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Urinary Tract Infection

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Preface

Increasing specialization in medicine is often blamed for the fragmentation of knowledge in many fields. In the diagnosis and treatment of infection, the differing approaches of microbiologist and clinician may have unfortunate consequences. Clinicians may not understand fully the techniques applied in the laboratory, and microbiologists may view their tests in a way which is not always relevant to the condition of the patient.

In this book urinary infection is considered in a way that may help to bridge the gulf between those who work in laboratories and the clinicians—both specialists and general practitioners—who see and treat patients. Investigation and management protocols are suggested in the light of the present state of knowledge in the field, and some possible directions of future progress are indicated.

There are few branches of medicine in which the necessity to diagnose and treat urinary infection does not arise, and urine is by far the commonest specimen received for examination in microbiology laboratories. I hope that this book will provide a simple and practical guide to the subject for undergraduates, for postgraduate laboratory workers and for clinicians of all kinds.

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Contents

1 Introduction

Urinary tract infection occurs commonly, worldwide and throughout the year, in people of all ages and both sexes, in hospital and at home, and it warrants the considerable attention which it has received over the past few decades. The two major factors responsible for the upsurge of interest in the subject in recent years were the advent of effective antibacterial therapy which, for the first time, allowed the physician to intervene in the natural history of the condition, and the development of maintenance therapy, dialysis and transplantation, for patients with renal failure. Once specific antibacterial treatment was available accurate diagnosis became necessary, and the complexity and expense of treating renal failure prompted efforts to define the causes and to prevent those which were preventable.

At the present time, then, what is the importance of urinary tract infection? First and foremost it is responsible for much troublesome morbidity; it accounts for the use of very large quantities of antibacterial agents, involving great expense and incurring the risk of unwanted side-effects, both to the individual patient in terms of interference with normal flora, and to the community as a result of selection of resistant organisms; lastly, in a small minority of patients it is the primary cause of renal damage, and, at present, is one of the few preventable causes of renal failure. Contrary to earlier beliefs that infection was very commonly the cause of renal failure—a belief which arose from the mistaken attribution of many types of interstitial nephropathy to infection—it is now recognized that infection is the primary disease in only about 20 per cent of patients accepted for dialysis programmes (Wing *et al.*, 1978).

The epidemiological studies carried out over the past three decades have shown that serious renal disease is rare amongst the very large number of patients who suffer from urinary infection, and have pinpointed the group of patients—young children—who are particularly at risk. However, these studies, which have proved that case-finding surveys are not cost effective, and that the majority of patients do not incur the risk of serious disease, have not been altogether helpful to individual patients. Attention has sometimes been diverted from the very troublesome symptoms from which many patients

suffer, so much so that lay organisations have been formed to offer advice which many patients have been unable to obtain from their doctors. Furthermore, whilst the conclusions drawn from the epidemiological studies have been quite correct, they have diverted attention away from the possibility of serious disease in the individual patient. Children continue to develop pyelonephritic scarring; 'infection stones' continue to account for about 10 per cent of all renal calculi, often causing severe renal damage; and adults with pyelonephritic scarring continue to develop hypertension. The index of suspicion for these conditions should remain high. An attempt will be made in this book to suggest ways in which medical effort could be directed towards identifying patients at risk from serious disease, whilst, at the same time, endeavouring to understand the pathology of the disease in those patients troubled with unpleasant, although benign, symptoms, and to suggest rational management protocols.

It is, perhaps, worthwhile examining some of the reasons for the confusion which still persists in the field of urinary infection. Disagreement and misunderstanding about terminology comprise probably one of the most important. Different meanings are attributed to the term 'urinary tract'; whilst anatomically it extends from kidney to urethral orifice, it has become customary to diagnose 'urinary tract infection' only if infection is present in the bladder or above, often excluding from consideration many possible urethral causes of urinary symptoms. There are historical reasons for fundamental differences in the use of the term 'chronic pyelonephritis'. For many years it was used to describe histological changes in the kidney which were attributed to infection, and as a clinical diagnosis for the condition believed to result in these changes. With the realization that a heterogeneous group of other disorders, including analgesic abuse, can result in a similar histological pattern the use of the term 'chronic pyelonephritis' has been questioned. Similarly, the use of the word 'cystitis' to denote infection in the bladder was questioned when careful studies revealed that bacteria could only be demonstrated in the urine of about half the patients in whom the clinical diagnosis had been made.

There have been attempts in recent years to standardize the terminology in this field, but they have not been widely accepted for two reasons. First, some of the terms which have been suggested imply an aetiology about which there is no general agreement; for example, the term 'reflux nephropathy' suggests that reflux is the primary cause of the renal damage, whereas the respective roles of reflux and infection in the pathogenesis of renal scarring are still debated. Secondly, some of the terms may rest on false premises; for example, the use of the term 'abacterial cystitis' as a diagnosis for patients with dysuria and frequency from whose urine no bacteria have been isolated may be inaccurate either because the infection is not in the bladder but elsewhere (for example, the paraurethral glands) or because the culture methods used have failed to detect the presence of bacteria. In trying to present an account of urinary infection at a time when the condition is still incompletely understood it seems advisable, therefore, to eschew the use of as many diagnostic labels as possible, preferring to describe the pathological processes involved and the symptoms to which they give rise. However, since the interstitial nephropathies due to causes other than infection are now described by their indivi-

dual names (for example, analgesic nephropathy), it seems reasonable to continue to use the term 'pyelonephritis' for renal damage resulting from infection, and the terms 'acute' and 'chronic pyelonephritis' for the associated clinical syndromes. In writing this book it has proved impossible to avoid the use of the term 'urethral syndrome'; it is widely used to describe a condition which, although ill-understood, continues to be the subject of regular comment and conjecture in the medical journals. It is possible, however, that some of the recent studies described here may eventually lead to a more accurate description of the conditions which have hitherto been included under this 'diagnostic umbrella'.

The term 'significant bacteriuria' will not be used. It has assumed pride of place in the field of urinary infection over the past 30 years, to the extent that the nature of the work from which it was derived has often been forgotten. The studies of Kass introduced a much-needed order into the diagnosis of urinary infection, but this advantage was, to some extent, counterbalanced by the disadvantage of the introduction of a rigid numerical criterion for diagnosis, resulting in a more limited view of urinary tract infection than that which had hitherto prevailed. Attention was concentrated on the presence of aerobic bacteria in bladder urine; organisms such as staphylococci, which had been recognized as urinary pathogens in the days when specimens were collected by catheter, came to be regarded as contaminants when the mid-stream method of collection was introduced, and the important role of staphylococci as pathogens in the urinary tract has only gradually been rediscovered over the past 15 years. Furthermore, the finding that about one-half of the patients with urinary symptoms did not have 'significant bacteriuria' led to the view that their symptoms were probably due to causes other than infection. Despite many reports in the intervening years, it is only now being recognized that patients with bladder bacteriuria may have counts of less than 10^8/l (10^5/ml) in the urine; other patients may have urethral or paraurethral infection due to organisms not detected by the conventional aerobic culture methods which have been used almost universally during the past 25 years. A further disadvantage of the use of the term 'significant bacteriuria' is that it is frequently misunderstood, both by clinicians and by laboratory staff. It is a relatively common misconception that bacteria in the urine are significant only if a certain number are present, and that lesser numbers are of no importance; the purpose of distinguishing between bladder infection and extraneous contamination has often been forgotten.

Another important cause of confusion is that the type of specimen collected from patients with urinary symptoms and the laboratory investigations undertaken may often depend upon the specialty of the clinician to whom the patient presents. The role of the laboratory in diagnosis is paramount; if rational diagnostic procedures are to be undertaken it is essential that the clinician—whether general practitioner, urologist, nephrologist, paediatrician, gynaecologist or venereologist—should consider carefully the type of specimen likely to be appropriate for diagnosis. He should also be aware of the procedures undertaken in the laboratory so that he may request additional ones when necessary, and the microbiologist should report his findings in such a way that they are helpful to the clinician. The microbiologist, as the linchpin of the

diagnostic process, is in a position to suggest appropriate diagnostic procedures, to assist the clinician in the detection of patients at risk, and to influence the use of antibacterial agents. Some types of clinicians, in particular urologists and gynaecologists, include operative procedures such as reimplantation of refluxing ureters, urethral dilatation and excision of infected paraurethral tissues, as well as diagnostic procedures such as cystometry, in their armamentarium for the management of patients with urinary infection or urinary symptoms; others adopt a purely 'medical' approach, based upon antibacterial treatment. Communication between practitioners of the two approaches is often poor, and the patient suffers. There is no doubt that those published studies in which there has been a multidisciplinary approach have been the most helpful in elucidating the pathogenesis of the disease and the development of rational treatment regimens. Extension of such studies, especially to include gynaecologists and venereologists who, hitherto, have seldom been involved, can only be to the advantage of patients. This is not to say that all patients with urinary symptoms require the advice of a multitude of clinicians. Multidisciplinary studies have already begun to elucidate many aspects—for example, the respective roles of surgical and conservative treatment in the management of reflux in children; combined studies of the pathogenesis and management of urethral infection might well lead to guidelines which could be followed by general practitioners or other individual clinicians.

A review of any type of infection must include some reflection upon the effect of the introduction of antibacterial drugs and changes and developments in laboratory diagnostic procedures. In the field of urinary tract infection the advantages of the introduction of effective antibacterial agents are obvious; it has become possible to prevent renal scarring in children, to preserve renal function in patients with renal damage consequent upon infection, to decrease dramatically the incidence of pyelonephritis of pregnancy, to diminish morbidity due to infection in patients undergoing surgery of the urinary tract or neighbouring structures, and to give rapid relief to patients with symptoms due to aerobic bacterial infection. There have been, however, some disadvantages. Resistant organisms have emerged, both as a result of repeated courses of antibacterial agents given to patients with recurrent infections, and also in hospital patients, in particular those with indwelling catheters. An attempt will be made in this book to suggest ways in which such disadvantages can be minimized. Another major problem which has arisen from the widespread use of antibacterial agents for treatment of women with urinary symptoms is that the causative organism has often been unknown, and therefore the efficacy of the agent used in doubt; in many cases the symptoms which have arisen as a result of the effect of treatment on the commensal bowel, urethral, vulval and vaginal flora have been even more unpleasant than those for which the patient originally sought medical advice. There is evidence, which will be discussed, that organisms such as lactobacilli which normally play a commensal role as part of a mixed indigenous flora may, by virtue of intrinsic resistance to widely used agents such as sulphonamides and trimethoprim, to which other commensals are sensitive, assume an increased importance and possibly a pathogenic role.

It has already been suggested, in the context of the use of the term 'significant bacteriuria' that changes in laboratory diagnostic procedures have not been entirely helpful. In recent years the possibility of anaerobic infection in the urinary tract, such as might occur in the relatively anaerobic conditions prevailing in scar tissue in the kidneys, has seldom been considered. Reports of isolation of anaerobes from the urine of such patients are found almost exclusively in the older literature; in recent years negative aerobic cultures have usually been accepted, even in the presence of pyuria, as indicating that infection is no longer present. A less restricted approach to urine culture has recently provided evidence of infection with anaerobes and other fastidious organisms in such patients.

Perhaps the limitations of aerobic culture of mid-stream urines have been greatest in the diagnosis of conditions such as so-called 'acute abacterial cystitis', both of men and women, and of the 'urethral syndrome'. These conditions were accurately observed and described by Moore, a urologist, 40 years ago. He reviewed the literature on non-tuberculous abacterial pyuria; he described patients both male and female with severe bladder inflammation from whose urine no organism was grown, but who responded dramatically to intravenous treatment with novarseno-benzol (Moore, 1940, 1945), and he attributed the disease to a virus. His clinical descriptions of the patients with 'abacterial cystitis' are so similar to those of the young men recently described by Abercrombie, Allen and Maskell (1978) and Finkelhor *et al.* (1981) that it now seems likely that *Gardnerella vaginalis* may have been the causative organism. Schaffhauser (1937) reported similar cases from whose urine he isolated what Moore described as 'a curious streptococcus'; this too could have been *G. vaginalis*, or possibly a fastidious streptococcus such as *S. milleri*, which has recently been shown to be associated with urinary infection. In addition, Moore carried out extensive clinical studies of young women with dysuria and frequency, and he concluded that 'in the majority of women . . . these symptoms are due not to recurrent cystitis, but to lesions of the urethra and para-urethral glands—a female prostatitis' (Moore, Hira and Stirland, 1965). No organisms were isolated from the urine of the majority of patients in whom he diagnosed infection distal to the bladder, but from his comments elsewhere it is clear that he suspected that the answer might lie in a more extensive bacteriological search. 'The clinician is entirely dependent upon his bacteriological colleagues for the results of urine cultures. No doubt organisms grow better if they are well entertained and given very good fare' (Moore, 1968). Recent clinical and bacteriological work on such patients, which will be described in this book, suggests the possibility that, had appropriate bacteriological techniques been available to him, Moore's hypothesis might have been confirmed. It also seems possible that much of the work on these patients in the intervening years may have obscured the issue. The history of medicine is full of such cautionary tales; the moral, that better communication between clinicians and laboratory is essential, is clear.

2

The pathogenesis of urinary tract infection

As far as we know at present, the normal urinary tract is sterile above the level of the distal urethra. With a few rare exceptions, including *Salmonella* spp and *Mycobacterium tuberculosis*, the organisms which gain access to the urinary tract and cause infection are commensals from neighbouring sites, and the manifestation of the disease which they cause may differ according to the site of infection in the urinary tract. It has been customary in recent years to define urinary infection as the presence of organisms in bladder urine, and when considering pathogenesis it is convenient to maintain this distinction between infection in the bladder or above, and infection of the urethra, prostate or paraurethral tissue.

Bladder bacteriuria and upper urinary tract infection

In the great majority of cases, infection occurs by the ascending route. The principal exceptions are salmonellosis, tuberculosis, histoplasmosis, infections in the newborn, and possibly some virus infections, in all of which the spread of infection is haematogenous. An earlier view (Thomson-Walker, 1926) that bowel organisms gain access to the blood stream through damaged mucosa in patients with intestinal complaints such as diverticulitis, constipation or the effects of excessive purgation, and cause urinary infection by haematogenous spread, is no longer held to be true. Animal experiments have shown that if *Escherichia coli* is introduced into the blood stream it is rapidly eliminated from the urine unless the urinary tract is obstructed by a procedure such as ligation of the ureters. This suggests that the 'washout mechanism' which operates in the normal urinary tract is effective in removing organisms introduced via the blood stream.

Haematogenous infection (Table 2.1)

Urinary infection with *Salmonella* spp, *Mycobacterium tuberculosis* (or, more rarely, *M. bovis*), *Schistosoma haematobium* or *Histoplasma duboisii* occurs as a secondary phenomenon to infection elsewhere in the body, and the organisms

Table 2.1 Organisms which infect the urinary tract via the haematogenous route

Bacteria	*Salmonella* spp. *Mycobacterium* spp
Parasites	*Schistosoma haematobium*
Fungi	*Histoplasma duboisii*
Viruses	Cytomegalovirus Adenovirus type 11 ?Other viruses

enter the urinary tract via the blood stream. Urinary excretion of salmonellae is usually symptomless, but can occasionally give rise to clinical signs of urinary infection (Barkin, Pfister and Ashbach, 1978). The presence of these organisms in renal tissue, however, may rarely precipitate a severe acute glomerulonephritis.

In tuberculous infection the organisms usually begin to multiply in the renal cortex; infection may then progress towards the pelvis, resulting in further foci of infection in the ureters and bladder. Rarely, the disease may remain confined to the renal parenchyma, giving rise to a diffuse interstitial inflammation with tuberculous granulomata (Mallinson *et al.*, 1981).

Schistosomiasis and histoplasmosis are outside the scope of this book and will not be considered further.

Rarely, urinary infection may develop as a secondary phenomenon in patients with candidaemia or with septicaemia with organisms such as the Enterobacteriaceae and *Staphylococcus aureus*.

It is also probable that urinary infection resulting from haematogenous spread of Gram-negative bowel organisms may occur in the newborn. Urinary infection in the neonatal period is commoner in boys than in girls, a situation which is reversed after the first year of life. At one time it was assumed that this difference was accounted for by a higher incidence of structural abnormalities of the urinary tract in boys. However, Bergström *et al.* (1972), in a study of 80 consecutive newborn infants with clinical and bacteriological evidence of urinary infection, found obstruction of urinary flow in only 5 patients; there were recurrences of infection in only one-quarter of the patients, almost all during the first 3 months of life, and there were no recurrences after the age of 18 months. Repeated radiological examination disclosed evidence of renal damage in only 3 patients. These facts, together with the observation that clinical evidence of infection often preceded the development of bacteriuria by some days, suggest that the mode of infection may be haematogenous at least in some patients, the organism possibly entering the blood stream of the baby during the process of delivery. It is likely that this would occur as frequently in girls as in boys, and it may be that the greater incidence of clinical manifestations of infection in boys is due to the comparative immunological incompetence of the newborn male.

Viruses enter the urinary tract from the blood stream during many viral illnesses, including measles, mumps, vaccinia and Coxsackie infection, and examination of the urine for the presence of viruses such as rubella and cytomegalovirus is used as a diagnostic tool. Their presence seldom gives rise to clinical symptoms or signs of urinary infection. There have been, however, reports of acute haemorrhagic cystitis associated with the presence of adenovirus type 11 in the urine (Numazaki *et al.*, 1973), and of lower urinary tract symptoms associated with cytomegalovirus in the urine in three male members of a renal unit staff (Davies *et al.*, 1979).

Ascending infection

Organisms from the bowel, the urethra, the perineal skin, and probably the vagina, the prostate, and the paraurethral tissues in women may gain access to the urinary tract via the ascending route. Many of these sites have a varied commensal flora and it is a balance of bacterial and host factors—some well understood and others less so—which determines whether organisms gain access to, and multiply in, bladder urine.

Host factors

Mechanical The washout mechanism—resulting from the mechanical effect of the passage of large volumes of urine and dilution of any organisms which may temporarily have gained access—is probably the most effective factor in maintaining the sterility of bladder urine. Anything which renders this mechanism less effective predisposes to urinary infection. Table 2.2 summarizes the principal mechanical factors which predispose to bladder

Table 2.2 Mechanical factors which predispose to bladder bacteriuria

Factors which facilitate ascent of organisms up the urethra
Catheterization, especially indwelling
Urethral, bladder or prostatic surgery
Sexual intercourse
Vaginal prolapse
Factors which result in stagnation of urine in the bladder
Overnight period without micturition (normal)
Infrequent micturition during the day
Inadequate fluid intake or urinary output
Obstruction:
Urethral valves
Urethral stricture
Prostatic hypertrophy
Constipation
Vesicoureteric reflux
Impairment of neurological control of the bladder
Bladder diverticula

bacteriuria. Mechanical factors which facilitate the ascent of organisms up the urethra are catheterization, operative procedures and urethral trauma resulting from sexual intercourse or vaginal prolapse. The overnight period during which the bladder fills slowly and the washout mechanism is suspended is of no clinical importance except as the basis for the timing of low-dose antibacterial prophylaxis (Chapter 6); however, a habit of infrequent micturition during the day is now recognized as common in patients, especially children, who are prone to urinary infection. The role of congenital urethral valves, post-infective or post-operative urethral strictures and prostatic hypertrophy as causes of outflow obstruction, and therefore of inefficient bladder emptying, is well known. It is also a common observation amongst clinicians who see children with urinary infection that many of them are constipated. At one time it was thought that faulty bowel and bladder function had a common neuropathic cause in these children and this, of course, may be true of some patients. Neurological investigation, however, is often negative, and x-ray investigation may demonstrate trabeculation of the bladder wall, suggesting that the loaded colon may have caused mechanical obstruction to urine outflow.

In recent years the role of vesicoureteric reflux—the backflow of urine from bladder to ureter—in the pathogenesis of urinary infection has become increasingly clear. There is no non-invasive means of diagnosing this condition, and therefore its incidence is not known; such data as there are, however (Jones and Headstream, 1958), indicate that the vesicoureteric 'valve' mechanism is normally competent. Factors such as a short intramural segment of the ureter, as seen in some young children and also in the ureter which drains the lower moiety of a duplex kidney, or acute inflammation around the ureteric orifice (Williams and Sturdy, 1966) may be associated with reflux. Reflux predisposes to urinary infection because, to a greater or lesser degree, it renders the washout mechanism less effective. If, during micturition, a large or small volume of urine passes up the ureter and then falls back into the bladder as the detrusor muscle relaxes, the result will be a pool of residual urine in the bladder after each act of micturition. This will have the effect of allowing organisms to persist and multiply. The natural history of reflux and its relevance to the management of urinary infection will be considered in later chapters.

Stagnation of urine in the bladder also occurs when neurological control of bladder emptying is impaired, and when pools of urine persist in diverticula.

Spread of infection to the upper urinary tract, the pelvis, calyces and renal tissue via the ascending route is also undoubtedly determined to some extent by mechanical factors, of which the best understood at present are vesicoureteric reflux and outflow obstruction. In both these situations infected urine may enter the ureters from the bladder, either actively during micturition or passively as occurs in the presence of severe degrees of reflux or of outflow obstruction. It is possible that organisms may also ascend from bladder to kidney in the absence of reflux, either as a result of backward peristalsis in the ureters, or of hormonally determined changes in tone of the ureteric musculature such as those which occur in pregnancy.

Properties of the bacteria themselves which might enable them to ascend to

the kidneys against the direction of urine flow will be considered later. The factors which determine whether organisms reaching the renal pelvis by the ascending route give rise to pathological changes demonstrable by radiological or histological means, are poorly understood. Some patients who have clinical evidence of acute bacterial infection of the kidney—fever, rigors, loin tenderness and bacteriuria—do not subsequently show any renal damage detectable by the imprecise methods available at present. One mechanism, however, which has recently been elucidated is intrarenal reflux, or pyelotubular backflow (Fig. 2.1). Ransley and Risdon (1974) reported

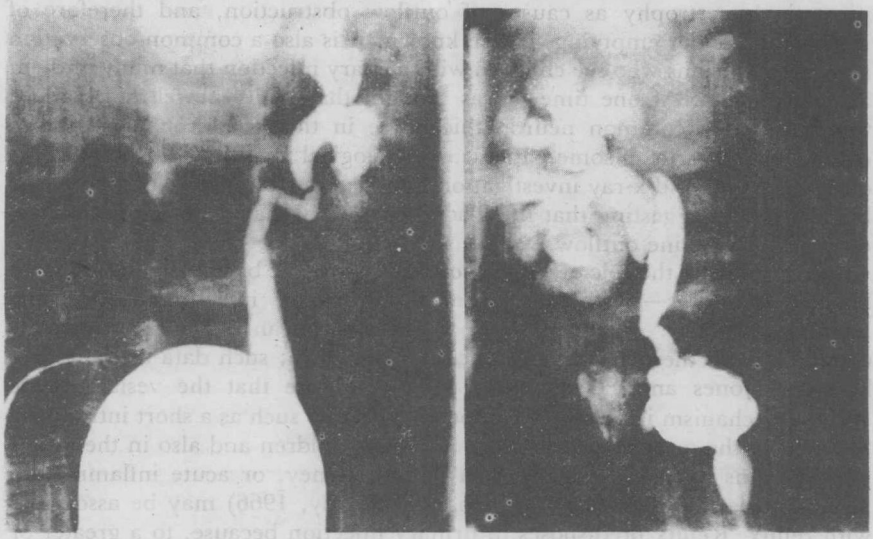

Fig. 2.1 Intrarenal reflux. Cystograms from (a) a boy of 1 year with recurrent urinary tract infection and (b) a boy of 2 weeks with spina bifida

experimental work in pigs which suggested that renal scars occurred only in those areas of kidney which were drained by compound papillae which were shaped in such a way as to allow backflow of urine into the renal parenchyma. They have subsequently reported (Ransley and Risdon, 1978) that such scarring occurs only when the urine is infected. It is known that there are some compound papillae in human kidneys, especially at the upper and lower poles (Ransley and Risdon, 1975; Tamminen and Kaprio, 1977), and these are the areas where pyelonephritic scarring most commonly occurs. It seems likely, therefore, that such scarring is the consequence of bacteriuria, vesicoureteric reflux and intrarenal reflux. Rolleston, Maling and Hodson (1974) retrospectively surveyed micturating cystograms from 386 patients with vesicoureteric reflux but without bladder outflow obstruction; they found 20 kidneys which showed segmental opacification which they attributed to intrarenal reflux of contrast medium. Twelve were in infants, and there was none in patients over the age of 4 years, which suggests that this phenomenon may be one of immaturity. Of the kidneys which showed radiological scarring,