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# Interstitial nephritis

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SUMMARY The clinical and pathological findings are reviewed in ten cases where renal biopsy showed abnormalities predominantly within the interstitium. In six the nephritis was considered to be drug-induced; in two the aetiology was slightly obscure but the most likely diagnosis was considered to be sarcoidosis. Of the remaining two cases one was chronic pyelonephritis and the other polyarteritis nodosa. The diagnosis and pathogenesis of the renal lesions are discussed and attention is drawn to the importance of distinguishing primary interstitial changes from those found in association with glomerular disease.

The value of renal biopsy in diagnosis of glomerular disease is well-established and may be used to predict response to treatment and prognosis. Similarly renal biopsy may provide clear and conclusive histological evidence of acute tubular necrosis, vascular abnormalities or end-stage renal disease. Yet in our group of patients biopsies have failed to reveal appearances which are characteristic of any of these conditions. The glomeruli appeared essentially normal and although tubular damage was present the most pronounced changes were found in interstitial tissues. Such cases have been labelled interstitial nephritis[1] and represent an ill-defined, heterogeneous group, both in clinical manifestation and pathogenesis. We report nine such patients and one in whom profound interstitial changes accompanied a segmental glomerulonephritis.

## Material and methods

The indication for renal biopsy was acute oliguric renal failure in five patients, raised blood urea concentrations with a normal urine volume in three patients and haematuria in one patient. In the remaining case a renal biopsy was performed during a renal sympathectomy for recurrent loin pain and fever.

The renal tissue was divided into three portions. The largest piece was processed for paraffin embedding and serial sections (4 $\mu$m) were stained by haematoxylin and eosin, periodic acid-Schiff, Goldner's trichrome, Martius scarlet blue and Congo red for amyloid. One piece was snap-frozen in liquid nitrogen and sections were stained by the direct immunofluorescent method for IgA, IgG, IgM, IgE, C3 and fibrinogen. The third portion was fixed in 4% glutaraldehyde and processed to epon embedding for electron microscopy.

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## Results

### HISTOLOGICAL FINDINGS

Major clinical and pathological features of all cases are summarised in Tables 1 and 2. All patients had either normal-sized or slightly enlarged kidneys on *x*-ray examination except case 9 where they were small and scarred with calyceal dilatation. In the first six patients it is highly probable that the renal condition was drug-induced but, since all were receiving more than one drug, incrimination of a single compound was usually difficult. Ooi *et al.*[2] have drawn attention to this problem of ascribing nephropathy to any one compound because of the extreme complexity of the drug history in many patients. In cases 7 and 8 the most likely diagnosis was sarcoidosis, although neither demonstrated all the typical features of this condition, and in case 9 a diagnosis of chronic pyelonephritis was made, principally on *x*-ray findings. It is noteworthy that this patient had also received ampicillin.

Case 10, although differing from the others in having segmental glomerulonephritis, is included here to illustrate the complexity of the diagnostic problem. This patient underwent two renal biopsies. The first contained seven glomeruli, six of which were normal but one of which had a segmental necrosis containing a few neutrophil polymorphonuclear leucocytes. In other respects the pathological findings bore a remarkable resemblance to some other cases (see Tables 1 and 2), notably a marked interstitial infiltrate with numerous eosinophils. Furthermore both IgE and IgG containing plasma

Table 1 *Clinical features of patients with interstitial nephritis*

| *Case No* | *Age (yr)* | *Sex* | *Antecedent illness* | *Drugs* | *Course* | *Diagnosis* |
|---|---|---|---|---|---|---|
| 1 | 72 | F | General malaise, dermatitis, acute oliguric renal failure | Bethanidine<br>Lorazepam<br>Cyclopenthiazide<br>Cotrimoxazole<br>Ibuprofen<br>Amitriptyline<br>Carbocisteine<br>"Junipah"-containing phenolphthalein | Alive but in chronic renal failure | Interstitial nephritis due to drugs. |
| 2 | 70 | F | Arthralgia, urticarial rash, eosinophilia, anuria | Diflunisal<br>Chlorpheniramine<br>Prochlorperazine<br>Trifluoperazine | Recovery (steroids) | Interstitial nephritis due to diflunisal. |
| 3 | 23 | F | Epilepsy, rash, acute oliguric renal failure | Phenytoin<br>Carbamazepine<br>Phenobarbitone<br>Diazepam<br>Paraldehyde<br>Chlorazepam | Recovered from renal failure but later committed suicide | Interstitial nephritis due to drugs. |
| 4 | 56 | F | Epilepsy, leg vein thrombosis, lobar pneumonia, arthritis, haematuria, eosinophilia | Phenobarbitone<br>Aspirin<br>Numerous antibiotics<br>Allopurinol<br>Alcohol<br>Cyclopenthiazide | Recovery (steroids) | Interstitial nephritis probably due to drugs. |
| 5 | 66 | F | Rash, fever, acute non-oliguric renal failure | Mefanamic acid<br>Chlorpheniramine | Recovery (steroids) | Interstitial nephritis due to mefenamic acid. |
| 6 | 22 | M | Tuberculous adenitis, chronic renal failure | PAS<br>Isoniazid<br>Rifampicin | Chronic renal failure. (Renal transplant performed) | Interstitial nephritis possibly due to drugs. |
| 7 | 16 | M | Fever, splenomegaly, lymphadenopathy, ascites, thrombocytopenia, raised blood urea concentration | Aspirin | Recovery (steroids) but persistent impairment of renal function | Possibly sarcoidosis in spite of negative Kveim. Granulomata in spleen. |
| 8 | 61 | F | Sixth nerve palsy, hypercalcaemia, splenomegaly, acute oliguric renal failure | Paracetamol<br>Phenylpropanolamine<br>Indomethacin<br>Ampicillin<br>Flucloxacillin | Recovery (steroids) | Possibly sarcoidosis in spite of negative Kveim. |
| 9 | 36 | F | Pulmonary tuberculosis, chronic peptic ulcer, recurrent fever, and loin pain | Ampicillin | Not known | Chronic pyelonephritis. |
| 10 | 59 | M | Arthritis, sinusitis, eosinophilia, acute oliguric renal failure | Phenylbutazone<br>Co-trimoxazole | Initial recovery with steroids but died later in renal failure | Polyarteritis nodosa. |

cells were observed on immunofluorescence. There was no evidence of immunoglobulins or complement in glomeruli and no electron dense deposits were found on electron microscopy. A second renal biopsy specimen from this patient, obtained eleven weeks later, showed a diffuse crescentic nephritis with an interstitial infiltrate now composed predominantly of mononuclear cells. A diagnosis of microscopic polyarteritis nodosa was made which was later confirmed at necropsy.

The pathological findings in the remaining nine cases are summarised below.

*Glomerular changes* when present were minor. In the majority of cases there was no abnormality on light or electron microscopy (Fig. 1). In four patients there was some evidence of nuclear crowding in mesangial stalks but no deposits were seen on electron microscopy and there was no fusion of foot processes of glomerular epithelial cells. There were two instances

Table 2 *Pathological features in patients with interstitial nephritis*

| *Case No* | *Glomeruli* | *Tubules* | | *Interstitium* | | | | | *Vessels* | *Immunofluorescence* |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *Epithelial damage* | *Contents* | *Inflammation* | *Cell type* | *Oedema* | *Fibrosis* | *Granulomata* | | |
| 1 | Normal | +++ | Polymorphs Red cells Protein | Diffuse +++ | Polymorphs Lymphocytes Plasma cells Eosinophils | ++ | ++ | Present | Normal | Minor granular deposition of IgG and C3 on some tubular basement membranes |
| 2 | Normal | +++ | Protein Red Cells | Diffuse in cortex. Focal in medulla +++ | Lymphocytes Plasma cells Eosinophils | +++ | + | Present | Intimal fibrosis in arcuate and inter-lobular arteries | Granular IgG and IgM, and linear C3 on tubular basement membranes |
| 3 | Slight increase in mesangial cells | ++ | Polymorphs Epithelial cells | Diffuse + | Lymphocytes Plasma cells Polymorphs Eosinophils | ++ | 0 | None | Normal | Negative |
| 4 | Slight increase in mesangial cells | + | Polymorphs Red cells Protein | Focal + | Lymphocytes Plasma cells Polymorphs | 0 | + | None | Normal | None available |
| 5 | 20 normal 2 hyalinised | ++ | Epithelial cell debris | Focal ++ | Lymphocytes Eosinophils Plasma cells | ++ | 0 | None | Intimal fibrosis in inter-lobular arteries | Negative |
| 6 | Periglomerular fibrosis and intraglomerular fibrosis | ++ | Protein Epithelial cell debris | Focal ++ | Lymphocytes | 0 | +++ | None | Intimal fibrosis in inter-lobular vessels | None available |
| 7 | Normal | +++ | Epithelial cell debris | Diffuse +++ | Lymphocytes Plasma cells Polymorphs | +++ | + | Present | Normal | A little IgA and C3 in mesangium of glomeruli |
| 8 | Normal | +++ | Protein casts Epithelial debris | Focal ++ | Lymphocytes Plasma cells Eosinophils Polymorphs | + | +++ | Present | Minor degree of intimal fibrosis of interlobular arteries | None available |
| 9 | Several hyalinised. Intra- and periglomerular fibrosis | + | Protein casts Polymorphs | Focal ++ | Lymphocytes | 0 | ++ | None | Intimal fibrosis and medial hypertrophy of arcuate and inter-lobular arteries | None available |
| 10 | 6 normal. One with segmental fibrinoid necrosis | ++ | Protein Occasional polymorphs | Diffuse +++ | Lymphocytes Eosinophils Plasma cells | ++ | 0 | None | Normal | IgG and IgE containing plasma cells |

of periglomerular and intraglomerular fibrosis but these were probably a reflection of the interstitial disease rather than of primary glomerular damage. These two cases were those in which clinical details indicated chronicity of the renal condition.

*Tubules* Damage to tubules was variable. Both proximal and distal portions were affected, although if epithelial damage was at all severe, it was very difficult if not impossible to distinguish between the two. There were focal areas where inflammatory cells penetrated the tubular basement membrane accompanied by necrosis of lining cells (Fig. 2). Such areas were not numerous. Many tubules were dilated and often contained neutrophil polymorphonuclear leucocytes, red blood cells, and epithelial cellular debris as well as protein casts within their lumen (Fig. 3). Evidence of regeneration with mitoses in tubular epithelial cells was seen only in case 5.

*Interstitial tissues* exhibited the most important features in biopsy specimens (Fig. 4). Most had some

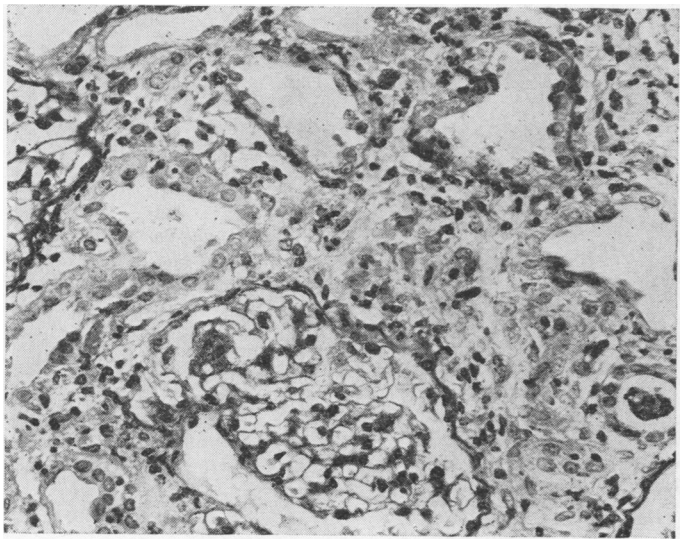

Fig. 1 *Case 4: normal glomeruli and oedematous interstitium with cellular infiltrate. Haematoxylin and eosin* × *175.*

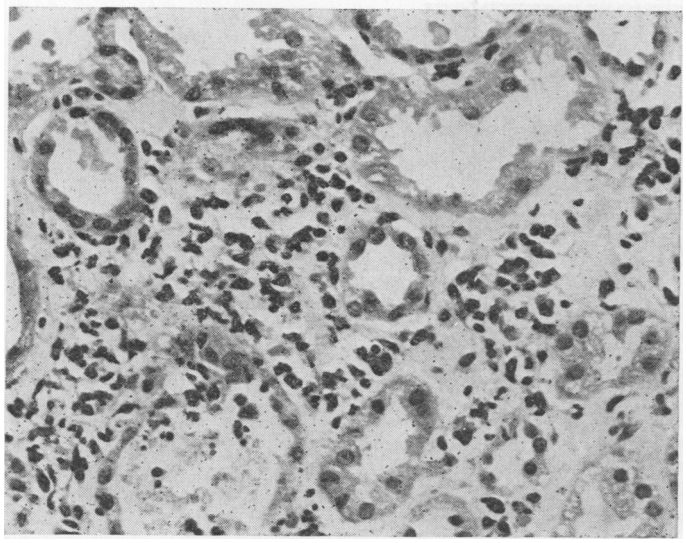

Fig. 2 *Case 10: tubular epithelial cell necrosis and penetration of tubular basement membrane by mononuclear inflammatory cells. Haematoxylin and eosin* × *175.*

degree of oedema or fibrosis with separation of tubules one from another. The cellular infiltrate was of variable density and composed primarily of mononuclear cells. These were mainly lymphocytes but in several cases plasma cells were prominent and in some there were foci of neutrophil polymorphonuclear leucocytes. Eosinophils were conspicuous in five cases, four of which were considered to be drug-induced. It was frequently not possible to assess distribution of the infiltrate on the material available but in those biopsy specimens where the corticomedually junction was present, there did appear to be a concentration of inflammatory cells in that region. Cellular infiltrates in the medulla were often less pronounced than in the cortex. A notable feature in four patients was the presence of small granulomata composed of histiocytes, lymphocytes, and plasma cells, but lacking Langhans giant cells (Fig. 5). There was no necrosis or caseation. In two of these patients the nephritis was thought to be drug-induced, in two the aetiology was slightly obscure but overall, clinical and pathological findings indicated a diagnosis of sarcoidosis. The granulomata observed were not, however, typical of this condition.

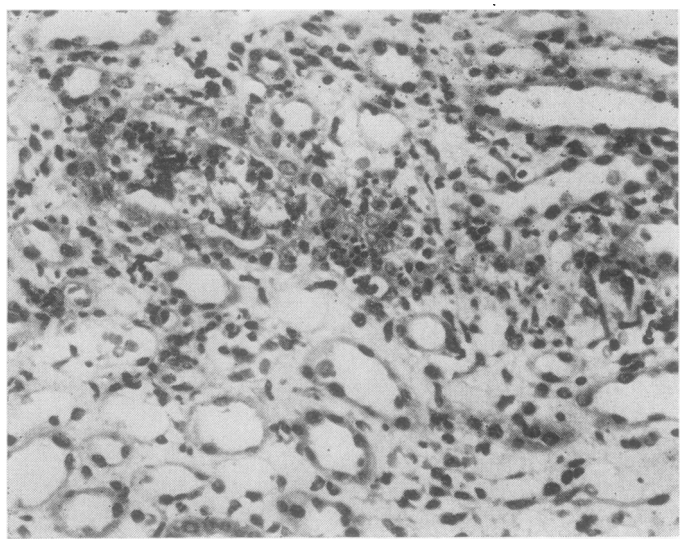

Fig. 3 *Case 3: polymorphonuclear leucocyte and epithelial cellular debris with tubular lumen. Haematoxylin and eosin × 175.*

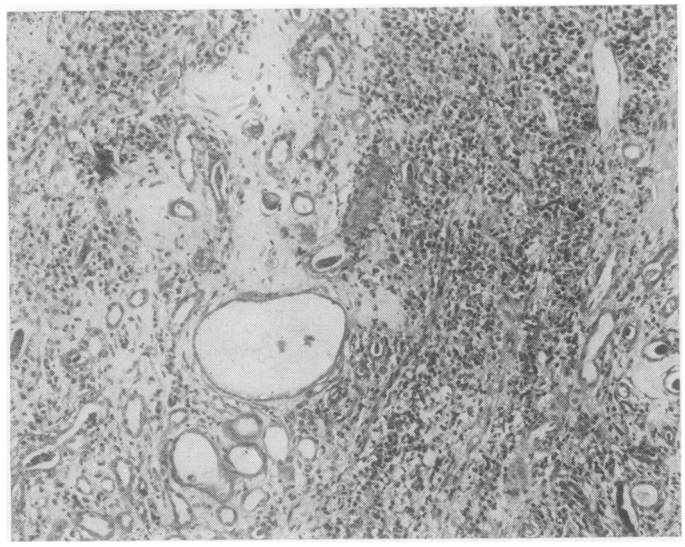

Fig. 4 *Case 1: severe interstitial inflammation accompanied by fibrosis and tubular epithelial cell atrophy. Haematoxylin and eosin × 100.*

*Electron microscopy*

Ultrastructural studies did not reveal any electron dense deposits in glomeruli or tubular basement membranes. They did show focal areas of damage to tubular epithelium with penetration by inflammatory cells (Fig. 6). Plasma cells were particularly prominent in the interstitial infiltrate. Ooi *et al.* drew attention to the presence of giant mitochondria and moderately dilated rough endoplasmic reticulum in tubular epithelial cytoplasm in interstitial nephritis.[2] These features were not noticeable in our cases.

*Immunohistology*

Immunofluorescent preparations showed two cases with immunoglobulins and complement on tubular basement membranes. In one this consisted of a minor focal deposition of IgG and C3; the other had a striking linear deposition of C3 in addition to granular deposits of IgG and IgM. In both cases, the evidence pointed strongly to drug-induced disease.

Staining for immunoglobulins and complement in glomeruli was negative in all patients except for one

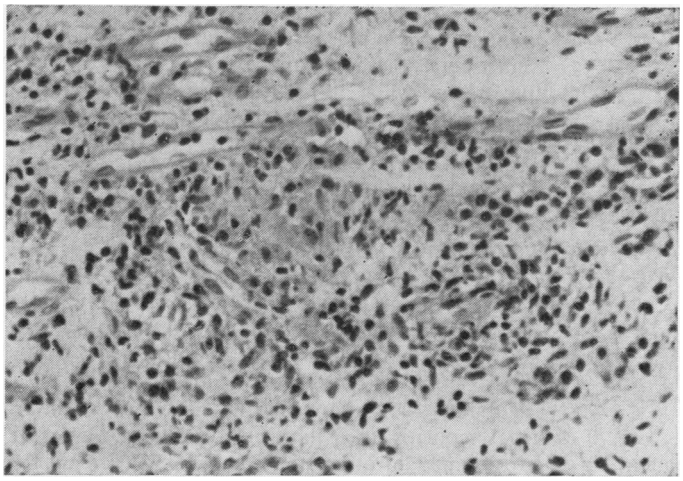

Fig. 5 *Case 2: medullary granulomata. Haematoxylin and eosin* × *300.*

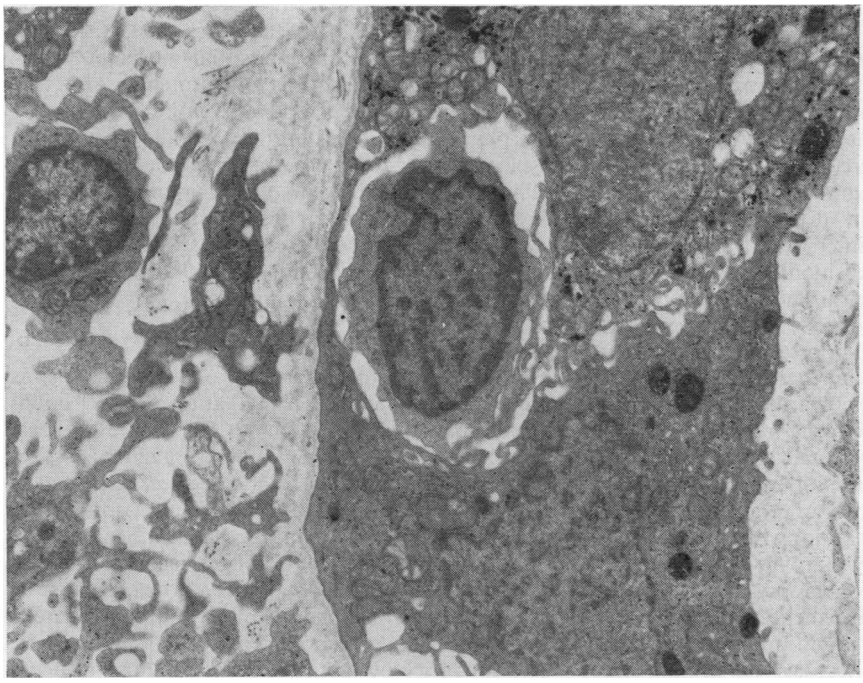

Fig. 6 *Case 2: lymphocyte between tubular epithelial cells. Electron micrograph* × *8000.*

case of sarcoidosis (case 7) where a little IgA and C3 was demonstrable in the mesangium.

## Discussion

### DIAGNOSIS

Two major problems relate to the diagnosis of interstitial nephritis on renal biopsy. The first concerns its distinction from interstitial changes occurring in association with glomerular disease; the second relates to the many possible aetiologies of the condition and the feasibility of distinguishing between them on biopsy material. Of particular importance is the diagnosis of interstitial nephritis due to drugs, often presenting with acute renal failure, since recovery is usual if the drugs are withdrawn. Many different compounds have been incriminated, some of which are listed in Table 3.[3–20]

The distinction from glomerulonephritis often presents no difficulty yet it must be noted that minor

Table 3 *Some drugs associated with interstitial nephritis*[3–20]

| *Drug* | *Reference* |
|---|---|
| Sulphonamides | Robson *et al.* (1970)[3] |
| Penicillin | Baldwin *et al.* (1968),[4] Méry (1970)[5] |
| Methicillin | Border *et al.* (1974),[6] Mayaud *et al.* (1975)[7] |
| Ampicillin | Ruley *et al.* (1974)[8] |
| Cotrimoxazole | Dry *et al.* (1975)[9] |
| Cephalosporins | Burton *et al.* (1974),[10] Wiles *et al.* (1979)[11] |
| Rifampicin | Nessi *et al.* (1976)[12] |
| Ethambutol | Collier *et al.* (1976)[13] |
| Phenindione | Sraer *et al.* (1972)[14] |
| Diphenylhydantoin | Muehrcke and Pirani (1972)[15] |
| Furosemide | Lyons *et al.* (1973)[16] |
| Phenylbutazone | Russell *et al.* (1978)[17] |
| Allopurinol | Gelbart *et al.* (1977)[18] |
| Diflunisal | Chan *et al.* (1980)[19] |
| Phenobarbitol | Faarup and Christenson (1974)[20] |

glomerular abnormalities are not infrequent in interstitial nephritis and in several of the patients reported here there were areas of mesangial nuclear crowding. In one patient this was associated with a little IgA and C3 in the mesangium. This was thought to be a case of sarcoidosis and it is possible there was some glomerular involvement[21] in addition to pronounced interstitial disease. A further problem is illustrated by case 10 where, apart from a segmental necrosis in one of seven glomeruli, the findings were very similar to those in drug-induced nephritis primarily affecting the interstitium. In particular there were numerous eosinophils together with IgE-containing plasma cells. The subsequent rapid progression of this man's disease to diffuse crescentic nephritis emphasises the importance of looking for glomerular involvement in these cases and considering the diagnosis of polyarteritis nodosa. This of course might also be drug-induced.[22] Such a diagnosis could easily be missed on a biopsy specimen containing inadequate numbers of glomeruli.

Interstitial nephritis without glomerular disease may be found in association with a number of conditions.[1] Its aetiology may be difficult if not impossible to determine on biopsy alone. Reliance on clinical and radiological evidence is often required, particularly in diagnosing conditions such as pyelonephritis, renal papillary necrosis or urinary tract obstruction, all of which may result in substantial inflammatory cell infiltration of the renal interstitium. This is illustrated by case 9.

Features in favour of a drug-induced interstitial nephritis include the presence of numerous eosinophils in the infiltrate, IgE-containing plasma cells and deposition of immunoglobulins and complement on tubular basement membranes. Unfortunately none of these features is specific for drug-induced disease and none is invariably present even in those instances where there is a clear indication of drug hypersensitivity. In the majority of instances a focal lymphocytic and plasma cell infiltrate predominates. Neutrophil polymorphonuclear leucocytes are not unusual and when numerous, raise the possibility of an acute infection and clearly this must be excluded. Unfortunately many of the drugs producing interstitial nephritis are antibiotics and will have been prescribed originally in order to treat an infection. Withdrawal of such drugs may thus present a therapeutic dilemma.

A further diagnostic problem is posed by the presence of granulomata. These are sometimes observed in cases of drug-induced renal disease, but may also be associated with sarcoidosis, and tuberculosis should of course be excluded.

Tubular changes are seen in most cases of interstitial nephritis, their nature depending more on the severity and duration of the condition than on the aetiology. Tubular atrophy with interstitial fibrosis typify chronic disease; more characteristic of the acute stages are focal areas of epithelial necrosis, often associated with interstitial oedema. Intraluminal inflammatory cells and proteinaceous casts are frequently present and it is notable that polymorphs within tubules are not found exclusively in pyelonephritis. Red cells are sometimes seen in the tubular lumen and haematuria may be a presenting feature. Their origin is a matter for speculation. It is unlikely to be glomerular and in all probability the red cells leak from peritubular capillaries in areas of acute inflammation.

## PATHOGENESIS

The underlying mechanisms producing the lesions are not understood. It seems that a variety of initial insults may give rise to similar histological appearances. Possible aetiological factors include: ischaemia; an immunological reaction; direct toxic action on renal tubular epithelium; infection; obstruction to urine outflow. That chronic ischaemic injury may result in cellular infiltration of the renal interstitium seems clear. The role of shock as a principal cause of acute interstitial nephritis is more doubtful. There is seldom a definite record of a hypotensive episode. The similarity of tubular lesions to those in acute tubular necrosis does not imply an identical cause. Furthermore the interstitial cellular reaction is absent or scanty, certainly in early stages of acute tubular necrosis, whereas it is a prime and early feature of interstitial nephritis. However, it must be borne in mind that the two conditions may coexist, particularly if antibiotics have been administered in a severe case of bacteraemic shock.

Tubular damage can be associated with deposition of immunoglobulins and complement components on the tubular basement membrane. This has been

reported in systemic lupus erythematosus[23] and in rapidly progressive glomerulonephritis where it is associated with circulating antiglomerular and antitubular basement membrane antibodies.[24] Antitubular basement membrane antibodies may also be responsible for tubulointerstitial damage occurring in some renal allografts. They have been reported to occur in association with tubular damage due to methicillin[6] but have not been found in many other instances of drug-induced disease. There was some evidence of a similar mechanism in two of our cases. Although these had a focal rather than a linear deposition of immunoglobulin, one had a striking linear deposition of C3. Electron dense deposits were not observed in the tubular basement membranes

It is possible that cellular immunity may play a part in causation. The evidence for this is largely conjectural and based on the observation that in many instances the cells causing disruption of the tubules are lymphocytes.[2] The presence of eosinophils and of IgE-containing plasma cells in the interstitial tissue[20] indicates that a type I allergic reaction may sometimes be important. In drug-induced interstitial nephritis, evidence for a hypersensitivity reaction rather than a direct toxic reaction to the offending drugs has been cogently summarised by Méry and Morel-Maroger (1976).[25] They noted that it occurred in only a small proportion of treated patients, was not dose-related, and was often accompanied by other evidence of hypersensitivity such as fever, skin rash, and eosinophilia. Furthermore, they claimed that circulating antibodies reacting with the offending drug could frequently be detected, that tests for cell-mediated immunity were sometimes positive, and that similar renal reactions occurred if further exposure to the drug or chemically-related compounds took place.

Interstitial nephritis was more frequently referred to in early literature before the antibiotic era, usually in association with infectious fevers.[26] These patients differed from most of the recently reported cases in that functional disturbance was minimal. Yet many patients with interstitial nephritis are suffering from infections either in the urinary tract or elsewhere in the body. Treatment of these patients with antibiotics must leave some doubt as to the part played by the underlying infection and the role of antibiotics themselves in the aetiology of the renal disease.

Primary renal papillary damage from any cause—for example, urinary tract obstruction, reflux, diabetes mellitus, sickle cell disease or analgesic abuse may be associated with inflammatory cell infiltrates in the interstitium.[27] To what extent this is related to mechanical damage produced by obstruction to urinary outflow and to what extent other factors are involved is not clear.

*Pathogenesis of renal failure*

The clinical presentation of interstitial nephritis varies from minor disorders of renal function to acute oliguric renal failure. The underlying physiopathology of the latter has received little attention. The lack of a hypotensive episode and the presence of normal glomeruli with patent capillaries excludes lack of glomerular filtration as a primary cause. Oliguria may occur in the absence of apparent obstruction to urine flow by medullary lesions although inevitably restricted biopsy material cannot provide conclusive evidence on this point and it is rarely possible to study these cases at necropsy. Tubular damage associated with back filtration of glomerular filtrate through focal areas in the necrotic tubules is another possible explanation. The presence of interstitial oedema which is a common finding in this condition would be in accord with such a hypothesis. This is an area where the relation of pathological findings to function is somewhat obscure.

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