Summary

Interstitial nephritis is an inflammatory process within the renal interstitium, and was one of the first observations made in the description of renal histopathology. Many different conditions are associated with an interstitial nephritis, and as a clinical diagnosis the term has little use unless causation is defined. However, there has been recent interest in the possibility of a common mechanism causing irreversible renal damage and eventually renal failure in many different types of interstitial nephritis. Such damage could take place due to blood-borne inflammatory mediators, or could be due to renal tubular inflammation related to abnormal components of the glomerular filtrate in renal failure, such as proteins or lipids. If such research were to result in effective therapy for interstitial nephritis, the progression of many forms of renal disease to end stage renal failure could be ameliorated.

Keywords: renal failure, immunological renal disease, nonsteroidal anti-inflammatory drugs, interstitial nephritis

Interstitial nephritis

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Interstitial nephritis is a pathological phenomenon, not a clinical syndrome. The diagnosis can only be made by microscopic examination of renal tissue, as first described by Councilman in the late 19th century, when he examined the kidneys of young children dying of diphtheria and scarlet fever. Despite some pioneering work in the 1940s and 1950s, a fuller understanding of interstitial nephritis awaited the widespread use of percutaneous renal biopsy in living subjects in the early 1960s. Interstitial nephritis and renal failure associated with phenacetin usage was identified, and the subsequent withdrawal of phenacetin from sale in most of the world was an important contribution to public health.

'Whether any useful purpose is served by perpetuating the term acute interstitial nephritis is debatable', wrote Robert Heptinstall in 1966 in the first edition of his authoritative textbook of renal pathology. It was recognised that a wide range of processes could produce inflammation in the renal interstitium, and that identifying this phenomenon did not necessarily convey any information about causation. However, we would suggest that the term 'interstitial nephritis' is of value in the modern era. Not as a diagnostic category, because we hope to be more specific about causation, but because of its importance as a pathological process. Interstitial nephritis is the final common pathway for many causes of renal failure. It occurs in processes as different as glomerulonephritis and renal allograft rejection. A greater understanding of the mechanisms of interstitial renal inflammation and damage may lead to more effective therapeutic intervention in the future for many types of renal disease.

Components of the renal interstitium

The components of the renal interstitium are primarily capillary blood vessels, dendritic leucocytes (also called passenger leucocytes or interdigitating cells), and connective tissue. Studies in renal transplantation provide some insights into interstitial nephritis, as acute cellular rejection is a process with some similarities to acute interstitial nephritis. Reference will be made to some relevant transplantation experiments below.

BLOOD VESSELS

There is a rich network of capillary blood vessels throughout the renal interstitium. Inflammatory cells enter the extravascular space by passing across the endothelium. This is partly a consequence of the expression of adhesion and homing molecules on the endothelial surface. VCAM-1 (vascular cell adhesion molecule-1) and ICAM-1 (intercellular adhesion molecule-1) are two such molecules, and their expression is upregulated in experimental and clinical interstitial nephritis. Monoclonal antibodies against ICAM-1 reduce interstitial cellular infiltrates in experimental interstitial nephritis, and may also reduce the reperfusion injury in clinical renal transplantation, which can be regarded as a clinical model of interstitial injury caused partly by leucocytes.

DENDRITIC CELLS

The normal kidney contains large numbers of these leucocytes. They are macrophage-like cells with long branches reaching in between other structures in the renal interstitium. Their purpose is to process and present antigens. Their potency to stimulate an immune response is greater than that of any other class of cell within the immune system. This stimulation may occur within the kidney, but transplantation experiments have also shown that dendritic cells can migrate to the spleen shortly after experimental transplantation, and that their removal from a graft reduces the severity of rejection after transplantation. The importance of dendritic cells in interstitial nephritis has not yet been demonstrated, but they are likely to play an important role, as interstitial nephritis is at least an inflammatory disease, and may often be an immune hypersensitivity response.
CONNECTIVE TISSUE

Even in renal diseases which are thought of as primarily glomerular (for example, nephritis in systemic lupus erythematosus), the extent of fibrosis in the interstitium on renal biopsy is the best predictor of long-term renal function.\textsuperscript{11-14} Currently much attention is being paid to the activity of fibroblasts and other connective cells within the kidney.\textsuperscript{15} This is because the kidney appears to have a capacity to develop progressive scarring and fail, even though the original disease process may have resolved. The best clinical example of this is reflux nephropathy, when some patients develop renal failure although vesico-ureteric reflux has stopped and there is no evidence of ongoing infection.

TUBULAR CELLS

Renal tubular epithelial cells are not strictly part of the interstitial compartment, but are relevant to this review for two reasons. First, the tubular basement membrane forms a border of the interstitium. In experimental models and occasionally in clinical cases, antitubular basement membrane antibodies may cause an acute interstitial nephritis.\textsuperscript{16} Secondly, an acute interstitial inflammatory infiltrate may cause renal failure with lymphocytic infiltration of the tubules (‘tubulitis’); this feature is a requirement for the histological diagnosis of cellular rejection in renal allografts.

Where is interstitial nephritis initiated?

Interstitial inflammation may be initiated by factors circulating in the blood which may either damage the vascular endothelium, or pass into the extravascular space and damage renal tubular cells. Indeed, these processes may follow each other. Renal allograft rejection is an example of this, as is damage caused by antitubular basement membrane antibodies.

However, in other circumstances, a factor in the urine (or glomerular filtrate) may be responsible for damage to renal tubular cells, perhaps with interstitial inflammation being further mediated by blood-borne factors such as inflammatory leucocytes. Bacterial pyelonephritis is one obvious example of this. More interestingly, attention has been paid in recent years to the possible toxic effects of substances filtered through abnormal glomeruli. Such work attempts to explain the link between primary glomerular diseases and interstitial nephritis, and also offer new avenues for therapeutic intervention.\textsuperscript{11-14}

Most attention has been paid to proteinuria in this respect. The selective proteinuria found in minimal change glomerulonephritis would not appear to cause tubular cell damage, even when this condition is present for many years. However, renal failure with interstitial nephritis is found in other types of glomerulonephritis with nonselective proteinuria.\textsuperscript{17} Experimental evidence does indicate that there is a link between the magnitude of proteinuria and the tubular catabolism of filtered peptides. Ammoniagenesis and complement activation may follow, with tubular cell damage.\textsuperscript{18,19} Since angiotensin-converting enzyme inhibitors have been shown to reduce proteinuria in some cases of glomerulonephritis, there may be role for these drugs in the reduction of tubular damage in glomerulonephritis.

Lipiduria is less well studied, but again plasma lipid fractions may be filtered in glomerulonephritis, and have been shown \textit{in vitro} to be damaging to cultured human renal tubular cells.\textsuperscript{20}

Histological appearance

Interstitial nephritis is characterised by a cellular infiltrate in its acute form. This is predominately lymphocytic, and lymphocytes may be seen amongst tubular cells, having crossed the tubular basement membrane.\textsuperscript{21} Eosinophils may be present, especially in drug-related interstitial nephritis. Granulomata may be present, especially in interstitial nephritis associated with tuberculosis or sarcoidosis. However, the presence or absence of either eosinophils or granulomata is not of great diagnostic importance. In the chronic form, interstitial fibrosis and tubular atrophy are prominent, and there is often irreversible renal failure. A cellular infiltrate generally accompanies areas of tubular atrophy but it is not always clear whether this inflammation has caused tubular damage, or follows tubular damage caused by another process such as ischaemia.

Acute interstitial nephritis

This is characterised by acute renal failure, and renal biopsy showing an acute inflammatory infiltrate in the renal interstitium.
FREQUENCY
In unselected series, acute interstitial nephritis is not a common diagnosis in the UK. For example, this was the pathological diagnosis in only three out of a series of 266 patients undergoing renal biopsy for all indications in one year in Birmingham. However, in cases of acute renal failure where the clinical diagnosis was not immediately clear, the incidence rose to 8–14%. In the UK, this may represent an overall incidence of approximately 1–4 cases per million population per year.

DIAGNOSIS
The only diagnostic investigation is renal biopsy, which should be performed whenever possible in acute renal failure of uncertain cause. There may be oliguric or nonoliguric renal failure, and mild to moderate proteinuria. Eosinophilia within the blood or in the urine or the drug history may be suggestive of a diagnosis of acute interstitial nephritis.

CAUSES
Some of the more common observed causes are shown in box 1. The commonest identifiable cause is a drug reaction, but the range of causative agents is very wide. If any particular drug is suspected as a cause of interstitial nephritis, reference should be made to the local drug information service or the pharmaceutical company database. It should be noted that interstitial nephritis may present after a particular drug has been taken for many months or even years.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)
In recent years this class of drugs has been increasingly recognised as a potent cause of acute interstitial nephritis. However, they may also cause acute renal failure due to a separate effect of reduction in renal blood flow, generally in combination with volume depletion, sepsis or surgery. Although the incidence of acute interstitial nephritis following the prescription of NSAIDs is very low, a significant proportion of patients presenting to European renal units with acute renal failure have interstitial nephritis caused by this class of drugs.

TREATMENT AND OUTCOME
Acute interstitial nephritis, particularly if caused by a drug that has subsequently been withdrawn, may resolve spontaneously with excellent recovery of renal function and a good long-term prognosis. Therefore, supportive treatment with control of hypertension, appropriate diet and dialysis should be given (box 2).

Steroid treatment may be used, but there is no general agreement that it is beneficial. Some patients appear to respond rapidly, but in others recovery is slow. The policy on steroid administration varies between individual renal centres.

Chronic interstitial nephritis
This is characterised by chronic renal failure, and a renal biopsy showing fibrosis and tubular atrophy in the renal interstitium.

FREQUENCY
A presumptive diagnosis of chronic interstitial nephritis is made in up to 10% of patients starting dialysis for end stage renal failure in the UK, although many possible cases are designated as renal failure of unknown cause because renal biopsy has not been performed. This represents an incidence of at least 10 cases per million population per year – much commoner than acute interstitial nephritis. In India and the Middle East, approximately 30% of patients starting chronic dialysis are considered to have chronic interstitial nephritis, a higher percentage than in the UK. Balkan nephropathy, an endemic disease of uncertain aetiology, may cause a remarkably high incidence of renal failure in some districts of the former Yugoslavia.

DIAGNOSIS
Like acute interstitial nephritis, this diagnosis can only be made by renal biopsy. Since chronic interstitial nephritis may cause renal scarring and contraction of the kidneys, the condition may be under-diagnosed as renal biopsy is not generally performed in cases with small kidneys. This is because the risk of post-biopsy bleeding is increased, and also because the chances of successful therapeutic outcome with small scarred kidneys is low.
CAUSES
All the causes of acute interstitial nephritis listed (box 1) may also cause a chronic interstitial nephritis. Furthermore, fibrosis in the renal interstitium is the common final pathway in nearly all types of end-stage renal failure. Even in conditions classified by their glomerular pathology (for example, nephritis in systemic lupus erythematosus, or membranous glomerulonephritis) the prognosis depends more upon interstitial changes than on glomerular changes.11-14 We briefly discuss below some of the current areas of interest in chronic interstitial nephritis.

NSAIDS
Although NSAIDs appear to cause an acute interstitial nephritis, it has been difficult to demonstrate whether they commonly cause chronic disease with fibrosis and end-stage renal failure. Large-scale studies have not shown large numbers of patients taking such agents developing chronic interstitial nephritis. Indeed, the reduction in analgesic-associated renal failure following the withdrawal of phenacetin has been sustained.4

CHRONIC INTERSTITIAL NEPHRITIS IN INDO-ASIANS
End stage renal failure in Indo-Asians living in the UK is much more frequent than in those of European ethnic origin, by a factor of up to 10.30 It has been noted that many patients of Indo-Asian origin present with uraemia and small smooth kidneys when examined by ultrasound. In some of these cases, renal biopsy has shown a chronic interstitial nephritis, although the majority of cases are not biopsied for the reasons given above.7,30 It has been suggested that the apparently high incidence of this condition could represent low-grade chronic tuberculous nephritis. Further studies are awaited, but attention is currently being paid to this potentially treatable cause of renal failure. Treatment with a combination of prednisolone and isoniazid has been used by some nephrologists, with dramatic improvement in renal function in some cases. Although most patients are culture negative for tuberculosis, studies looking for tuberculosis by more sensitive molecular methods are awaited before such patients can confidently be treated with steroids alone.

ISCHAEMIA
Ischaemia may be a cause of interstitial fibrosis. Although this may be histologically similar to an interstitial nephritis of immune causation, it would be preferable to classify 'ischaemic nephropathy' as a clinicopathological entity separate from the classic forms of interstitial nephritis where tubular damage appears to be caused by an immune reaction with cellular cytotoxicity.

There are two clinical settings in which ischaemic interstitial nephritis are of particular interest. The first is cyclosporin nephrotoxicity, which is a common cause of mild renal dysfunction in many patients receiving this drug, but may cause end-stage renal failure when the drug cannot be stopped.31 This occurs principally after heart or heart-lung transplantation. The nephrotoxicity caused by the newer immunosuppressive agent tacrolimus (FK 506) may unfortunately be quite similar.32

Ischaemic nephropathy may also contribute to many cases of end-stage renal failure in the setting of generalised atheromatous vascular disease, particularly if there is renal artery stenosis. This ischaemia may be caused by low-grade cholesterol embolisation to small intra-renal blood vessels, as well as the haemodynamic effects of arterial narrowing. Large numbers of patients are receiving dialysis treatment because of this phenomenon, and any effective treatment or prevention would probably have a significant impact on the pattern of dialysis provision, especially in the context of an ageing general population.33

TREATMENT AND OUTCOME
Fibrous tissue within the kidney and atrophy of renal tubules are irreversible changes. The treatment of chronic interstitial nephritis therefore depends primarily upon removing any identifiable cause and general therapy, particularly meticulous control of the blood pressure. Unfortunately, the cycle of tubular loss and interstitial fibrosis within the kidney may be progressive despite these measures, and some patients will develop end-stage renal failure. If the renal biopsy does show a degree of active inflammation within the kidney, as well as chronic changes, a trial of steroids may be given.

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<th>Summary/learning points</th>
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<tr>
<td>- interstitial nephritis is a cause of potentially reversible renal failure</td>
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<td>- there may be acute inflammation or chronic fibrosis</td>
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<td>- renal biopsy is required to establish the diagnosis</td>
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<td>- drugs are a common cause of acute interstitial nephritis</td>
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<td>- steroid treatment may be effective in acute interstitial nephritis</td>
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Box 3


Medical Anniversary

WILLIAM PRICE, 4 MARCH 1800

William Price (1800–1893) was born in Ty'nycocdcae, South Wales, the third son of Reverend William Price. He was to become one of the most romantic and rebellious characters in Welsh medical history. He qualified at St Bartholomew's in 1821, and entered practice in Nantgarw, moving later to nearby Pontypridd. He wore the dress of ancient druids, with fox-skin head-dress, white tunic, scarlet waistcoat and green trousers. He ridiculed orthodox religion and sanctimonious preachers and advocated cremation; indeed, he cremated his beloved five-month-old son that he had named Jesus Christ. He died in Llantrisant on 23 January 1893, just short of his ninety-third birthday. — DO James
Interstitial nephritis.

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