A STUDY OF CHRONIC URINARY INFECTION

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Introduction

Improved diagnostic methods and effective drugs have determined much recent interest in pyelonephritis which is recognised as a common, frequently progressive disease. Acute infections of the urinary tract, which may subside spontaneously, usually respond to treatment and do not relapse but must be distinguished from the urethral syndrome by careful midstream urine examination (Gallaher, Montgomerie, and North, 1965). Chronic urinary infection is difficult to eradicate and recurrence is a problem. (Murdoch et al, 1966).

The difficulty of making a diagnosis of pyelonephritis is acknowledged by Black (1966). There is confusion about the difference between chronic glomerulonephritis and chronic pyelonephritis when either presents in an advanced stage (Lancet, 1966). Phenacetin nephropathy has been increasingly recognised and nephrocalcinosis may mimic the disease. Local damage caused by infection secondary to developmental or acquired defects is often referred to as pyelonephritis and many think that the concept of cystitis should be replaced by this more generic term. However, for the purpose of this study the expression chronic urinary infection has been preferred.

Selection of patients and methods

The selection of patients was based on history, examination and the results of investigation, each patient selected being seen at monthly intervals.

A history of more than one attack of dysuria or frequency with or without associated abdominal pain was required. Symptoms of bladder irritability were usually volunteered if the illness was short but strangury and dysuria were not often elicited when the history extended over many months or years (cf. Leather, 1963). Constitutional upset was often vague, but low-grade fever, anorexia and lassitude were present when infection had been persistent and severe. In an untreated adult tenderness over the bladder or kidneys was often found.

Investigations included three first morning midstream specimens of urine obtained with the standard precautions, peripheral blood count, blood urea, intravenous pyelogram, micturating cystogram and cystoscopy.

The criteria for diagnosing urinary infection have been reviewed by Brumfit and Percival (1964), the aim being to assess white cell excretion and bacterial density quantitatively. A white cell excretion rate of 400,000 per hour has been suggested as the upper limit of normal (Hutt, Chalmers, MacDonald and de Wardener, 1961), a count of 10 W.B.C. or over per cubic millimetre always being associated with an excretion in excess of 400,000. The estimate of white cells per high-powered field is inaccurate because it offers a slender margin of differentiation between normal and abnormal. During the past decade the importance of bacterial counts has been repeatedly stressed, 100,000 or more bacteria per millilitre of urine indicating infection. Many techniques of bacterial counting have been described but in this series the dilution method was used.

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The interpretation of white cell excretion and bacteriuria has to be made according to the age of the patient, history, recent drug treatment and the urinary output. The significance of results may be obscured by precipitant treatment and it is usually possible to prescribe sodium citrate while awaiting the results of culture and sensitivity; one dose of an effective drug is sufficient to inhibit the bacterial count. In doubtful cases the correlation of pyuria and bacterial infection is high (Fairley and Barraclough, 1967), but equivocation is best avoided by repeating the urine examination after a short interval without treatment. With infants the results of urine bag collection depend on the care taken in obtaining the specimen and its early examination. This counsel of perfection may be attainable in military hospitals, but if urine bag collection cannot be carefully repeated, bladder puncture may be useful.

The prednisolone provocation test was tried on many patients but did not prove useful. The results confirmed the information already obtained more easily from routine microscopy and the bacterial count did not change significantly during or after the test.

Each patient had an intravenous pyelogram, notwithstanding a normal urine examination, as it is known that pyelonephritic scarring may be found in the later stages of the disease when urine culture is sterile (Black, 1966). Hodson and Wilson (1965) have stressed the importance and value of this examination.

Micturating cystograms, though a difficult procedure in children, are useful in demonstrating bladder neck obstruction, urethral valves, diverticuli and in offering an explanation for hydronephrosis when ureteric reflux is found. The cause and effect relationship between urinary infection and ureteric reflux has been discussed by Smellie, Hodson, Edwards and Normand (1964) and congenital defects with reflux noted by Roberts and Roylance (1966) and by Johnston (1966).

Cystoscopy confirms and supplements the cystogram, providing direct positive or negative evidence of urethral or bladder abnormality and determining the probable nidus of infection by means of differential bacterial counts (Stamey, Govan and Palmer, 1965). The bladder may look normal in the presence of significant bacteriuria, but when all investigations are unrevealing and catheter specimens of urine are sterile it can be reasonably concluded that the patient does not have urinary infection.

The population at risk in the area served by the British Military Hospital, Hannover in March 1966 was given to the nearest hundred as follows:—Males 7,000, females 3,000, children, 5,100. Total 15,100.

Patients referred to the hospital included most presenting with recurrent urinary infection and nearly all those with an associated abnormality of the intravenous pyelogram (I.V.P.). The patients seen can be almost equally divided into those without any apparent pyelographic abnormality (Group I) and those with some definite change (Group II).

The age, sex, presentation, urinary white cell count, causative organism and cystoscopic appearance of Group I patients are shown in Table I. Micturating cystograms performed on cases 6, 18 and 27 were normal. Twenty-eight of the patients, most of whom were treated with nitrofurantoin for periods of three to twenty-six weeks, were well, with normal urine, six to eighteen months after therapy. Two patients were receiving long-term treatment and remained clear of infection. Case 2, a hydrocephalic infant treated with Spitz-Holter valve, had a neurogenic bladder with persistent infection. The presenting

attack of pyocyaneus septicaemia and urinary infection responded to colomycin, but the urinary infection persisted despite a rotation of nitrofurantoin, sulphadimidine, ampicillin and tetracycline, finally clearing on combined therapy with ampicillin and nitrofurantoin. Case 18, who had chronic prostatitis, and was suspected of self-instrumentation, continued to have infection with a rapid change of antibiotic sensitivities despite a full course of rotation therapy and combined drugs.

Thus of 32 patients 29 after treatment were well with normal urine on follow up. Two were well on long-term treatment and one had failed to respond to long-term therapy.

Similar data on the 29 patients in group II including IVP reports are shown in Table II. Ureteric reflux was demonstrated on micturating cystograms in cases 38, 54 and 56. Two patients were lost to follow-up and one (case 34) died aged six weeks with polycystic kidneys. Sixteen of the remaining 26 were well with normal urine on long-term treatment, most with nitrofurantoin. Two (Cases 60 and 61) who respect-

Table I
Patients with normal intravenous pyelogram

Case	Sex	Age in years unless shown	Presentation	Urine WBC/cu.mm	Culture	Cystoscopy
1	M	10 days	Vomiting	20	<i>E.coli</i>	
2	F	9 months	<i>Ps.pyocyaneus</i> Septicaemia	60	<i>Ps.pyocyaneus</i>	
3	F	2	Haematuria	20	<i>E.coli</i>	
4	M	2	Haematuria	> 100	<i>B.proteus</i>	
5	F	5	Incontinence	10	<i>E.coli</i>	
6	M	6	Enuresis	20	<i>E.coli</i>	
7	M	6	Splenomegaly	> 100	<i>E.coli</i>	
8	F	6	Enuresis	40	<i>E.coli</i>	
9	M	8	Dysuria	> 100	<i>E.coli</i>	
10	F	8	Enuresis	10	<i>E.coli</i>	
11	M	18	Fever and backache	12	<i>E.coli</i>	
12	M	18	Cystitis x 3	RBC only	<i>E.coli</i>	Inflammation right ureteric orifice
13	M	19	Strangury	20	<i>E.coli</i>	Normal
14	M	20	Cystitis x 2	RBC only	<i>B.proteus</i>	Basal cystitis
15	M	20	Cystitis (treated)	RBC only	Sterile	Haemorrhagic cystitis
16	M	20	Loin pain	> 100	<i>E.coli</i>	Haemorrhagic cystitis
17	M	21	Cystitis x 4	RBC only	<i>E.coli</i>	Normal
18	M	21	Cystitis x 3 for 2 years	50	<i>E.coli</i>	Ulcer below right ureteric orifice and basal cystitis
19	F	21	Antenatal urinalysis	> 100	<i>E.coli</i>	
20	M	22	Cystitis x 3	RBC only	<i>E.coli</i>	Inflammation left ureteric orifice
21	M	24	Cystitis x 10	30	<i>E.coli</i>	Basal cystitis
22	F	25	Cystitis x 4	50	<i>E.coli</i>	
23	F	25	Postnatal routine urinalysis	10	<i>E.coli</i>	
24	M	26	Strangury	30	<i>E.coli</i>	Basal cystitis
25	F	26	Right loin pain	20	<i>E.coli</i>	
26	F	29	Cystitis and fever	80	<i>E.coli</i>	
27	F	30	Cystitis x 5	20	<i>E.coli</i>	Normal
28	F	32	Right loin pain	10	<i>E.coli</i>	
29	M	35	Rigors and dysuria	50	<i>E.coli</i>	Normal
30	M	37	Left loin pain	> 100	<i>E.coli</i>	Normal
31	F	39	Abdominal pain and fever	> 100	<i>E.coli</i>	
32	F	50	Frequency	30	<i>B.proteus</i>	Normal

Table II
Patients with abnormal intravenous pyelogram

Case	Sex	Age in years unless shown	Presentation	Urine WBC/cu.mm	Culture	Intravenous pyelogram	Cystoscopy
33	M	3 weeks	Pyrexia, failure to thrive	> 100	<i>B.proteus</i>	?Minimal hydronephrosis	Normal
34	F	4 weeks	Haematuria	> 100	<i>B.proteus</i>	Failure to concentrate dye	
35	F	6 months	Pyrexia	10	<i>B.proteus</i>	Right duplex ureter	Ureterocele
36	F	6 months	Right abdominal mass	6	<i>E.coli</i>	Hydronephrosis with cyst right kidney	
37	M	3	Tender right loin	20	<i>E.coli</i>	Minimal dilatation left ureter	Normal after treatment
38	F	7	Pyrexia and enuresis	20	<i>E.coli</i>	Bilateral hydronephrosis with clubbing of calyces	
39	F	7	Pyrexia and tender right loin	30	<i>E.coli</i>	Duplex right pelves and hydro-ureter	Urethral valves
40	M	9	Diurnal enuresis, incontinence	Nil	Sterile	Gross bilateral hydronephrosis	
41	M	13	Complicated acute nephritis, phimosis	20	<i>E.coli</i>	Clubbing left mid-calyces	Tight phimosis
42	M	20	Pyrexia, frequency and tender right kidney	8	<i>E.coli</i>	Right renal cyst and duplex ureter	Normal
43	F	21	Tender left kidney	10	<i>E.coli</i>	Clubbing left upper calyx	Incompetent ureteric orifices
44	F	22	Pyrexia and tender left kidney	30	<i>E.coli</i>	Cortical scarring left kidney	
45	F	22	Tender left kidney (treated)	10	Sterile	Clubbing left lower calyx	Incompetent ureteric orifices
46	F	23	Pyrexia and tender right kidney	> 100	<i>E.coli</i>	Minimal right hydronephrosis	
47	F	23	Cystitis x 6	10	<i>E.coli</i>	Cortical scarring right kidney	Right ureteric calculus
48	F	24	Tender right kidney	20	<i>E.coli</i>	Right minimal hydronephrosis	
49	F	25	Bilateral loin pain	12 (treatment prior to MSU)	Sterile	Early clubbing right calyces	Normal
50	F	25	Cystitis x 8	> 100	<i>E.coli</i>	Cystic segment right kidney	
51	F	27	Cystitis, tender left kidney	10	<i>B.proteus</i>	Early clubbing left kidney	Right ureteric calculus
52	F	29	Cystitis for 9 years	20	<i>E.coli</i>	Right ureteric calculus and cortical scarring	
53	F	29	Right pyelonephritis 7 years	20	<i>E.coli</i>	Right hydronephrosis	Normal right ureteric orifices
54	F	30	Abdominal pain	5 only	<i>B.proteus</i>	Dilatation left upper calyx	Ureterocele
55	F	31	Right pyelonephritis 11 years	10	<i>E.coli</i>	Non-function right upper duplex kidney	
56	F	38	Pyelonephritis 8 years	30	<i>E.coli</i>	Bilateral cortical scars	Incompetent ureteric orifices
57	M	41	Rigors, tender right kidney	50	<i>E.coli</i>	Gross right hydronephrosis	Normal
58	M	41	Dysuria and loin pain	10	<i>E.coli</i>	Clubbing left mid-calyx	
59	F	45	Cystitis, tender right kidney	30	<i>E.coli</i>	Fullness right calyces	Normal
60	F	45	Cystitis 20 years	20	<i>E.coli</i>	Contracted right kidney	
61	M	51	Pyrexia and loin pain	50	<i>E.coli</i>	Slight cortical scars	

ively refused surgery and adequate treatment, were well despite persistent urinary infection and eight underwent surgery as shown in Table III.

Table III
Surgical treatment of eight patients

Case Number	Operation	Subsequent treatment
35	Correction of ureterocele	Long term sulphanamides
40	Correction of urethral valves	Ampicillin
41	Circumcision	Long term nitrofurantoin
42	Removal of duplex ureter	Six weeks nitrofurantoin
50	Partial right nephrectomy	Three years nitrofurantoin
52	Ureterolithotomy	Long term nitrofurantoin
53	Removal aberrant right renal artery	Long term nitrofurantoin alternating with ampicillin
55	Correction of ureterocele	Long term nitrofurantoin

Case 40, a boy aged 9 years, who presented with enuresis and fixed specific gravity polyuria was found to have bilateral hydronephrosis, hypertension and early uraemia. There was a history of urethral valve obstruction operated on late in infancy. Earlier correction of this might have prevented further hydronephrosis but some antenatal renal damage must be assumed to occur with these congenital defects. The other operation cases were well, with normal urine on follow-up.

While acknowledging that patients 34 and 40 were suffering from congenital abnormalities rather than pyelonephritis, it is probably true to say that given immediate long term treatment patient 56 would not have progressed to her stage of chronic atrophic pyelonephritis and had patient 61 accepted the benefits of treatment his outlook would be much improved.

Discussion

On the evidence of this series it appears that if patients are treated by effective long-term therapy, deterioration is at least checked. If a predisposing abnormality is corrected in time the outlook is good.

If the original infection is not contained either because it is not recognised, treatment is not effective or too brief, or patients fail to take their drugs as prescribed, a chronic cystitis develops and ureteric reflux occurs, a finding suggested by animal experiments and confirmed by micturating cystograms (Johnston, 1966). Operative correction of this reflux may be necessary if it is still present after the infection has been controlled (Scott, 1966). It is important to note that reflux has other causes, such as bladder neck obstruction, urethral valves, duplex or ectopic ureters and the neurogenic bladder (Rosenheim, 1963, Bettex, Genton and Scharli, 1966).

The consensus of present-day opinion regarding chemotherapy is that the longer follow-up is conducted after or even during therapy the greater is the incidence of relapse, the highest peak of which is found in the first six months (Stansfeld, 1966). The aim in this series was to prescribe according to bacterial sensitivities and to take urine cultures at monthly intervals for up to two years or longer. Sulphonamides are still used a great deal for treating supposedly simple cystitis, the type of infection that is dealt with in general practice and to which Garrod, Shooter and Curwen (1954) referred when discussing the natural history of the disease. In this respect long-acting

sulphonamides fulfil many of the attributes of the ideal drug despite their protein-binding capacity. However, for most patients referred to hospital, and this series was no exception, sulphonamides had already been tried and relapse had occurred so that the majority were started on nitrofurantoin if the symptoms and signs suggested a lower urinary tract infection, and ampicillin if classical pyelonephritis had been diagnosed.

Resistance to these drugs was found much less commonly than to the sulphonamides or tetracyclines and it was interesting that, unlike previously reported series resistance seldom developed (Little and de Wardener, 1966, Stansfeld, 1966).

When resistance occurred in the absence of anatomical defects or changing resistance persisted, combined therapy with ampicillin and nitrofurantoin was started. This approach has been well explored in the past with regard to tuberculosis and bacterial endocarditis; more recently it has been used to eradicate bacterial L forms in chronic urinary infection and it may be that some of these patients do not harbour bacterial variants (Gutman, Schabler and Wedgwood, 1967). Finally, the possibility of using resistance blockers such as mepacrine and spermine has been explored with encouraging results by Sharda, Cornfield and Michie (1966).

Summary

Sixty-one patients with chronic urinary infection admitted to British Military Hospital, Hannover between 1964 and 1966 are described. They fall into two groups, 32 without any apparent abnormality of the intravenous pyelogram and 29 with definite pyelographic changes. Of this latter group eight were operated upon.

An evaluation of long-term drug therapy is attempted and the need for antibiotic combinations discussed in relation to chronic disease with bacterial resistance.

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