respectively, though these differences may be slightly misleading owing to the greater natural longevity of women. During the whole period 40 of 66 deaths in patients aged under 65 were related to bleeding compared with only 12 of the 38 deaths in the older group (χ^2 test, $p<0.001$); in these intercurrent disease was the more common cause. Analysis of patients aged over 70 compared with those aged 66-70 showed a similar outcome, except that deaths related to bleeding accounted for one fifth of all deaths in the older group. The equivalent figure in the group aged 66-70 was 52% (13 deaths). Virtually all deaths related to bleeding occurred within six months of initial presentation. Rebleeding occurred in a greater proportion of elderly patients (χ^2 , $p<0.01$) and also more often (table II).

TABLE II—Treatment and outcome in patients studied. Figures are numbers (percentages) of patients

	Age group (years)	
	≤65	>65
No of patients	146	61
Mortality due to first bleed	39 (27)	10 (16)
Patients requiring balloon tamponade	51 (35)	16 (26)
Emergency surgery for bleeding	5 (3)	4 (7)
Patients who rebled	61 (42)	38 (62)
Bleeding risk factor (per patient month)	0.09	0.12
Deaths (bleeding related: non-bleeding-related):		
Months 0-6	36:8	10:10
Months 7-12	1:4	1:4
Months 13-18	1:3	1:3
Months 19-24	1:0	0:2

Comment

These results show that elderly patients with bleeding varices managed in an active sclerotherapy programme have a similar outcome to younger patients managed the same way. Twenty four (40%) of the elderly patients were transferred from other hospitals, but as survival in these was similar to patients from our own hospital, bias within groups seems unlikely. Though the aetiology of liver disease was in different proportions in the two groups, analysis of survival

within subgroups showed it to be independent of aetiology. Based on the evidence of clinical trials, most younger patients with bleeding varices are now managed—at least initially—by injection sclerotherapy.^{2,3} Not unreasonably, clinicians caring for the elderly have been reserved about the benefits of sclerotherapy in their patients, as these trials included very few elderly patients. Also such patients are often admitted to geriatric wards where emergency access to endoscopy is not readily available; and endoscopy is an essential requirement for sclerotherapy.

Our results showing the benefits of active management of bleeding varices in the elderly are supported by a study in Cologne of 61 elderly patients.⁴ Though full details of recruitment of patients were not given, those workers achieved 50% survival in both young and old groups at 24 months using a similar regimen to ours. The increased rebleeding rate seen in our elderly patients was also noted in a study of 14 patients reported by Roberts *et al* and led to more hospital admissions but seldom caused death. We emphasise that both the group in Cologne and we performed endoscopy and sclerotherapy within 12 hours of admission to hospital. This not only reduces blood loss but also reduces hepatic decompensation, which is an important cause of death. We believe that active treatment of an elderly patient bleeding from varices is well worth while and should not be denied on the basis of age alone.

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Accepted 7 November 1988

Human papillomavirus infection and cervical intraepithelial neoplasia in women with renal allografts

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Abstract

An increased prevalence of cervical cancer has been observed in immunosuppressed women, but controlled studies are rare. Biopsy specimens from 49 women with renal allografts and 69 non-immunosuppressed controls (with no history of cervical intraepithelial neoplasia, vulval warts, or abnormal results of cervical smear tests) were assessed for colposcopic appearance, cytological and histological diagnosis, and the presence of human papillomavirus types 6/11 and 16/18 DNA sequences. At colposcopy 26 (53%) of the women with allografts had cervical abnormalities compared with 20 (29%) of the controls. The prevalence of cervical intraepithelial neoplasia was significantly higher in the women with allografts (24 (49%) compared with 7 (10%)). The overall rate of detection of human papillomavirus DNA did not differ significantly between the two groups. There was, however, a significant difference in the rate of detection of human papillomavirus type

16/18 DNA (27% in the women with allografts and 6% in the controls).

These data confirm that pathological and virological changes affecting the cervix are significantly increased in immunosuppressed women and emphasise the need for regular colposcopic examination.

Introduction

An increased prevalence of malignancy in general¹ and of both intraepithelial and invasive neoplasia of the female genital tract has been observed in immunosuppressed patients.^{2,3} Porreco *et al* reported a 14-fold increase in the prevalence of cervical intraepithelial neoplasia in women with renal allografts over that in women of the same age in the general population,⁴ and this was confirmed by others.⁵⁻¹¹ In 1977 zur Hausen suggested that human papillomavirus might be implicated in the pathogenesis of neoplasia of the lower genital tract.¹¹ Analysis of the results of a large number

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Br Med J 1989;298:153-6

of studies suggested that human papillomavirus types 16 and 18 are most commonly related to higher grades of cervical intraepithelial neoplasia and invasive cancer and types 6 and 11 with lower grades of neoplasia and cervical warts.¹²

We studied the prevalence of cervical disease and human papillomavirus infection in a group of women with renal allografts and compared it with that in a group of non-immunosuppressed women matched for characteristics known to influence cervical neoplasia.

Patients and methods

We recruited 49 women with renal allografts who were receiving routine follow up at the Edinburgh Nuffield Transplantation Unit and asked them to attend the Lothian area colposcopy clinic between March 1986 and October 1987. Over the same period 69 women who had been admitted to a gynaecological ward in Edinburgh Royal Infirmary for elective operations were recruited as controls provided they had had normal results from cervical smear tests within the previous two years and did not have a history of cervical intraepithelial neoplasia. Patients and controls completed a questionnaire requesting information on parity, age at first intercourse, number of sexual partners, smoking habit, and current contraceptive practice. For the women with renal allografts information on the type, duration, and extent of immunosuppressive treatment they had received was also obtained. Subjects in both groups had pelvic examinations. Colposcopy was performed and assessments made before and after 3% acetic acid and Schiller's iodine solutions were applied. If the transformation zone was abnormal two adjacent specimens were taken from the abnormal area by colposcopically directed biopsy. If no abnormality was seen two adjacent biopsy specimens were taken at random from the transformation zone. One specimen from each pair was fixed in formaldehyde for histological examination and the other snap frozen in liquid nitrogen for DNA hybridisation. In addition, a cervical smear was taken with an Ayre's spatula from the women with renal allografts.

HUMAN PAPILLOMAVIRUS TYPING

Preparation of DNA probes for human papillomavirus was as described by Rudlinger *et al.*,¹³ with mixed types 6 and 11^{14 15} and types 16 and 18^{16 17} human papillomavirus DNA. Probes were radiolabelled with phosphorus-32 to an activity of 1×10^6 counts/min/ml.

Extraction of DNA—Biopsy specimens were suspended in 10 mM trometamol (TRIS) 10 mM edetic acid and 0.5% sodium dodecyl sulphate (pH 8) and treated with 500 µg proteinase K (Sigma)/l for 16 hours at 37°C. The DNA was extracted with phenol and precipitated with ethanol before being dried and resuspended in 10 mM trometamol and 1 mM edetic acid (pH 8).¹³

DNA-DNA hybridisation—Portions of 1-10 µg DNA were transferred to Genescreen membranes (New England Nuclear Laboratories) and denatured in

0.5 M sodium hydroxide and 1 M sodium chloride for five minutes and then neutralised in 1 M trometamol (pH 7.5) and 1.5 M sodium chloride for five minutes. The membranes were baked in a vacuum at 80°C before hybridisation with mixed type 6/11 or type 16/18 probes labelled with ³²P at moderate temperature (midpoint -22°C) and high temperature (midpoint -9°C) and then exposed to x ray film (Kodak X-omatic) at -70°C for 24-72 hours.

Statistical methods—Statistical analyses were carried out by Student's *t* test, χ^2 test (with linear trend or Yates's correction where applicable), and Spearman's rank correlation test.

Results

Matching characteristics—There was no significant difference between the women with renal allografts and the controls with respect to age, age at first intercourse, number of sexual partners, use of the contraceptive pill, and smoking habit. Parity, however, was significantly higher in the control group (table I).

Clinical examination—Five women with renal allografts had external genital warts, of whom one had recurring warts that persisted despite treatment, and two had undergone vulvectomy for vulval carcinoma. None of the controls had warts or cancers.

Findings at colposcopy—The upper limit of the transformation zone was seen in all cases. Twenty six (53%) of the women with allografts had abnormal findings on colposcopy compared with 20 (29%) of the controls ($p < 0.01$). Abnormalities ranged from minimal to dense aceto-white areas with vascular abnormalities (mosaicism and punctation).

Histological findings—Table II shows that a significantly higher proportion of the women with allografts had cervical intraepithelial neoplasia (24 (48.5%) compared with 7 (10%); $p < 0.0001$). All of the women with

TABLE II—Histological findings in women with renal allografts and controls. Values are numbers (percentages) of women

Findings	Women with renal allografts (n=49)	Controls (n=69)
Normal	14 (29)	48 (70)
Koilocytes only	11 (23)	14 (20)
CIN grade I	11 (23)	6 (9)
CIN grade II	8 (16)	1 (1)
CIN grade III	5 (10)	

CIN=Cervical intraepithelial neoplasia.

cervical intraepithelial neoplasia in both groups (except two with allografts who had grade III disease) had koilocytosis. Hence 33 (67%) women with allografts had koilocytosis (22 of whom had neoplasia) compared with 21 (30%) controls (seven of whom had neoplasia). Three of the women with allografts with cervical intraepithelial neoplasia grade III had a history of the disease and had been treated on several occasions either by laser ablation or cold coagulation. In the control group the woman with cervical intraepithelial neoplasia grade II had had a normal cervical smear two months previously, while the six women with grade I disease had all had normal smears within the past two years.

Cervical cytology in women with renal allografts—Thirty eight of the women had normal cervical smears, and 11 had smears showing various degrees of dyskaryosis. The history of findings on cervical cytology in this group was interesting: 14 had not had a previous smear, three had not had a smear for more than 10 years, 12 had had a smear between five and 10 years previously, and 16 had had one within the past five years. Four of the women had a history of cervical intraepithelial neoplasia and had been screened

TABLE I—Characteristics of women with renal allografts and controls

	Women with renal allografts (n=49)	Controls (n=69)	<i>t</i>	χ^2	p Value
Mean (range) age (years)	40 (20-61)	39 (23-71)	0.3		0.78
Mean (range) parity	1.6 (0-6)	2.4 (0-6)		9.561	<0.005
Mean (range) age at first intercourse (years)*	20 (16-27)	19 (14-27)		3.485	0.06
Mean (range) No of partners*	2.3 (1-9)	2 (1-6)		0.075	0.78
No of smokers	18	32		3.0	0.09
No taking contraceptive pill	4	15		2.8†	0.09

*Data on nine women with renal allografts and 18 controls were incomplete.

†With Yates's correction.

regularly ever since. Thus only 20 (41%) of the women had been screened adequately.

Human papillomavirus DNA hybridisation—There was no significant difference between the groups in the rate of detection of total of human papillomavirus DNA (table III), which was 45% in the women with allografts compared with 38% in the controls, or human papillomavirus type 6/11 DNA, which was 25% in the women with allografts (three women had mixed type 6/11 and type 16/18 infection) compared with 32% in the controls. The detection of type 16/18 DNA, however, was significantly higher in the women with allografts than the controls (27% v 6%; $p<0.005$).

TABLE III—Types of human papillomavirus DNA detected in women with renal allografts and controls. Values are numbers (percentages) of women

Type	Women with renal allografts (n=49)	Controls (n=69)	χ^2 *	p Value
6/11	9 (19)	22 (32)	0.841†	0.36
16/18	10 (21)	4 (6)	8.378†	<0.005
Mixed 6/11 and 16/18	3 (7)			
None	27 (55)	43 (62)	0.141	0.70

*With Yates's correction.

†Including three women with mixed type 6/11 and type 16/18.

Discussion

Our results support the findings of others that the prevalence of cervical intraepithelial neoplasia is increased in women with renal allografts.^{6-10, 18} This is the first study, however, to have compared these women with controls matched for age and other factors known to be associated with cervical intraepithelial neoplasia.¹⁹ Altogether 49% of the women with allografts had cervical intraepithelial neoplasia; when those with abnormal cervical smears were excluded (to make the group comparable with the control group) 42% had neoplasia compared with 10% of the controls, a four-fold increase in prevalence. Koilocytosis was present in all but two of the women with allografts, who had cervical intraepithelial neoplasia, suggesting a viral association. This is consistent with the findings of Sillman *et al*, who observed koilocytosis and cervical intraepithelial neoplasia in all of 20 immunosuppressed women.²⁰

Schneider *et al* showed that human papillomavirus types 16 and 18 were associated with a higher rate of progression and more severe grades of cervical intraepithelial neoplasia.²¹ We found a significantly higher rate of detection of human papillomavirus type 16/18 DNA in the women with allografts (27% compared with 6%), which suggests that this difference is directly related to the high grades of cervical intraepithelial neoplasia observed in these immunosuppressed women.

This study, like that of Cordiner *et al*,¹⁰ showed a high rate of false negative results of smear tests (42% in

the women with allografts). High rates of false negative results have also been observed by others (S McNair and G E Smart, unpublished data and Shield *et al*,²² who discussed possible reasons for this). False negative results of smear testing may be more commonly associated with the lower grades of cervical intraepithelial neoplasia as the disease is often patchy and may be merely an expression of human papillomavirus infection. Interestingly, in this study all of the false negative results were found in women with cervical intraepithelial neoplasia grade I or grade II. We did not find, however, that false negativity was related to the size of the lesion or transformation zone. If colposcopic biopsies had not been performed 16 out of 24 of all the lesions would have been missed. This indicates the need for colposcopic examination in women with renal allografts, irrespective of the results of previous cervical smears.

An average time lag of 58 months between the start of immunosuppressive treatment and the development of malignancy has been observed.¹ Our study was not longitudinal so we cannot draw any such conclusions, but there did not seem to be a clear relation between the detection of cervical intraepithelial neoplasia and the duration of immunosuppression (table IV). Neither can we comment on any difference between the women who were taking azathioprine and those taking cyclosporin A as the number taking cyclosporin A was too small. There seemed, however, to be a trend towards infection with human papillomavirus type 16/18 being more common in those who had been immunosuppressed for more than five years.

We suggest that immunosuppressed women are at greater risk of developing cervical intraepithelial neoplasia and human papillomavirus type 16 or 18 infection. Cervical smear tests do not seem to provide a reliable screen in these women. There is as yet no quick or easy method of detecting and typing human papillomavirus. We therefore recommend that immunosuppressed women should be offered long term colposcopic surveillance and, when necessary, early local treatment for this potentially premalignant but easily curable condition.

We thank Professor H zur Hausen for supplying the human papillomavirus types 6, 11, 16, and 18 probes; Dr R Prescott, University of Edinburgh, for statistical analysis; and Dr J L Anderton and Dr J R B Livingstone for allowing us to study their patients. We also thank the nursing staff of ward 34 of Edinburgh Royal Infirmary and all staff of the Lothian area colposcopy clinic. This study was supported by a research grant from the Scottish Home and Health Department.

TABLE IV—Influence of duration of immunosuppression on histological findings and types of human papillomavirus DNA detected in women with renal allografts and controls

Duration of treatment (years)	No of women	Histological findings*						Type of DNA		
		Normal	Koilocytes	CIN grade			6/11†	16/18‡	Mixed 6/11 and 16/18	
				I	II	III				
1-3	22	9	3	5	4	1	7	4		
4-5	9	1	3	2	2	1	2	1		2
6-10	11	4	2	2	1	2		2		
>10	7		3	2	1	1		3		1

CIN=Cervical intraepithelial neoplasia.

*Spearman's rank correlation coefficients=0.1898.

† $\chi^2=2.06$; $p=0.15$.

‡ $\chi^2=2.29$; $p=0.13$.

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(Accepted 31 October 1988)

Late renal failure due to prostatic outflow obstruction: a preventable disease

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Abstract

Nineteen patients presenting with late renal failure due to prostatic outflow obstruction (mean age 68.7 years; mean serum creatinine concentration 1158 $\mu\text{mol/l}$) were identified from the admission records of two renal units. As late renal failure secondary to prostatic enlargement is preventable case records were analysed retrospectively in an attempt to identify aspects of management in which preventive efforts might be of value. Delays in referral were common, with a mean of 2.8 years between the onset of prostatic symptoms and time of referral, six patients being referred who had had symptoms for more than three years. Four of five patients who had had a prostatectomy were known to be in renal failure at the time of operation but were not referred until 2-13 years later, when prostatic symptoms had recurred and there was evidence of progressive nephropathy with dilatation of the upper urinary tract. Two patients died on admission and eight (47% of survivors) required long term dialysis, most patients (80%) requiring some dialysis support during the initial period.

These findings suggest that progressive nephropathy caused by prostatic outflow obstruction might, in part, be averted by more adequate screening of renal function in men with untreated prostatism and closer follow up of patients with uraemia at the time of prostatectomy.

Introduction

Though prostatic symptoms are known to occur in up to 40% of men over 65,¹ the prevalence of renal failure due to prostatic disease is essentially unknown. Dilatation of the upper urinary tract has been reported in about 5% of men being investigated in hospital for prostatism,^{2,3} and though the pressure-flow relations within the bladder associated with upper tract dilatation have been greatly clarified,⁴⁻¹⁰ there has been surprisingly little emphasis on the progressive effects on the kidney leading to irreversible renal failure.

Late or end stage renal failure secondary to prostatic outflow obstruction should be amenable to prevention if cases are recognised early and the obstruction relieved. New cases of late or irreversible disease arise each year, however, and figures from the European Dialysis and Transplant Association registry showing that 3-5% of end stage renal disease in patients over the age of 65 is due to acquired obstruction¹¹ indicate that prostatic enlargement may be an important cause of end stage renal disease. The explanation for these late

and undiagnosed cases is not clear. It has been suggested that severe obstruction may occur without prostatic symptoms,¹ but whether lack of symptoms adequately explains these apparent failures in detection or whether there are other aspects of management that might be improved is not clear.

The purpose of this report is to identify aspects of management in which preventive efforts might be of value. By means of retrospective analysis we studied patients with late renal failure referred to two renal units over several years.

Patients and methods

The study was carried out on patients who were admitted to the renal units at the Churchill Hospital, Oxford, and St James's University Hospital, Leeds. These two units serve populations of about 2.4 million and 2.0 million respectively. Patients with a diagnosis of prostatic hypertrophy and obstructive uropathy or nephropathy were identified from three sources: (a) the databases of the renal units; (b) Hospital Activity Analysis based on diagnosis on admission; and (c) personal recall of cases. These sources were known to be incomplete as not all patients were coded at the time of study and some codings were known to be incorrect. Also patients in Oxford who were managed without dialysis were not entered into the database for chronic renal failure and the aetiological diagnosis was not always made at the time of admission. Patients with congenital obstruction or acquired obstruction not due to prostatic disease were excluded from the study. Cases of obstruction due to infiltration of the lower ureters by prostatic carcinoma were also excluded. The diagnosis of obstruction was confirmed by ultrasonography of the kidneys and urinary tract and in some cases by intravenous urography. Cystoscopy was carried out to confirm the diagnosis and obtain tissue for histological study.

Thirteen patients in Oxford and six in Leeds were identified for further study. Most were admitted between January 1984 and March 1987 (see table). Eleven patients had been referred from regional hospitals outside Oxford, and five patients in Leeds had been referred from other hospitals in the area.

The case notes of patients were examined and information on the following extracted: age at admission; duration of prostatic or uraemic symptoms, or both; interval between seeing a doctor and referral to hospital; treatable conditions on admission (urinary tract infection, hypovolaemia, nephrotoxic drugs, medical conditions contributing to renal failure); whether a diagnosis of prostatic obstruction was made

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Br Med J 1989;298:156-9