Cox, 1966; Cox *et al.*, 1968) obtained urethral specimens using a specially designed instrument. We have previously used the term “introital” swab to define what is more correctly a periurethral

swab. We have also previously shown and subsequently confirmed that colony counts of the same organism are obtained in the same proportion of instances from urethral urine (VB₁) and periurethral swabs in normal women and patients alike.

By dividing patients into “persistent”, “intermittent”, and “non-” carriers of introital bacteria on the basis of swabs taken at clinic attendances we previously showed (O’Grady *et al.*, 1970) that recurrent infection was more frequent in “persistent” carriers. Though we excluded swabs taken at the time or within two or three days of infection the work of Stamey *et al.* (1971) suggests that this period may be insufficient to exclude periods of introital carriage directly related to episodes of infection. In the present study we sought to establish whether introital carriage was a special feature of women with lower urinary tract symptoms when care was taken to examine swabs only at times remote from urinary infection. We found no evidence of unusual carriage on serial study during interinfected periods and it appears, therefore, that there is little practical advantage in attempting to define patients who regularly have a high periurethral enterobacterial carriage rate in the hope that identification of such patients might indicate those who are at particular risk from recurrent bacteriuria or lead to treatment of the introitus which might in turn reduce the potential for recurrent reinfection or, in the case of patients with the urethral syndrome, eliminate their symptoms.

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Adrenergic, Coagulation, and Fibrinolytic Responses to Heat

B. J. BRITTON, CHRISTINE HAWKEY, W. G. WOOD, MURIEL PEELE, J. KAYE, M. H. IRVING

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Summary

Two groups of volunteers were exposed to heat in a sauna bath—one group for 10 minutes and the other for 15. There

was no change in plasma adrenaline concentration until the subjects emerged from the sauna bath, when there was a slight increase in concentration. Factor VIII and thromboelastograph patterns did not change but marked activation of fibrinolysis was stimulated by exposure to heat. These findings support the concept that fibrinolysis is not mediated by direct adrenergic activity.

Department of Surgery, St. Bartholomew’s Hospital, London EC1A 7BE

B. J. BRITTON, M.B., F.R.C.S., Lecturer in Surgery

W. G. WOOD, B.Sc., Ph.D., Biochemist

MURIEL PEELE, A.I.M.L.T., Research Technician

M. H. IRVING, M.D., F.R.C.S., Assistant Director, Surgical Professorial Unit
Department of Chemical Pathology, St. Bartholomew’s Hospital, London EC1A 7BE

J. KAYE, M.Sc., M.C.B., Senior Biochemist

Nuffield Institute of Comparative Medicine, London Zoo, London N.W.1

CHRISTINE HAWKEY, B.Sc., Ph.D., Head of Haematology Section

Introduction

The factors that initiate the changes in coagulation and fibrinolysis which occur during stress situations such as surgery have still not been elucidated. Many years ago it was suggested that adrenaline played a significant role in the activation of coagulation and fibrinolysis (Cannon and Gray, 1914; Biggs *et al.*, 1947). More recently the advent of the