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ASPECTOS CLINICOS

Acute renal failure from tubulointerstitial disease

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Introduction

Elsewhere in this symposium, acute renal failure as a part of systemic disease, including vasculitis, sarcoidosis, lupus, and uveitis will be dealt with (see articles by Serra, and by Angel Frutos). Here therefore, I will consider only acute tubulointerstitial nephritis unassociated with any of these forms of illness.

Acute tubulointerstitial nephritis (TIN) was described as early as glomerulonephritis[1-3], but suffered a relative eclipse until the condition was «rediscovered» in the 1960s[4] and 1970s[5-7]. Then, interest in the immunological mechanism of tubulointerstitial damage induced in animal models[7-9] stimulated further interest in the human disease.

Tubulointerstitial nephritis is not common: estimates as a percentage of all acute renal failure range from 1-3 %[10, 11]. In the French cooperative study of acute renal failure (Kleinknecht, personal communication) 2,175 patients with acute renal failure were identified, of whom only 17 (0.8 %) were shown to have TIN. However, this proportion rises to 8-22 % when cases of acute renal failure of obscure origin are considered[10-13]. Acute tubulointerstitial nephropathies are certainly underdiagnosed, especially when circumstances suggest that acute tubular necrosis might be present, and a biopsy is not performed. In Richet's series[10], 218 of 976 patients were biopsied, whereas in the collaborative study, only 77 of 2,175 had a biopsy. As an example, in one of our patients acute renal failure occurred: he had undergone a thoracotomy to remove a carcinoma of the bronchus; sepsis occurred with some mild hypotension, and to begin with there was no suspicion that anything other than acute tubular necrosis was present. However, a renal biopsy showed an intense interstitial nephritis; the patient had received both B-lactam antibiotics and a non-steroidal anti-inflammatory agent, for post-operative pain.

Another feature which leads to the diagnosis being missed is that urine output is often maintained in many forms of TIN, especially those associated with non-steroidal anti-inflammatory agents (see below). The differential diagnosis is therefore between non-oliguric acute tubular necrosis— a much commoner event, and becoming commoner in modern practice— and acute TIN. Often no renal biopsy will be done, and renal biopsy is crucial to the diagnosis of TIN.

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Clinical picture

Tubulointerstitial nephritis may occur at any age, and overall there is no particular *sex ratio;* however this conceals variations in individual subgroups considered below, in that B-lactam antibiotic-associated TIN is three times as common in males, whereas those with NSAID-induced disease show a modest preponderance of females. There may be a *systemic syndrome*, particularly in those associated with drug ingestion: this consists of a maculo-papular rash, fever, arthralgia, and a varying degree of acute renal failure up to the requirement for dialysis. However there may be no systemic symptoms suggesting an allergic event whatsoever, and the clinical diagnosis rests on suspicion only. Even in the «classical» allergic nephritis induced by methicillin (see below), only 33 % or fewer of patients showed all three of fever, rash and eosinophilia. The question of TIN and systemic disease, including uveitis, is dealt with in the article of Assumpta Serra in this symposium.

Microscopic *haematuria* is invariable, macroscopic haematuria common, and red cell casts may be observed in the urine[14]. Proteinuria is always present, and in a few patients may be of nephrotic dimensions. This is almost always in association with treatment using non-steroidal anti-inflammatory drugs[15-17], but may also occur very rarely following antibiotics[18] or other drugs[11]. Thus, the differential diagnosis between TIN and a severe glomerular nephritis may be impossible clinically, and the diagnosis of tubulointerstitial nephritis established only on renal biopsy.

Oligoanuria is not common in TIN, with the exception of rifampicin-induced disease, and normal volumes of urine are often passed throughout the illness, which delays or apparently negates the diagnosis. As noted above, this is particularly common in NSAID-associated TIN; one of our patients, a 72 year old priest, arrived at the hospital quite well, still passing good volumes of urine but with a plasma creatinine of more than 2,000 µmol/l.

The main *functional derangements* relate to uraemia, but a consistent hyperchloraemic acidosis has been noted[22, 23], together with impaired concentrating ability

which may persist for many months after the acute episode in those cases which recover renal function[24]. Acute renal failure from TIN is often mild, and in only about one third of cases in most series, including our own, has it been necessary to dialyse the patients.

Eosinophilia is variable, commoner in methicillin-related cases, but occurs overall in only half of all drug-related TIN; *eosinophiluria* may be present also as a major component (40-100 %) of the usual leukocyturia[19-21], but whilst the presence of either (or especially both) suggests strongly a diagnosis of TIN, their absence is of no value in excluding the diagnosis. It must be remembered, however, that eosinophiluria is found in many other conditions urinary tract infections, papillary necrosis and atheroembolic disease amongst them. Staining for urinary eosinophils increases the utility of this finding very greatly: the Hansel stain is more specific and sensitive than the Wright stain[20, 21], although it is only about 50 % predictive of the presence of a TIN[21]. In our hospital the easiest way to get this stain done— not routinely available in either haematology or in chemical pathology, and therefore done infrequently and badly— is through the cytology service, since it is in routine use in that laboratory. *Raised IgE concentrations* are found in only about one third to one half of patients (see below).

Renal imaging is most useful in excluding other causes of acute renal failure, such as obstruction; on ultrasound the kidneys are normal in size or modestly enlarged, with increased cortical echogenicity[25]. The uptake of ^{67}gallium citrate is increased[13], but this occurs also in other forms of renal disease including nephrotic syndromes and acute pyelonephritis, and is thus of little diagnostic help. Also the test takes 48 hours at least to perform. It may, however be of use in following the course of the infiltrate in biopsy proven cases.

Renal histological findings in acute tubulointerstitial nephritis

It has been emphasised already that renal biopsy is the central observation in the diagnosis of TIN. The most striking feature in all cases is, by definition, the presence of numerous cells in the renal interstitium[5, 7, 11]. The numbers of such cells is of course much more than that found in normal kidneys (55 ± 13/mm^2 [mean ± SEM] in our own studies)[26], but is also more than that usually seen in acute tubular necrosis. In some cases, however, it may be difficult to say whether sufficient cells are present to justify a histological diagnosis of TIN.

The only study which has examined this problem that I am aware of is that of Burdick et al.[27]. They found a mean ± SEM of 451 ± 101 cells/mm^2 in 9 patients with acute tubular necrosis, with some segments as high as 800 cells/mm^2; thus the upper 95 % confidence limit for kidneys with only ATN can be calculated as 1,057 cells/mm^2. They studied allograft rejection as a contrast group (2,269 ± 215 SEM). However, the mean numbers of cells in patients diagnosed as TIN in our studies (Figure 1) was about 1,315/mm^2 with an SD of 330; therefore the lower 95 % confidence limit is only about 700, giving an overlap with those diagnosed as acute tubular necrosis.

Another problem of differential diagnosis is patients with preexisting glomerular disease who are being treated with a drug, and then develop rapid loss of function, perhaps up to acute renal failure[28, 29]. The renal biopsy may reveal an interstitial infiltrate, but in numbers and composition the infiltrate in a number of forms of glomerulonephritis (see[30] for review and Fig 1) is indistinguishable from that seen in acute TIN. At the moment there is no way of distinguishing histologically what is happening, and the only safe course is to stop all drugs.

The cortical interstitial infiltrate is mainly made up of mononuclear cells, principally lymphocytes on optical microscopy, but with some plasma cells and numerous monocytes/macrophages, and a few eosinophils, which although they have received much attention are numerically insignificant (see below). These cells may be more or less confined to the interstitium, or be seen within tubules, in which case breaks in the tubular basement membrane may ben seen on PAS or silver methenamine staining (Figure 2). Eosinophils are variously present in small numbers in all forms of acute TIN (Table I). Polymorphs are notable for their rarity.

In some patients epithelioid, non-caseating granulomas are seen within the interstitium (granulomatous TIN)[31, 32] (Figure 3). These are particularly related to drug-associated TIN, but may be seen in idiopathic cases, and of course in tuberculosis and sarcoidosis. There is some suggestion that these patients with granulomas do worse in the long run than those without[18].

Various signs of tubular injury of varying chronicity may be seen also; in this connection one must be careful to take the age of the patient into account when interpreting the histological findings, in view of the normal ageing changes seen in tubules and interstitium. Varying degrees of interstitial oedema are seen. The glomeruli are usually normal, or show only signs of ischaemia, such as wrinkling of the basement membrane. Vessels will show only changes consistent with age, but in a tiny group of patients an active vasculitis is present, which may not be confined to the kidney; these cases are almost always in drug-related TIN[11] (see Serra, this symposium).

Immunohistology

In primary TIN, immune aggregates are normally absent both in tubules and in the interstitium, although in rare cases a linear deposit of IgG may be seen along the tubular basement membrane (especially in methicillin-induced nephropaathy, see below) or more common, but still rare in primary TIN, coarse immune aggregates. Fibrin(ogen) antigens are present in a widespread fashion in the interstitium[11, 105].

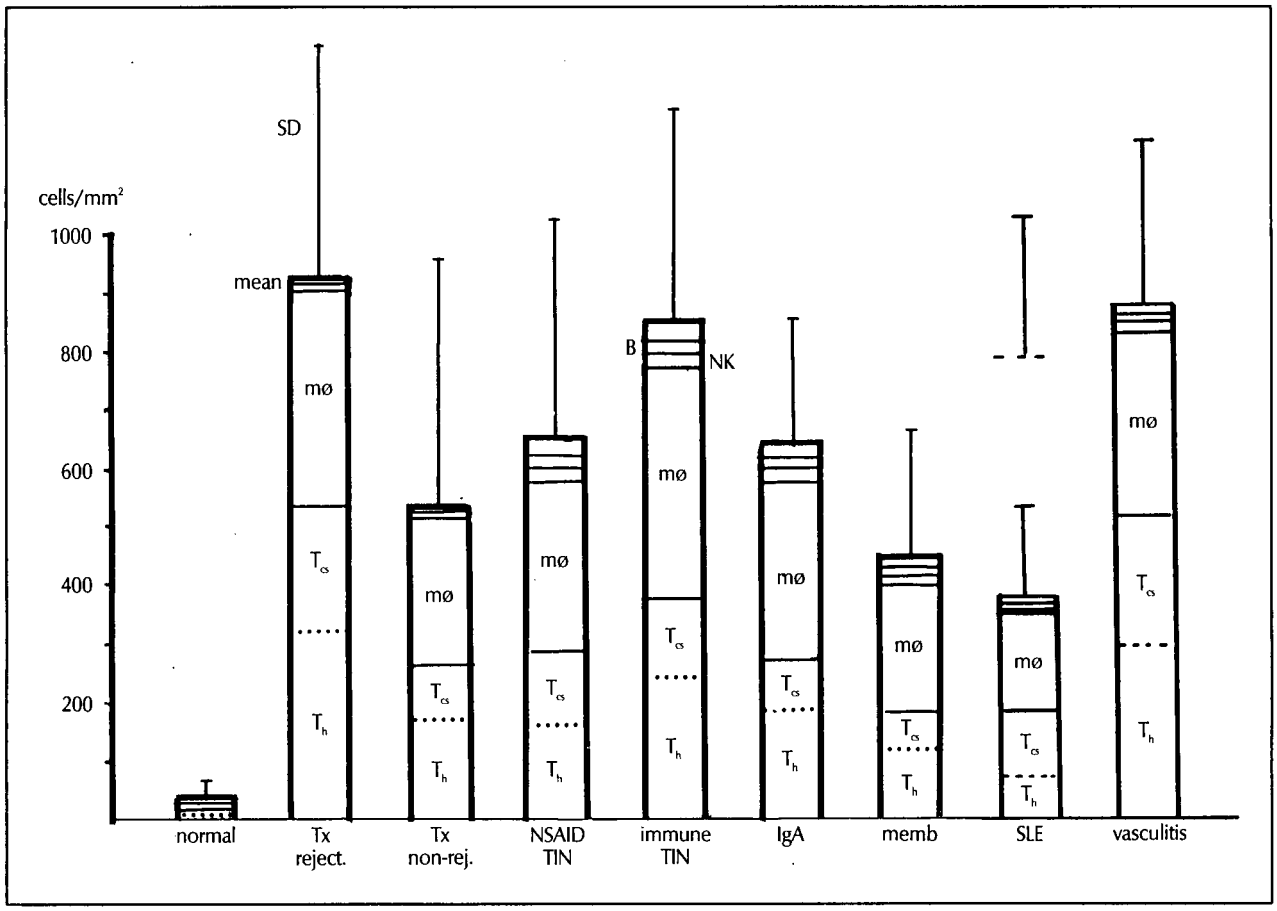

Fig. 1.—The numbers and phenotypes of cells infiltrating the interstitium in allograft rejection, in tubulointerstitial nephritis and in some forms of glomerulonephritis. The bars show the mean, the lines one SD of mean counts from numbers of patients. Data from primary «immunological» and drug-related TIN are shown separately, but are similar. In all cases the majority of the cells infiltrating the interstitium are CD4 + ve T lymphocytes (T_H), although in some patients with lupus and with drug-induced nephritis early in their course CD8 + ve lymphocytes (T_c) are the major species. The remainder are mainly macrophages (O), with a minority of NK cells, B Cells plasma cells neutrophils and eosinophils. The total numbers in the different types of interstitial infiltrate are surprisingly similar, and not so much highert than those found in patients with acute tubular necrosis (see text). Apart from the allografts receiving baseline immunosuppression, all these data are from untreated patients, with the exception of the data in lupus nephritis, who were all under treatment; two patients not on treatment are shown by the higher line in the lupus column, suggesting that the lower interstitial counts found in lupus nephritis are the result of treatment. From reference 30 with permission; data from reference 26 for tubulointerstitial nephritis, unpublished data on allografts, and see 26 for references to data on glomerulonephritis, lupus and vasculitis.

Recently it has become possible to phenotype the cells infiltrating the interstitium in primary tubulointerstitial nephritis using murine monoclonal antibodies[15-17, 26, 32, 34] and Fig 1. Despite the number of papers, the total number of patients with tubulointerstitial nephritis who have been studied still remains small, especially when divided into the various different categories. However, the majority of the infiltrating cells in all studies have been, as in glomerulonephritis and transplant rejection, T lymphocytes. There is some difference of opinion as to which subset (T helper/inducer or T cytotoxic/suppressor) predominates, which probably relates to different aetiology, different stage of disease, or different treatment received before biopsy. However, in the great majority of patients with TIN T helper cells predominate, with Ts/Th ratio below unity; although we found that in some of early biopsies in acute drug-induced TIN, CD8 + ve cytotoxic/suppressor T cells were in the majority[26].

Most of the remaining cells, forming up to half the infiltrate in some cases, are monocytes/macrophages. There are very few cells expressing B cell markers, although mature plasma cells are present in slightly larger numbers[17, 26]. We also analyzed the eosinophil infiltrate quantitatively (Table I). Eosinophils are never found in the normal interstitium, but were present in 7/10 patients with NSAID-induced TIN, but were present also in lesser numbers in patients with more chronic interstitial infiltrates.

In all, the quantitative and qualitative histological re-

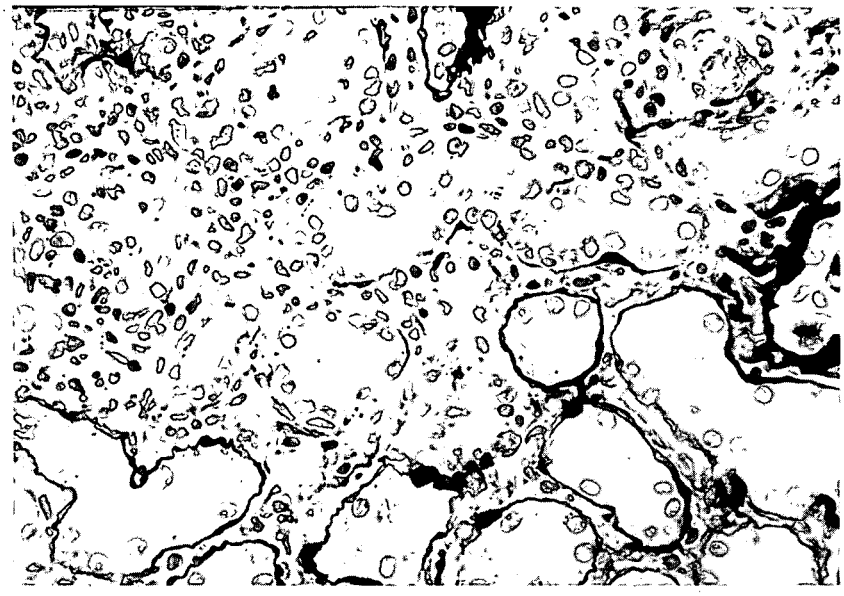

Fig. 2.—Tubulointerstitial nephritis. In the upper left portion of the field, there is a dense interstitial infiltrate of mononuclear cells. The basement membrane, stained with silver, is broken as infiltrating cells attack the tubules. Silver methenamine, original magnification × 200.

Table I. Numbers of interstitial eosinophils in different forms of renal disease

	N.°	N.° of eosinophils /100 tubular X sections mean ± SD
Control kidneys	7	0
TIN from NSAIDs	10	22 ± 11
Idiopathic TIN	5	22 ± 19
«Immune» TIN*	7	1 ± 1
Hypokalaemia, gout	5	11 ± 6

* Sarcoidosis, uveitis, biliary cirrhosis.

semblances between acute TIN and acute allograft rejection are so great that without clinical information it may be impossible to distinguish between the two in an allograft recipient. Obviously, this has implications in thinking about the immunopthogenesis of TIN, as discussed below.

Sub groups

For convenience the more acute forms of immunologic tubulointerstitial injury, can be placed into four groups: those associated with infections, those following drug in-

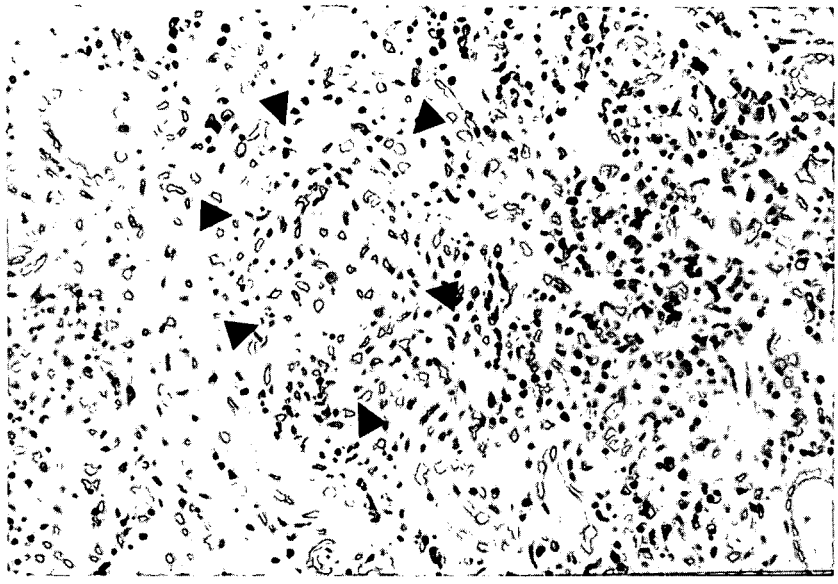

Fig. 3.—Multinucleate cells are beginning to form an epithelioid granuloma (arrowheads) within the interstitium of a patient with interstitial nephritis. Haematoxylin and eosin, original magnification × 250.

gestion, those associated with other immunological disorders (dealt with elsewhere), and an apparently idiopathic group in whom no precipitating or associated factors can be found.

Tubulo-interstitial nephritis associated with infections

The attention paid recently to drug-induced acute interstitial nephropathies (see net section) has obscured the fact that acute allergic interstitial nephritis was first described in detail by Biermer in 1860[1], and later underlined by others[2,3], in association with streptococcal and diphtherial infections. This can stil happen[35-37], and presumably in parts of the world where infectious disease is still rife, infection-associated tubulointerstitial disease remains common, although reports to confirm this are lacking. The exception may be congenital syphilis, in which a common lesion is an interstitial nephritis, still rife in poorer parts of the world. Since the introduction of effective antibiotic therapy[37], cases of syphilitic and scarlatinal nephropathy have become rare, and acute interstitial nephritis became an almost forgotten disease in the 1950s and 1960s[4,38,39].

However in children[41-43], even in the developed world, drug-associated interstitial nephropathies are relatively uncommon, and the majority of the rather rare cases of acute interstitial nephritis are infection-related[41] or related to immune disorders. Finally, one must remember in the present climate of thought, a tubulointerstitial nephritis is more likely to be attributed to the drug given to treat the infection, than the infection itself!

Table 2 gives a list of infections which may be complicated by acute interstitial nephritis[1-3,35-63]. In streptococcal infections[1-3,35-38,41], symptoms appear 1-2 weeks after the infection are often non-specific with fever, malaise and weight loss, and the diagnosis is suspected in only half the cases[41] until renal failure makes its presence known. Anaemia is often severe, and blood eosinophilia present in only half the cases; the ESR is usually very high. Complement levels are usually normal, which is a differential point from acute post-streptococcal glomerulonephritis.

Special forms of infection-related interstitial nephritis

In most cases of infection-related tubulointerstitial nephritis the renal damage is the result of an allergic reaction, with no organisms within the renal parenchyma. However, acute renal suppuration with acute renal failure and a dense infiltration of polymorphonuclear leukocytes within the kidney may be seen. These patients are often debilitated (e.g. by immunosuppression, cancers or diabetes). The commonest organisms are *E Coli, Proteus, Staphylococcus aureus* or *Candida*[57]. The patients are usually very unwell, with swinging fever and all the signs of septicaemia.

In cases of *tuberculosis*[46] also, Ziehl Nielsen stains may shown mycobacteria within the kidney, but the evolution of such cases in usually chronic, over months or years rather than days.

Table II. Infections associated with acute interstitial nephritis

Organism	Reference(s)
Bacteria	
Streptococcus	Biermer[1], Klein[2], Councilman[3], Ellis[41], Knepshield[36], Webster and Hall[35], Kimmelstiel[37], etc.
Diphteria	Councilman[3], Kimmelstiel[37]
Brucellosis	Dunea[39], Muehrcke[40]
Legionella	Paulter[44], Case Records MGH[45], Buysen[59]
Pneumococcus	Ellis[41], Buysen[59]
Tuberculosis*	Laudet[46], Mignon[31]
Yersinia	Iijima[57]
Enterobacteria	Singhal[60]
Spirochaetes	
Syphilis*	Kimmelstiel[37], Muehrcke[40]
Leptospirosis*	Bain[47], Lai[48], etc.
Viruses	
EB virus	Woodroffe[49]
Measles	Kannerstein[38], Wilson[12]
BK virus*	Rosen[50]
Cytomegalovirus*	Platt[51]
Hantaan virus*	Van Ypersele[52], Cosgriff[53]
Others	
Toxoplasma	Guignard and Torrado[54]
Mycoplasma	Pasternack[55]
Rocky mountain spotted fever*	Walker and Mattern[56]
Mediterranean spotted fever	Galicia[58]
Candida*	Ramsay[57]
Leishmaniasis	Duarte[63]

* With direct invasion of renal tissue.

In *leptospirosis*, leptospirae can be demonstrated within the kidney in about two thirds of cases[11,47]. In some patients interstitial infiltrates may persist for weeks or months after the acute illness. The clinical diagnosis is usually not difficult in the presence of fever, myalgia and jaundice, but very frequently the event leading to infection cannot be identified. It is now rare in most European countries, although in rice growing countries, and in the Po valley in Italy, it remains common.

Another specific form of infection-associated interstitial nephritis is that associated with *hantavirus* infection[52,53]. Rodents are again the vector for the virus and the disease, common in the Orient and Asia, is increasingly recognized in Europe (although it has scarcely been recorded in the UK as yet). After an incubation period of 10-30 days, high fever, loin pain, nausea and vomiting, chills, intense myalgia and sweating appear, together with a brief acute renal failure. In Europe, severe haemorrhagic symptoms (which gives this condition several of its different names) have usually been absent or slight. The severity of the disease varies greatly between geographical areas, mainly related to differing local strains of the virus.

Clinical course of infection-related nephritis

Most forms of post-infectious interstitial nephritis are self-limiting, and it is obvious that the primary infection should be treated. Few patients have been given corticosteroids, and their administration is probably unnecessary. Complete recovery of function and urinary findings is usual, but may take three months or more from onset. However after some infections, including EB virus infections, permanent renal damage may occur, leading to end stage renal failure (see[11] for review).

Drug-induced acute allergic interstitial injury

With the huge increase in the consumption of various chemotherapeutic agents over the past three decades, drug-related acute interstitial nephritis has come to dominate this area of medicine. Even so, we must not forget that overall, drug-induced tubulointerstitial nephritides are relatively rare. Acute interstitial nephritis represents only 1 or at most 2 % of the renal biopsies done in an average renal unit[10]; our own figures were 51 cases (18 drug-related) in 2,600 biopsies performed 1970-1986[12].

More than 80 different drugs have been implicated as causing acute inflammatory tubulointerstitial nephritis [4-7, 11, 13, 63-71] (for detailed reviews up to 1988) (Table III). To shorten the reference list to this article, only more recent, new associations described in 1982 or later are referenced separately[72-83]. Many of these attributions rest, however, upon single case reports, many of the patients described had received more than one drug, any many were severely ill with other diseases. Thus any drug implicated by only a single report– unless this is a definitive report, for instance describing recrudecence on rechallenge– then one cannot be sure the association exists. The reaction of acute interstitial nephritis occurs in only a minute number of patients taking most drugs (methicillin being the exception), and appears not to be dose-related (but see the comments on allopurinol below).

Table III. Drug-induced tubulointerstitial nephropathy (Those drugs reported with any frequency are shown in capitals)

Non-steroidal anti-inflammatory drugs		B lactam antibiotics	
Mefanamate	Fenoprofen	Metchicillin (G)*	Penicillin (G)
Naproxen	Tolmetin	Ampicillin (G)	Amoxycillin
Diflusinal	Piroxicam	Nafcillin	Carbenicillin
Ibuprofen	Zomepirac	Oxacillin (G)*	Cloxacillin
Phenylbutazone*	Diclofenac	Cephalothin*	Cephalexin
Indomethacin	Ketoprofen	Cephradine	Cephaloridine
		Cefotaxime	Cefoxitin
		Piperacillin	

Other antibiotics
Sulphonamides (G), and Cotrimoxazole (G), Rifampicin (G), Polymyxin (G), Kanamycin, Gentamicin, Colistin, Ethambutol, Chloramphenicol, Tetracylines, Vancomycin, Erythromycin (G), Ciprofloxacin, Norfloxacin, Isoniazid.

Diuretics
Frusemide, Thiazides (G), Chlorthalidone, Triamterene (G), Tielilic acid (G)*.

Other drugs:
Diphenylhydantoin (G), Glafenine, Phenindione (G)*, Allopurinol (G), Cimetidine, sulphinpyrazone Aspirin Cambamazepine, Clofibrate*, Azathioprine, Phenobarbitone, Alpha methyl DOPA, Gold and Bismuth salts, Diazepam, D-penicillamine, Alpha interferon, Phenacetin, Paracetamol, Phenazone and relatives*, Foscarnet, Valproate, Captopril (G), Antypyrine (G)*, Carbimazole, Acyclovir, Azathioprine, Warfarin.

* No longer in general use.
G: May cause granutomatous interstitial nephritis (see reviews [6, 7, 10, 11, 13, 31, 65-68, 70, 71] and more recent case reports and series [73-115] for detailed references).

The clinical picture has been described already: in a few patients, reviewed in[71], a vasculitis associated with TIN has been seen. In addition to the drugs listed by Grunfeld and colleagues[71] (penicillin, allopurinol, indomethacin, and fenoprofen) we have seen a similar case following diclofenac. Hepatic damage[71] with hepatitis, sometimes granulomatous as in the kidney, has been described after rifampicin, allopurinol, salazopyrine, phenindione and clometacin, a drug used in France but not in the UK.

A few drugs accunt for the great majority of reports of acute tubulointerstitial nephritis; they are worth considering in a little more detail:

i) B-lactam antibiotics: Penicillins and cephalosporins

More than 100 cases of *methicillin*-associated nephritis had been recorded[67, 85] up to the early 1980s. With the introduction of agents such a flucloxacillin for the treatment of resistant staphylococcal infections this has now become rare, and we have biopsied only one penicillin-related case since 1970, a reaction to ampicillin in a patient with lymphoma. Ampicillin is now probably the commonest cause of acute antibiotic induced TIN, since single case reports involving this drug are to longer published. Acute TIN has been reported with a number of other penicillins still in frequent use (Table III) although on a much smaller scale. The sex incidence of penicillin-induced acute TIN is about 2-3:1 male:female and it may be seen from infancy[86] to old age[85], although there is a predominance of older children and young adults; treatment was for 2 to 44 days before symptoms arose. The underlying infections were almost all caused by penicillinase-producing staphylococcus aureus, but several patients given prophylactic drugs before cardiac surgery, without infections, have developed the condition.

Methicillin was apt to induce acute TIN: as many as 17 % treated with the drug developed renal impairment[87]. The immunologic mechanisms are better understood in penicillin-induced than in any other form of drug-induced TIN[22, 23] (see below). Rechallenge with the drug leads to a recrudescence[85, 86], and all β-lactam antibiotics are best avoided in patients developing penicillin-related acute TIN. This may not be easy, since a number of cephalosporins have also been implicated (Table II).

Obviously once any drug is suspected it should be withdrawn, but some patients continue in renal failure for a prolonged period even after withdrawl[22, 23, 86]; a few have suffered permanent renal damage[24, 88]. Hardly surprising, patients with oliguric renal failure seem to do worse than those with non-oliguric renal failure, or only mild uraemia, as do those with diffuse interstitial infiltrates[64]. Most patients however, eventually recover complete renal function.

The question of whether to give corticosteroids in this or any other form of drug-induced nephritis remains unresolved. The most critical study is that of Galpin et al.[89], which still leaves much to be desired; they found, in a retrospective analysis, that those patients with methicillin-induced TIN who had been treated with prednisolone had a shorter period of oliguria than those who were not so treated.

ii) Rifampicin

About 60 cases of rifampicin-associated acute TIN had been reported[65-67], since the first report in 1971[90], always in association with tuberculosis. Usually, the treatment regime has been variably intermittent[90], and only a handful of cases have resulted from continuous daily treatment. Unlike methicillin-induced TIN, the sex incidence is almost equal. Acute symptoms include chills, dark-coloured (but not haematuric) urine, myalgia, fever, headache and a rash. Thrombocytopenia and haemolysis have been reported. Two thirds of the patients required dialysis. There may be a proliferative glomerulonephritis as well[91].

Most patients with rifampicin-induced TIN have abrupt oliguria and require dialysis. There is no evidence that prednisolone is of use, and the condition has been described arising during concomitant steroid therapy[92]. Most patients make a full recovery, but a few suffer permanent interstitial fibrosis. One of our own two patients went on to dialysis treatment 8 years after incomplete recovery of renal function; he had been treated with prednisolone throughout.

iii) Non-steroidal anti-inflammatory drugs (NSAIDs)

In the developed world, many millions of mainly older individuals are taking these drugs, which are now available off prescription in many countries. Even though in general safe, reports of case of renal toxicity resulting from NSAIDs are increasing. Several important aspects of the renal toxicity of NSAIDs, reviewed elsewhere[93-96] are not relevant here, such as the sensitivity of volume-contracted patients to inhibition of vasodilator prostaglandins, the reversible hyperkalaemia, fluid retention, and hypertension. Renal papillary necrosis has been reported also[95], and interactions with urinary infections[97] or diuretics[98].

The first case reports of TIN arising from use of these drugs came in 1979[99, 100], and such cases are now a feature of all renal units; in our own unit we have more than 20 cases in the last 10 years. Those cases published up to 1984 are reviewed in references[55-57], and are now so common as not to excite comment in the literature unless some special feature be present. Almost all the various NSAIDs in clinical use, which are of many different chemical structures, have been implicated (Table II).

Most of the patients developing this problem are over 60 years of age, and it is unclear whether this merely represents the age-group likely to ingest the drugs, or some particular sensitivity of the aged to their challenge. Sometimes the drug has been taken for months or years, in others only briefly. Rather rarely do the patients manifest clinical signs of their reaction, other than renal failure such as rash, fever, eosinophilia; and it is necessary to take a careful clinical history to exclude ingestion of NSAIDs purchased without a medical prescription. The affected patients usually remain polyuric rather than becoming oliguric, so that renal failure may not be suspected until very late.

Of considerable interest is the fact that patients taking NSAIDs, particularly those taking fenoprofen, frequently develop a full nephrotic syndrome in addition to the TIN[15, 99, 100], the glomeruli showing minimal changes with only foot process fusion on electron microscopy[15-17, 99]. This has been reported also other NSAIDs including piroxicam, indomethacin, tolmetin, ibuprofen and zomepirac[95]. Possible pathogenesis is discussed below.

Withdrawl of the offending drug usually leads to resolution, and there is no evidence that steroids hasten or improve the results. The nephrotic syndrome also usually remits also, but occasional patients remain in renal failure with torrential proteinuria, as in one of our own cases. Four of the first twelve in our series had only partial recovery of renal function, even allowing for age (see below), and Adams et al.[101] first reported irreversible chronic renal failure and interstitial fibrosis in six patients.

On the continent of Europe, an analgesic drug *glafenine* is in common use, which is a well-recognized cause of acute renal failure from the insolubility of the compound in tubular fluid[66]. However, a tubulointerstitial nephritis has also been documented with this drug[16, 31, 102].

iv) Diuretics

Despite being in common use for many years, especially in the elderly, only about 30 cases of diuretic-induced TIN have been described[13, 28, 29, 64, 65, 103]. *Thiazides* and *frusemide* have been most commonly implicated, and are of course both chemically related to sulphonamides, but *triamterene*[104, 105] and *chlorthalidone*[106] have also been accused. Both patients with various forms of glomerular disease[28, 29], and those without[103] have been affected. The usual symptoms of fever, uraemia, rash and eosinophilia were present in many (but not all) patients. Withdrawl of the drug, with or without steroid treatment (which is of unproven value) led to recovery of function in all cases. Transfer to bumetanide appears to be safe, if a diuretic is nee-

ded, because so far as I am aware, no case of bumetanide-associated TIN has been described. We have observed only one case of diuretic induced acute renal failure, associated with frusemide treatment in a nephrotic child, who made a complete recovery.

v) Other drugs

As Table II shows, many other drugs have been implicated on more or less secure grounds as causing acute interstitial nephritis.

Sulphonamides have long been known as a cause of acute TIN[64-69], and about 40 cases of acute renal failure from TIN associated with *co-trimoxazole* ingestion have been recorded[66, 68]. Unlike diuretics, signs of hypersensitivity were usually absent.

A number of cases of *allopurinol* sensitivity have been described[107, 108] some with granuloma formation[108] (see below), mostly in patients with pre-existing renal impairment and relative over-dosing[109] or on treatment with thiazides, which leads to increased blood concentrations. These data appear to contradict the statement that drug-related hypersensitivity reactions are unrelated to dosage or plasma concentrations.

The uricosuric drug *sulphinpyrazone* has also been reported as a cause of allergic TIN on several occasions[110], and *cimetidine* has been implicated as a cause of TIN in several patients[111]. The now obsolete anticoagulant, *phenindione* was reported to cause acute TIN in about 30 cases[67, 112]; although its use is now limited, recently a case of TIN apparently arising from *warfarin* was reported[84]. Several reports (e.g.[113]) incriminate *diphenylhydantoin* as causing allergic TIN, and finally, a handful of recent papers incriminate *vancomycin*[114] and *ciprofloxacin*[115] (as well as norfloxacin) as causes of TIN.

It is worthwile re-emphasising that almost all the other drugs on the list in Table II refer to single case reports, or to a few isolated instances at most, and these associations should be treated as unproven.

Tubulointerstitial nephritis associated with other systemic immune disorders

TIN in association with glomerulonephritis, sarcoidosis, vasculitis, lupus, Sjögren's syndrome[117, 118], biliary cirrhosis and isolated uveitis is dealt with in other articles within this symposium, to which the reader is referred. An excellent review of this subject elsewhere is that of Mery and Kenouch[116].

«Primary» tubulointerstitial nephritis

In a few cases the TIN appears isolated[42, 106, 119-125]. One tiny sub-group are children[42, 106, 122] with isolated anti-TBM antibodies and progressive renal failure. In one patient[122] the disease recurred in the allograft with graft failure (personal communication from patient). Most patients with isolated TIN have not shown obvious signs of hypersensitivity with eosinophilia, although a few have[123], and in the majority deposits on the TBM, where sought, have been absent. In the majority of this isolated group, the patients presented insidiously in renal failure of greater or lesser degree, usually with moderate volumes of dilute urine, occasionally with a Fanconi syndrome. Presumably they represent reactions to environmental agents which have escaped notice.

Mechanisms of injury in tubulointerstitial nephritis

A number of other excellent reviews of tubulointerstitial injury have been published recently[8, 9, 11, 126-131], and the reader is referred to these for more detail on the topics discussed in this section.

The cells of the interstitium

Strangely, descriptions of normal human cortical interstitial cells are almost completely lacking[132], and our data come almost entirely from the rabbit and the rat. The type I cortical («fibroblastic») cell[132-134] is an obvious candidate for the secretion of the new collagen which involves the interstitium in all forms of interstitial nephritis.

Even less is known of the type 2, «mononuclear» or «lymphocytelike» cells, some of which are resident monocytes of bone marrow origin. Amongst the other bone marrow-derived cells within the interstitium are dendritic cells[135], a cell with complex cytoplasmic processes usually found in intimate association with the periglomerular capillaries. Dendritic cells, like mcrophages, express class II MHC antigens (Figure 4) and thus can present antigen to T helper lymphocytes during the early phases of the induction of an immune response.

Anti tubular basement membrane (TBM) nephritis:

Information on the immunological mechanisms of injury is scanty for human disease, and much extrapolation from animal models is needed[8, 9, 11, 126-131, 136]. As with the study of glomerular injury, a disproportionate amount of thinking and experimental effort has gone into understanding diseases dependent upon direct combination of antibody specifically directed against tubular structures, i.e. anti-TBM nephritis. This is because these are the mechanisms most easily understood, and also those most accesible to experiment. This accessibility should not mislead us into thinking that this is, clinically, other than an occasional curiosity in humans. In a series of 65 cases of human TIN, we have yet to observe a single case with anti-TBM antibody.

Even in the rodent and guineapig anti-TBM antibody nephritis, secondary cell-mediated immune mechanisms

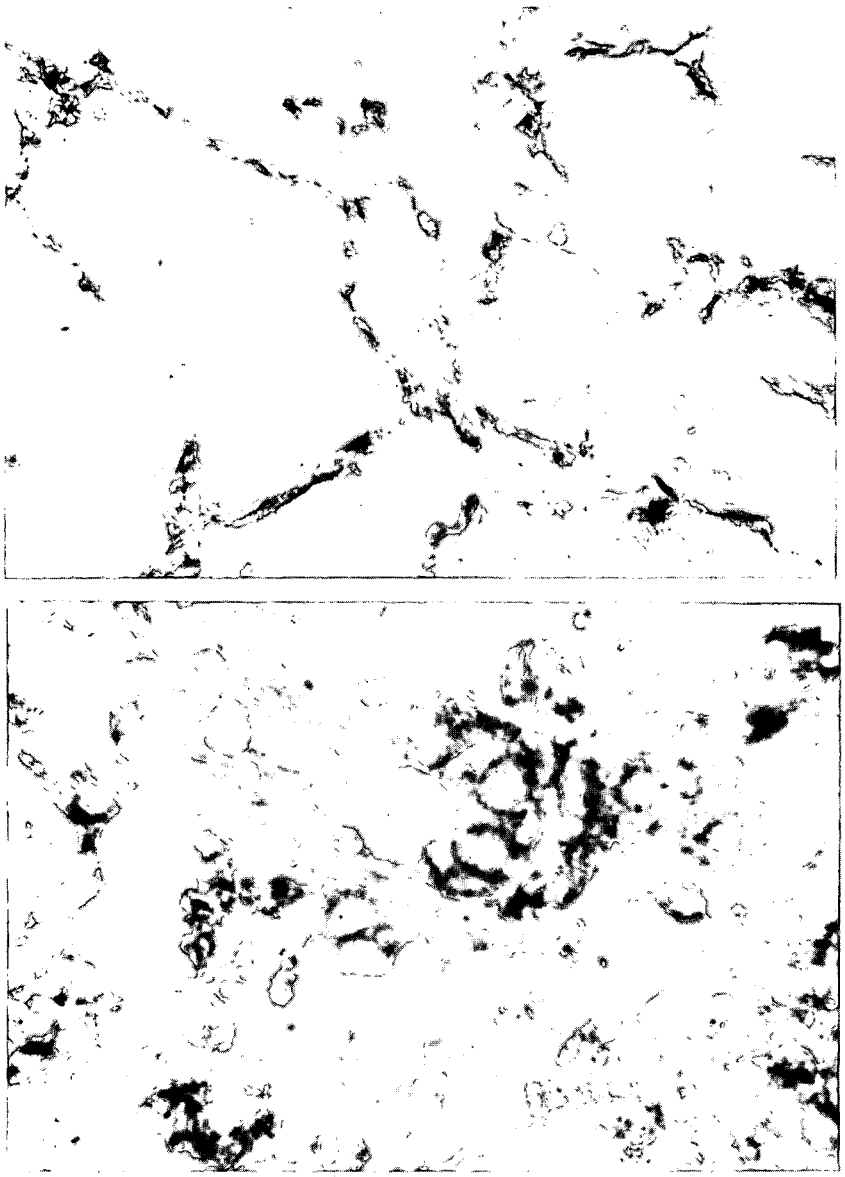

Fig. 4.—Expression of MHC class II antigen revealed by monoclonal antibody (DK-22) directed against invariant parts of the MHC class II molecules, and developed by immunoperoxidase labelling. (a) shows DR expression in a normal kidney: only a modest number of resident interstitial cells express DR antigen. (b) from a patient with acute TIN. The tubules now express diffuse cytoplasmic DR, with the nuclei showing as «holes» within the diffusely stained cells (from Cheng, et al.[26] with permission).

play a crucial role[8, 9, 127-130, 136]. In humans, rather rarely anti-TBM antibodies can be demonstrated in serum[8, 9, 122, 123, 137-143] with linear binding of IgG to the tubular basement membrane on immunofluorescent staining. In some cases of methicillin-induced nephritis[22, 23] also there is linear fluorescence along the TBM, and the serum contains antibody directed against the dimethoxy-phenyl-penicillinoyl hapten bound to the TBM. As with the experimental models, however, the relation of this to the prominent cell-mediated events in the kidney is not clear and in the majority of cases no such antibody is evident. In a few other cases of drug-induced TIN, anti-TBM antibodies have been identified[106, 107, 113, 140, 142, 143]. Recently the TBM antigen against which at least some human anti-TBM antibodies are directed has been identified as a 48 kD glycoprotein[144], homologous to the antigen in the original Steblay guinea pig model[138] and in rabbits[128].

Tubular immune deposit disease:

A few apparently idiopathic cases of human TIN show immune aggregates along the TBM[123, 125] but in humans immune complex interstitial nephritis is found almost exclusively in systemic lupus nephritis, in Sjogren's syndrome[117, 118], and in essential mixed cryoglobulinaemia (see Angel Frutos in this volume, and[116]), together with isolated cases of various proliferative glomerulopathies[42, 145, 146].

Cell-mediated immune injury:

Direct cell-mediated interstitial nephritis is probably the main mechanism of injury in human TIN. Two main channels of injury are recognized: delayed hypersensitivity, and direct T-cell cytotoxicity. A *delayed hypersensitivity* reaction occurs when, in an immunized host, macrophages present antigens to primed T helper cells. Delayed hypersensitivity reactions are characterized by a high proportion of T helper/inducer cells bearing the CD4 phenotype[147], and invading monocytes, which presumably mediate at least some of the resultant injury by release of intracellular contents.

In *direct cytotoxicity*, cytotoxic T cells bearing the CD8 phenotype come into close contact with target cells, and kill them by several poorly understood mechanisms. Thus the infiltrate in vivo would be expected to be rich in cytotoxic CD8-bearing cells[148]. Exactly what makes a cell a target cell is not yet clear, but display of foreign antigens, either from alloincompatibility, or from viral transformation, are examples well-studied in vitro.

A third possible mechanism is antibody dependent cell-mediated cytotoxicity, or *ADCC* for short. In this reaction, cells expressing natural killer activity (NK cells) which may be of varied origin, bearing Fc receptors, react with the Fc portion of cell-bound antibody to cause cell lysis. Neilson and colleagues[149] have suggested this mechanism may operate in experimental anti-TBM nephritis.

Obviously all three channels of reaction as well as antibody-mediated injury could operate together in vivo in animal models or human diseases. In experimental animals it has not been easy to induce purely cell-mediated models of interstitial nephritis[126, 128, 150, 151], transferrable by spleen or lymph node cells, but not by serum, with no evidence of immune deposits in the tubules or of anti-TBM antibodies. In a spontaneous model of interstitial nephritis in *kdkd* mice, cell transfer of the nephritis was possible, using cells bearing a cytotoxic T cell phenotype[152].

Thus in human TIN, it seems likely that the main mechanism of injury in the great majority of TIN is by one or more of the cell-mediated mechanisms. Since in most cases T-helper cells are in the majority in the interstitial infiltrate (Figure 1), together with many monocytes, a predominance of delayed hypersensitivity reactions is likely, rather than direct cytotoxicity. T cells are capable of inducing granuloma formation[31, 147] and the spectrum of drug-induced and post-infectious TIN suggests that committed T-helper cells may be the key agent. However, it has been possible in only a few patients to demonstrate in vitro cellular sensitivity by blast transformation in response to the drug (diphenylhydantoin[113], cimetidine[111], carbamazepine etc.[104]).

There is some clue from patients with drug-induced TIN, however, in particular those with TIN in association with ingestion of NSAIDs, that early in the reaction cytotoxic/suppressor cells are in the majority[17, 26], and on occasion these may be seen invading the renal tubules and potentially causing damage (Figure 5). It is quite possible that both delayed hypersensitivity and direct cytotoxic mechanisms are both operating in many patients.

Cells bearing a NK phenotype are rare in the infiltrate in all studies including our own (Figure 1), so that ADCC reactions (of which mechanism NK cells are the effector) seem unlikely as an important mediator mechanism in human TIN. The role of the sometimes prominent plasma cell infiltrate is not known. Only occasionally has this infiltrate been shown to synthesize IgE (see below).

Direct hypersensitivity (type I) reactions are another possible type of injury in acute TIN. In this type of reaction[69], exposure (for example to a drug) leads to T cell activation, with maturation of specific B lymphocytes into plasma

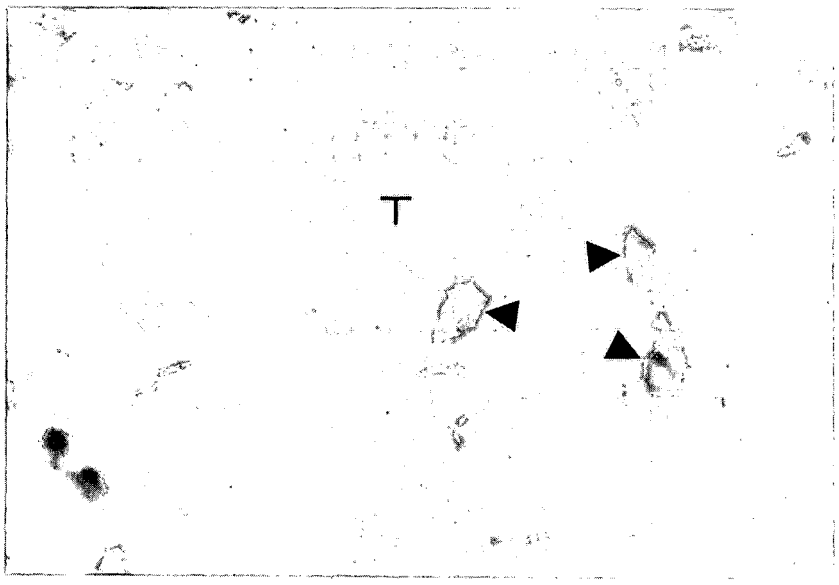

Fig. 5.—Two CD8 + ve cytotoxic cells (arrowheads) invading a renal tubule in a patient with tubulointerstitial nephritis. Immunoperoxidase and haematoxylin counterstain. Original magnification × 800.

cells capable of producing IgE antibody directed against the drug, or a drug-protein combination (i.e the drug acts as a hapten). The IgE antibodies then bind to cells, including mast cells and basophils. Contact with the antigen leads to binding with the cell-bound antibody, followed by a complex series of events leading to release of mediators of inflammation from the sensitized cell, including eosinophil chemotactic factors.

Many patients with TIN, especially those following drug ingestion, display signs of direct type I hypersensitivity, including high serum concentrations of IgE[123, 141], fever, rashes, eosinophilia and eosinophiluria[19-21], correlating with the presence of eosinophils in the interstitial infiltrate. Skin tests with the offending drug may be positive[113]. This total picture is particularly well documented for methicillin- and diuretic-associated TIN, but IgE-bearing plasma cells were noted in the interstitial infiltrate of one patient with phenobarbitone sensitivity[154] and IgE along the basement membrane of another[123]. Whether the eosinophils so often observed contribute to tissue injury, or how, is not known.

NSAID associated TIN:

The TIN associated with the administration of NSAIDs is of particular interest because of its association with a nephrotic syndrome of minimal change pattern in some patients[15, 95, 99]. Although all chemical types of NSAID seem capable of inducing TIN, fenoprofen seems to be the most commonly observed provoking agent[95]. A predominance of cytotoxic/suppressor T cells was observed early in the course of our own patients exposed to NSAIDs[26], but many cases T helper/inducer cells were in the majority.

It has been suggested that the minimal change nephrotic syndrome in general is a disorder of T lymphocytes[155], although the evidence in favour of this hypothesis remains controversial[156]. The nephrotic syndrome usually remits as well as the TIN on stopping the NSAID, which supports strongly the idea that the drug is also the cause of the nephrotic syndrome. In addition a number of cases have been reported in which the nephrotic syndrome was the only manifestation, without any associated TIN[157-160], again with a variety of NSAIDs of different chemical structures. Although these clues are tantalizing, a way of linking the observations has yet to appear.

The active participation of the renal tubular epithelium in immune injury

It has become clear in the past decade that, far from being an «innocent bystander» during immune injury, the cells of both glomerulus and tubule participate actively in inflammatory events (Table IV).

Tubular MHC expression

In the normal human kidney only dendritic cells and capillary endothelium express MHC molecules of class I or II in any quantity[161-163] (Figure 4a) but during the cellular infiltration of primary tubulointerstitial nephritis[26] as well as allograft rejection[164-167], and in glomerulonephritis[168] dramatic changes take place, presumably as result of secretion of cytokines such as Y interferon and IL-1[169, 170]: the quantity of MHC class I antigens expressed by tubular cells is greatly increased, whilst MHC class II antigens, normally almost absent in proximal tubular epithelium, become strongly positive (Figure 4b, Figure 6). This could permit the tubular cells to act as antigen presenting cells an initiate or amplify immune responses[171], as may happen in autoimmune thyroiditis[172, 173], insulinitis in type I diabetes[174], and a number of other immunologically mediated

Table IV. Participation of renal tubular epithelia in immune injury

Expression of MHC class I and II antigens.
Expression of adhesion molecules- (e.g. ICAM-1, VCAM-1).
Secretion of growth factors (e.g. PDGF).
Secrertion of complement components (e.g. C3, C4).
Secretion of cytokines (e.g. TNF alpha, ?IL-1).

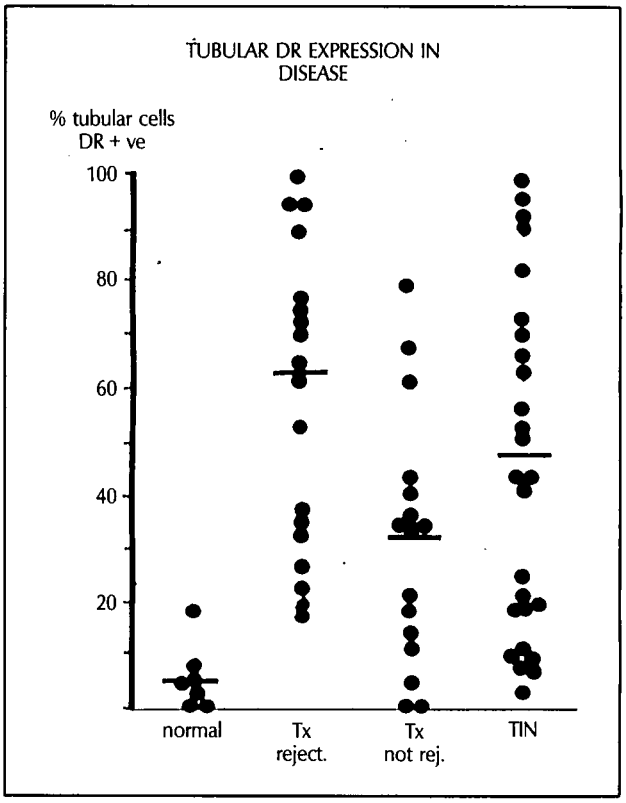

Fig. 6.—Percentage of tubular epithelial cells expressing DR antigen, in normal, allografted kidneys and kidneys suffering from tubulointerstitial nephritis. Data from Cheng, et al.[26], and unpublished. Tx rejec. = rejecting renal allografts, Tx not rej. = renal allografts with renal dysfunction for reasons other than rejection (cyclosporin toxicity, acute tubular necrosis, etc.).

disorders affecting other organs[175], thus setting up a potential «vicious circle» through initiation or amplification of immune injury by participation of epithelia within the target organ itself.

In a mouse models of TIN and lupus, Neilsen[176], Rubin-Kelley[175, 177] and their co-workers have shown that MHC class II bearing murine renal tubular cells may indeed act to present antigen *in vitro*, but it is not clear yet whether cultured *human* tubular cells can present antigen *in vitro* or *in vivo*. Kirby and colleagues[178] have shown recently that untreated cultured human renal epithelial cells cannot induce proliferation of allogeneic cells, but can do so only in the presence of IL-2, present in abundance in human nephritic and rejecting kidneys, as judged by up-regulation of IL-2 receptors on T cells within the organ. For presentation of antigen to take place between an antigen-presenting cell and T-helper lymphocyte, a number of accessory (co-stimulatory) signals may be necessary it the T cell is to become specifically sensitised[175]; again, it is not clear yet if renal tubular epithelium is capable of such accessory signals (see next section) or whether all these *in vitro* data are reflected by events *in vivo*.

However keratinocytes[179] and thyrocytes[173, 175, 180], even though they express MHC Class II antigens, may not be capable of presenting antigen to helper T cells *in vitro*. They may, nevertheless, have important roles in influencing the biological activity of adjacent vascular endothelium[179]. Also, in our study[26] expression of large amounts of MHC class II antigen by 100 % of tubular cells was seen in some patients durint he acute phase of the disease, who later made complete recoveries; so a «vicious circle», if set up, is not necessarily irreversible.

In almost all cases of human TIN studied, we have shown that tubular expression of all MHC class molecules is up-regulated[26] including class I as well as class II (Figures 4b and 6). Increased expression of class I antigen by tubular epithelium would render these cells more susceptible to direct injury by CD8 + ve cytotoxic cells, since this reaction normally takes place in the context of MHC class I recognition[169].

The whole question of the active participation of tubular cells in immunological renal injury has been reviewed by Rubin-Kelley and Jevnikar[175] with especial emphasis on their studies in lupus prone MLR/*1pr* mice, and by Muller et al.[181].

Expression of adhesion molecules by renal tubules

Expression of adhesion molecules such as integrins and selectins[182, 183], for example ICAM-1 and 2, ELAM-1, VCAM, PECAM would also render both hypersensitivity reactions and cytolytic attack more likely, since at least some of these molecules can act as accessory factors during MHC class II-restricted antigen presentation[175], and also in permitting migration of mononuclear cells and leukocytes, by binding to their specific ligands on mononuclear cells (ICAM 1 and 2 to LFA-1; VCAM-1 to CD49/CD29; etc.)[182, 183]. Adhesion molecules also play a role in adhesion of potentially cytolytic cells to their targets, including kidney cells[183] and anti ICAM-1 monoclonal antibodies have been shown to abrogate experimental allograft rejection[185].

In the context of cell adhesion, the CD4 and CD8 molecules characteristic of helper/inducer and cytotoxic T cells respectively also act as accessory factors promoting adhesion, «welding» the cell-cell contact mediated by the MHC-CD3 interaction.

Increased expression of ICAM-1 by human[186, 187] and murine[188] renal tubular epithelial cells has been described in both primary and secondary glomerulonephritis, and *in vitro* this expression is augmented by cytokines such as IL-1 and TNF alpha[181-184]. There are no observations on human TIN as yet. In human nephritic kidneys we have shown that is accompanied by increased display of VCAM-1, interestingly only in renal tubular cells, and not apparently on the peritubular capillary endothelium[189], and without expression of ELAM-1. The ICAM-1 is mainly displayed on immunohistochemical study at the apical part of the tubular cells, in contrast to MHC class II expression, which is mainly basolateral. The functional significance of this observation, if any, is not clear yet[190].

Expression and secretion of cytokines by renal tubular epithelium

Although renal tubular cells *may* produce IL-1[176], this has been questioned[175]. Certainly, however, murine tubular cells are capable of expressing and secreting tumor necrosis factor alpha (TNFα)[191], and recently synthesis of platelet derived growth factor has been described by medullary, but not cortical tubular cells[181]. Human tubular epithelia also secrete C3 *in vitro*[192] and C4[193]. Whether this secretion may lead to damage, to protection, or both, requires further study.

Induction of fibrosis

Since most acute tubulointerstitial nephritides heal, I will not discuss the induction of fibrogenesis, which occurs in a minority of patients. I have dealt with this elsewhere[27], and the reviews of Muller[181] and Kuncio and Nielson[194] can be consulted also.

How is interstitial nephritis triggered?

We must confess almost complete ignorance of how the events just outlined might be released by exposure to a drug or infectious agent. Obviously one possible mechanism is protein binding of the drug so that it forms a hapten, and triggers an immune response to the neoantigen formed by the drug-protein complex. One must also postulate that in some way the drug-protein complex is capable of targetting injury ot the renal tubule, either by

binding to that structure exclusively (as may be the case in methicillin-induced TIN), or by antigenic mimicry. Another possibility is that the agent in some way induces loss of established self-tolerance to tubular antigens, and thus triggers a cell-mediated attack[176].

Any hypothesis must explain also how it is that the vast majority of individuals do *not* develop acute TIN when exposed to common infections or commonly used drugs; millions are exposed, and only a handful develop TIN. Presumably, as in animal models, genetic factors play a major role; but no genetic risk factors have so far been identified, either with the MHC or elsewhere. One possible way genetic factors might operate is through genetically-controlled levels of expression of MHC antigens in reponse to inflammation, both in promoting antigen presentation (class II) and in promoting tubular epithelial cells as targets for cytotoxic lymphocytes (class I); but this is entirely speculative at the moment.

Treatment and outcome

To my mind, there is no good evidence that any treatment other than palliation of anaemia or acute uraemia by transfusion or dialysis, or removal of the precipitating agent if one can be identified, makes any difference to the outcome of primary, infection- or drug-related TIN. Given that these patients are often ill and uraemic, random use of immunosuppression on theoretical grounds does not seem justified. The main exceptions to this sta-

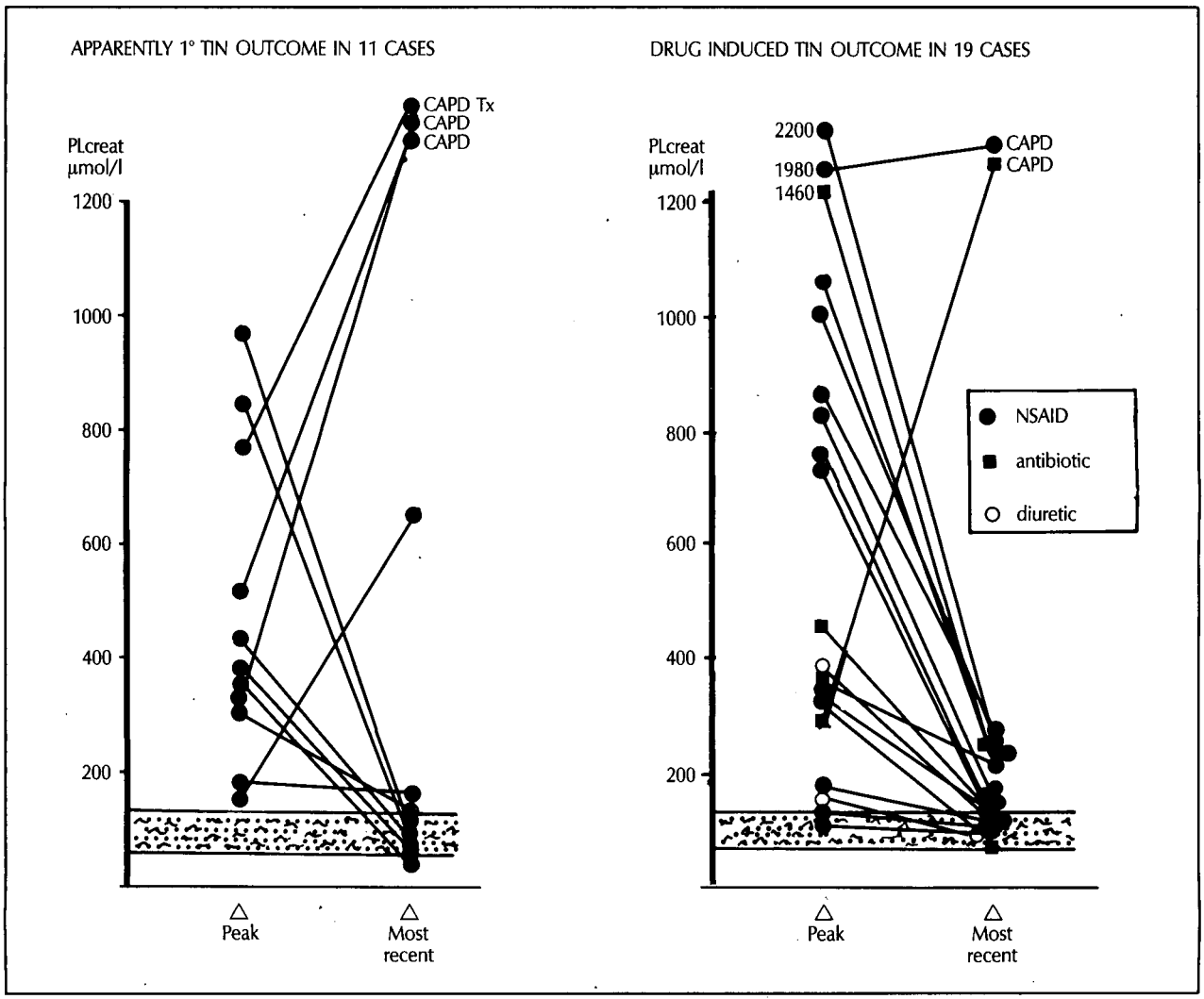

Fig. 7.—Plasma creatinine at presentation in our patients with acute tubulointerstitial nephritis seen between 1980 and 1987: Left, drug-induced; right, apparently idiopathic. Note that in a number of instances recovery of renal function is incomplete. The range of normal plasma creatinine is shown by the shaded box at the bottom of each diagram.

tement are of course those cases of TIN in association with lupus, with sarcoidosis or uveitis, or with vasculitis (see Serra this volume). Also, patients with interstitial granulomas[31,32] might be expected to do better with corticosteroid therapy than others, and their prognosis appears poorer[13]. Another pointer to a poor outlook in most series in the presence of oligoanuria rather than a maintained urine output, but there are many exceptions both ways.

Recovery of glomerular function is usual, but is sometimes incomplete (Figure 7)[22-24,26,86,88] but in assessing this, the age of those suffering from the condition must be taken into account; thus in NSAID-associated acute TIN, the average age in almost all series is 65-75 years. At this age, recovery of glomerular function may be incomplete even in acute tubular necrosis (see Kjellstrand, this volume).

Conclusions

Acute allergic tubulointerstitial nephritis is often missed until the patient is severely ill, and despite a relatively benign outcome in the majority of cases, deserves more attention than it has received. In addition, we have much to learn about the mechanisms of damage in this group of conditions. Treatment centres round the identification and removal of the provoking agent, if one can be identified, and palliation of uraemia by dialysis until renal function recovers. Non-steroidal anti-inflammatory agents should always be remembered as a cause, since the can be obtained off prescription. Corticosteroids will only occasionally be necessary, usually in TIN as a part of systemic disease or in those with interstitial granulomas. In those patients with severe renal failure, dialysis will of course be needed, and the patients will suffer all the problemas of uraemia and failure of electrolyte regulation. Recovery of renal function is usual, but may be incomplete, especially in oliguric and elderly subjects.

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