# TUBULOINTERSTITIAL NEPHRITIS: IMMUNOLOGIC MODELS, PATHOGENETIC MECHANISMS, AND CLINICAL SYNDROMES

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I. Progress in understanding the pathogenesis of interstitial or tubulo-interstitial nephritis (TIN) has been slowed by the myriad of diverse disease processes associated with a cellular infiltrate of renal parenchyma, a misperception of the role of bacterial infection of the kidney, and a paucity of experimental models. In recent years elucidation of the major immunopathogenetic mechanisms causative of glomerular injury and development of several experimental models have resulted in better insights into immunologically mediated tubulointerstitial nephritis.

After some general considerations regarding TIN and its relative importance in medical practice, I will focus discussion to immunologic mechanisms implicated in pathogenesis of TIN in experimental animals and review evidence of immunologic mediation of TIN in human clinical practice.

Tubulointerstitial nephritis is characterized by the presence of inflammatory cells in the interstitium of the kidney in intimate proximity to tubules, associated with a variable amount of tubular distortion, disruption, injury and atrophy. The term implies that the primary focus of inflammation is non-glomerular and non vascular, although both may be involved secondarily. The cells are usually lymphocytes, plasma cells, and macrophages, although polymorphonuclear leucocytes (PMN) and eosinophils maybe conspicuous in certain cases; the cell infiltrates may be focal or generalized, but tend to be primarily cortical. The distinction between acute and chronic interstitial nephritis is not clearly delineated: it is easiest to define when the character of the cellular infiltrate is typical of acute responses, viz, polymorphonuclear and when there is edema rather than fibrosis and scarring. Chronic TIN is marked by absence of PMN's and presence of fibrosis and scar (1). Temporal considerations of clinical events are of little help in

description of lesions pathologically or characterization of their evolution. II. Councilman wrote in 1898 (2), "The textbooks on pathology do not denote much space to this condition. Most authors do not recognize acute interstitial nephtitis as a special type of disease." Yet we are indebted to his excellent paper for a clear description of the occurrence of the problem in the course of several infectious diseases, such as scarlet fever and other streptococcal infections, and in diphtheria. His particular contributions were defining the participation of plasma cells and lymphocytes, establishing the bacteriologically sterile character of the inflammation, and indicating its frequency in the pre-chemotherapeutic and-antibiotic eras.

Three reports of relatively recent vintage are worthy of note, because they document the clinical occurrence of TIN, are associated with recognition that it usually is not caused by bacterial infection of the kidney, and indicate that it is an important morphologic entity associated with progression to renal failure.

Angell et al (3) culled the pathological case files of their service and documented 12 patients with "active," chronic, non obstructive pyelonephritis whose urine cultures consistantly were negative or had trivial growth; 7 of these 12 patients progressed to renal failure, although none had history of or documented urinary tract infection. They suggested that "active chronic pyelonephritis" may not be caused by bacterial infection, and felt that their data indicated that disease progression did not depend on bacterial presence.

On the other hand, Chazan and associates (4) reported 5 patients with severe renal failure which improved spontaneously or with steroid therapy, and in whom they could not ascribe an etiology. The renal biopsies of each had notable edema, round cell infiltrates, and tubular damage.

Finally, Murray and Goldberg (5,6,7) contributed their analysis of the clinical epidemiology of chronic interstitial nephritis. They reviewed charts of patients admitted to the University of Pennsylvania Hospital during a 4 year period; from the 430 patients diagnosed with any form of chronic renal disease they eliminated all who did not have recent onset of renal failure, or whose clinical evaluation suggested primary glomerular or underlying systemic disease. A total 101 patients were considered retrospectively to be instances of chronic interstitial nephritis. Where histopathologic material was available (37 patients), it was confirmatory of the diagnosis. These investigators attempted to relate the interstitial process etiologically to one or more of several possible contributory factors to implicate them in the genesis of the TIN. Table 1 indicates that their best judgment implicated underlying anatomic abnormalities and analgesic abuse as the primary cause in 51% of the patients. Hence, 30% of newly diagnosed renal failure at their institution was thought to represent TIN, and while bacterial infection of the kidney may have contributed, they did not think it was the primary cause of the nephritis in a single instance.

Suki and Eknoyan (8) have written about tubulointerstitial nephritis and their classification encompasses such a variety of diseases as to be encyclopedic (Table 2). Nonetheless, their perspective is very useful because it tabulates effectively the numerous diseases which may be associated with TIN and stresses implicitly the limited ways that the kidney as an organ can respond to diverse injuries.

Having considered some generalities regarding TIN subsequent discussion will be more limited in scope. It is not my intent to dissect the many entities associated with renal interstitial infiltrates (9-25) or toxic renal injury;

instead I will concentrate on apparent immunologic issues, particularly as they relate to the central feature of TIN - cellular infiltrate and renal injury. The character of the infiltrating cells and the circumstances of development of the lesion, particularly in the course of infections and apparent drug reactions, have raised issues regarding pathogenesis of TIN and relationship to immunologic mechanisms. In recent years experimentalists have induced several models of TIN, and inferences derived have been useful in consideration of the problem. I will attempt to analyze them and synthesize the general principles involved.

## III. Antibiody-mediated experimental models of TIN

### A. Tubular basement membrane (TBM) antibodies

Induction of glomerular antibody-mediated autoimmune glomerulonephritis with glomerular-rich fractions of heterologous species concomitantly raises antibodies which react to tubular basement membranes. In vivo fixation of these antibodies is seen as membrane-bound IgG on the TBM; eluates from such kidneys contain IgG which will bind to TBM of an indifferent, non-immunized recipient (26,27). In such animals the heavier Ig deposits are to glomeruli, and the experimental disease is manifested primarily by glomerular injury, tubular involvement has been considered an associated but less important facet of the experimental disease (Tables 3,4).

TBM antibodies also can be elicited by immunizing susceptible rats with a kidney suspension in adjuvant and pertussis vaccine (28); although the rodents develop membranous glomerulonephropathy, the first demonstrable events are severe TIN with tubular Ig fixation, complement ($C^1$) participation, PMN infiltrates followed by round cells, tubular destruction, and apparent renal glucosuria. Use of bovine TBM as immunogen elicits a primary TIN without

glomerular involvement (29). In these last two models the pathogenicity of the antibodies has been established by elution and transfer experiments.

The guinea pig also is susceptible to induction of TIN caused by TBM antibodies. As described by Steblay and Rudofsky (30), the disease is induced by TBM in adjuvant, is caused by circulating antibodies which bind to cortical TBM; this is followed by a round cell infiltrate, tubular disruption, giant cell formation, renal glucosuria, and eventually fatal renal failure. This model has been most informative. Passive transfer of serum antibody induces TIN predictably within days (31), providing an accelerated disease in which all the features of the actively induced model are operative. Initial Ig fixation is required, and it is complement mediated, apparently through the alternative complement pathway (32-34); subsequent events depend on an initial influx of radiosensitive cells derived from the bone marrow, apparently not PMN's (35,36). Once the mononuclear infiltrate is established, TIN progresses and cannot be restrained by radiation. The disease depends on Ig and C'3; in the absence of either TIN does not occur. Moerover, it progresses by cell mediation; without radiosensitive cells it does not occur. Further, the lesions are not induced by cell transfers from immunized animals (37).

Hall and coworkers (38) have defined an important phenomenon in this model by transfer of TBM antibody-rich $IgG_1$ or $IgG_2$ isotypes. Characteristic TIN was induced with either isotype; however, TBM antibody titers at day 14 were higher than could be accounted by the passive transfer, and contained both isotypes. Hence, they have documented the induction of autoimmune autologous anti-TBM antibodies, and suggested that such recruitment ("autoimmune amplification") is a crucial event in the induction of the progressive TIN. Whether radiosensitive cells are required to recruit macrophage and monocyte

mediation or to initiate autoantibody production is not clear, but there are no data presently which support a role for delayed-type hypersensitivity in this model despite the characteristic round cell infiltrate.

B. Circulating immune complexes

In contrast to antibodies with TBM specificity, circulating immune complexes also can cause TIN. Experiments by Brentjens et al (39) in rabbits injected with bovine serum albumin (BSA) indicated that extraglomerular renal immune deposits of antigen, Ig, and C'3 occurred in chronic but not in acute serum sickness. By light microscopy there was evidence of cellular infiltrates particularly in the cortex, with fraying and splitting of TBM, tubular atrophy, and fibrosis in those animals making a vigorous antibody response. Electron microscopy showed dense deposits, presumed to be immune deposits, in the walls of peritubular vessels, in interstitium, along TBM, and in Bowman's capsule. In this model the presumed pathogenesis is deposition of circulating immune complexes initiating a phlogogenic response.

C. Immune complex in situ

Immune complexes formed in situ also can cause tissue injury (40) and TIN. In the rabbit immunized repetitively with suspensions of homologous rabbit kidney homogenate (41) or supernate (42) discontinuous deposits of Ig form along the tubular basement membranes of proximal tubules. This leads to tubular degeneration, atrophy, cortical and even medullary fibrosis with a sparse mononuclear cell infiltrate, and renal glucosuria. Transfer of serum caused similar, though focal, proximal tubular Ig deposits; using fluoresceinated eluates Klassen et al (43) were able to show binding of eluted Ig to lesions of diseased kidneys, as well as binding to proximal tubule cell cytoplasm. They postulated that the deposits were immune deposits formed locally by

antigen diffusing from proximal tubule cells in an animal with circulating antibodies specific for those antigen(s).

Autoimmune TIN also can be induced by immunization of rats with a product of cellular secretion - Tamm Horsfall protein (THP), a normal component of urine and major component of urinary casts. In rats immunized with THP in adjuvant with pertussis vaccine, nodular deposition of rat IgG and C'3 occurs along the basal portions of thick ascending limb of Henle's loop and early distal tubule, the cells which apparently produce and secrete THP. Following Ig deposition a round cell infiltrate occurs (44).

D. Cytotoxic antibody

Several tubular lesions were associated with TIN in Sprague - Dawley rats immunized by homologous rat kidney in adjuvant and pertussis vaccine (45). Although these rats also developed glomerular disease, TIN is an unusual feature. Rats developed granular deposits of Ig and C'3 along proximal tubules and often in tubule brush borders; in addition, some rats had *in vivo* Ig staining of ascending thick limb of Henle's loop and distal tubule. Sera from these animals stained corresponding sites of normal rat kidney sections, suggesting not only *in situ* immune complex formation but the possibility of cytotoxic antibodies as well.

E. Locally produced antibody

Canine adenovirus infection in susceptible dogs results in a marked cellular response in the interstitium (46). In the lesions viral antigen can be demonstrated by immunofluorescence in infected tubule cells; moreover, using the same technique, plasma cells containing anti CAV antibody were shown in the vicinity of the lesions. Anti CAV antibodies were eluted from kidneys of 2 animals. The data suggest that locally produced antibody may contribute to the interstitial

nephritis (47).

IV. Cell-mediated models of TIN

A. Delayed-type hypersensitivity

There have been no suitable models for cell-mediated immunological injury causing interstitial nephritis. Lehman and Wilson (48) attempted cell transfers from BN rats immunized with TBM into non-immunized recipients by inoculating the cells directly under the renal capsule; although mild focal lesions resulted, they concluded that sensitized cells are not central to the pathogenesis of the nephritis.

However, Van Zwieten and associates (49) succeeded in eliciting interstitial inflammation with histologic characteristics of delayed hypersensitivity in renal cortex of both rats and guinea pigs by direct intrarenal injection of heat-aggregated bovine gamma globulin in previously sensitized animals; moreover, cell transfer experiments in the rat succeeded in transferring the reactivity to non-immunized rodents.

V. Uncertain mechanisms of TIN

There are a number of other models of tubulointerstitial nephritis of uncertain mechanism. Included in this category are spontaneous TIN in CBA/J mice, TIN with LCM viral infection in SWR/J strain mice, and TIN following repetitive immunization of rats with E. coli in adjuvant. There are suggestions that these may be mediated by cellular mechanisms but insufficient data are available at present (50-53).

Despite the difficulties in establishing a model of primary cell-mediated immune response causative of TIN, and the preponderance of experimental data implicating humoral mechanisms eliciting a cellular infiltrate, nonetheless these models have provided us with several important principles:

1. In general, antibody binding (or immune complex localization) is the pivotal event in eliciting TIN: cellular infiltrates occur subsequently. Such cell responses may or may not be polymorphonuclear-dependent, and a role is seen for the monocyte as a critical effector of inflammatory response.

2. Secondary, complicating, or mixed autoimmune mechanisms may operate concomitantly or sequentially; for example, TBM antibodies may occur in immune complex glomerulonephritis.

3. Passive administration of isotype-specific TBM antibodies in the guinea pig can cause loss of natural tolerance to autologous antigens and secondary autoantibody production. This phenomenon called "autoimmune amplification" has important implications.

4. After initial fixation of antibody and initiation of TIN, the pathogenetic antibodies may be difficult to demonstrate.

5. TIN may progress by fibrosis and atrophy in the presence of a scant cellular infiltrate.

6. Genetic factors have a crucial role in several of the models. This is expressed as ease or resistance to antibody induction; it is also reflected in apparent resistance to nephritogenic sequellae of antibody binding when an excess of antibody is transferred passively (54,55). Moverover, the importance of antigen deletion or of antigenic differences represented in organs has been demonstrated by active immunization (29), serum transfer (55), and renal transplantation (56).

## VI. Clinical tubulointerstitial nephritis

Clinical interest in tubulointerstitial nephritis has developed concomitantly

with elucidation and analysis of experimental models. This has been fostered and emphasized principally by McCluskey and his associates (57-59). The numbers of cases of TIN studied thoroughly by immunopathologic methods are relatively few; nevertheless, certain groups of patients are conspicuous, either because of their similarity to the apparent pathogenetic mechanisms of the experimental models or because of the similarities of their clinical presentation.

A. The most frequently recognized tubulointerstitial nephritis due to systemic disease occurs in systemic lupus erythematous (SLE) with kidney involvement (60,61). Brentjens et al reported a detailed analysis of renal biopsy material from 45 patients with SLE, and compared them to 34 patients with membranous nephropathy (MN) and 80 patients with minimal glomerular disease (MGD) (Table 5). Their data show that TIN occurs frequently with SLE, more consistently and severely in diffuse proliferative glomerulonephritis (89%), but also occurs with great frequency in kidneys showing less severe glomerular changes (60). They also demonstrated interstitial binding of antisera with specificity for thymidine and cytosine, reactive with denatured DNA, in 19% of all these SLE kidneys tested - suggesting that TIN, like SLE glomerulonephritis, is due to immune complexes of DNA and anti-DNA, persumably from circulating immune complexes. In contrast, significant mononuclear cell infiltrates were present only in 8 to 10% of kidneys with MN or MGD; immunofluorescent tests in these latter kidneys indicated extraglomerular deposits of Ig associated with TBM and/or interstitium in only 1 of 111 patients.

B. TIN in primary glomerulonephritis

On the other hand, focal localization of Ig to tubules occurs frequently in GBM antibody-mediated glomerulonephritis. Wilson and Dixon (62) have indicated

its frequent occurrence in Goodpasture's syndrome due to GBM antibodies, and Lehman et al (63) reported that extraglomerular Ig deposits were detected most often in the kidneys from three groups of patients: anti-GBM nephritis, SLE, and renal allograft recipients. Tubular Ig in GBM nephritis is due to TBM antibodies, as demonstrated in eluates.

Despite the frequency of tubular and interstitial Ig deposits in these groups, their pathogenetic relevance to human nephritis is largely circumstantial and inferential, because of the usually severe character of clinical and morphologic disease attributable to concomitant glomerular involvement. This relationship is typified by the recent report by Andres et al (64) who reported severe TIN in patients with crescentic glomerulonephritis due to anti-GBM disease and concomitant TBM antibodies, whereas crescentic glomerulonephritis due to GBM antibodies only or caused by mechanisms other than GBM and TBM antibodies had mild to moderate interstitial nephritis. It is difficult to judge the relative pathogenetic impact of the tubulointerstitial Ig deposits in the absence of precise quantitative estimates of antibody (29) and immune complex load.

Other reports detail apparent immunologically mediated TIN in association with or in the course of glomerulonephritis. THe several cases reported from a single center (65) would suggest that immunologically mediated TIN is a more common event than the few individual case reports would suggest.

Morel-Maroger (66) described the case of a 40 year old man with severe, apparent post-streptococcal glomerulonephritis who had serial renal biopsies during his 28 week illness. Whereas biopsies 1 and 2 were essentially free of interstitial inflammation and tubular Ig deposits, biopsies 3 and 4 had severe TIN in addition to glomerular disease, and extensive TBM staining (at biopisy 4);

TBM antibodies were detected in the patient's serum. Tung and Black (67) described a similar case complicating nephrotic syndrome due to membranous nephropathy; this patient had extensive TIN and glomerular Ig deposits along TBM apparently antedating the development of circulating TBM antibodies. Their patient later developed clinical evidence of Fanconi syndrome. Levy et al (68) described a case of Fanconi syndrome in a child in whose renal biopsy membranous nephropathy was associated with linear Ig deposition on many tubule basement membranes. The youngster had circulating antibodies reactive with TBM and pulmonary alveolar basement membranes, but not GBM; he later had several bouts of pulmonary infiltrates apparently due to intraalveolar hemorrhage. In all three of these causes there were circulating TBM antibodies, TIN, and TBM deposits of immunoglobulin. Nevertheless, the sequence of clinical events, as well as histologic evidence of TIN before TBM antibodies were detectable in two of the cases, raised doubt that the TBM antibodies were primarily responsible for TIN.

A patient reported by Shwayder et al (69), who had received multiple prior courses of antibiotics, was studied because of development of nephrotic syndrome and Fanconi syndrome. The patient with apparent immune complex glomerulonephritis also had Ig fixation to proximal tubule cells and a severe TIN. The patient's serum contained antibodies to proximal cell antigen, and cryoprecipitate isolated from serum contained renal tubular epithelial (RTE) antigen and RTE antibodies. No TBM antibodies were detected.

C. Primary tubulointerstitial nephritis

Bergstein and Litman (70) studied a 6 year old boy with primary TIN who had linear Ig deposits along TBM, circulating TBM antibodies, and renal tubular acidosis with glucosuria.

D. TIN with Sjögren's syndrome and renal tubular acidosis (RTA)

Numerous reports attest to the occurrence of RTA in some patients with Sjögren's syndrome (SS), a disorder characterized by a variety of autoimmune and serological abnormalities. Renal biopsies have been done in several patients with SS (71-75), and TIN with round cell infiltrates has been thought by some (73) to be the most characteristic histopathologic abnormality in the SS kidney. Shioji and coworkers (76) studied 14 patients with SS; 4 had RTA and 10 did not. Renal biopsies done in the 4 RTA patients indicated a TIN or scarring; 4 of the 10 non-RTA patients were biopsied also, and no abnormalities were noted.

Relatively few reports describe immunohistochemical studies of kidneys in patients with SS; most are negative, or describe fluorescence of the cellular infiltrate (77). Other reports describe intracytoplasmic granules in tubule cells (71,78). However, Winer and associates (79) described a 49 year old man with established SS who developed TIN; by biopsy he had irregular granular deposits of IgG and C'3 along many TBM. His findings were thought to be compatible with TIN caused by immune complex formation in situ.

There are few studies which implicate immunologically mediated TIN in RTA. Pasternack and Linder (80) described 4 patients with distal RTA and renal mononuclear call infiltrates particularly involving distal tubules. All patients were reported to have "Ig localized to the tubuli and interstitial infiltrations surrounding the tubuli. The tubular cytoplasmic fluorescence was homogeneous, and continuous with that of occasional tubular casts --." All 4 patients had serologic evidence of numerous autoimmune antibodies, including ANF in all four. Additionally, Ford has described occurrence of antibody to Henle loop cells found in 6 patients whose renal function was not studied (81);

Chanarin et al (82) reported 2 patients who had Henle loop antibodies, one of whom had RTA. Feest and associates perferred renal biopsies in 10 patients with distal RTA (83); TIN was usually associated with nephrocalcinosis and/or recurrent urinary tract infection. Immunofluorescent test of the biopsies showed no Ig or C'3 deposits relative to interstitium.

Hence, there are few data which link humoral mechanisms to TIN in Sjögren's syndrome or to RTA, except in the cases enumerated in sections VIB,C above. Although the pathogenesis of SS is uncertain, TIN when it occurs, may contribute to tubular functional abnormalities and RTA by anatomic disruption, by secretory products of the infiltrating cells, or by some facet of cellular immunity.

E. Obstructive uropathy and vesicoureteral reflux

As described several months ago by Dr. Hull, chronic atrophic or non-obstructive pyelonephritis may be a misnomer. The cellular infiltrates, cortical scars, and tubular atrophy consequent to reflux nephropathy need not be caused by bacterial invasion of renal parenchyma (84). Indeed, renal insufficiency caused by vesicoureteral reflux may be irreversible and relentlessly progressive (85). Similarly, obstructive nephropathy may lead to interstitial cell response, fibrosis and TIN (86). The pathogenesis of TIN in both vesicoureteral reflux and obstructive uropathy and pyelotubular backflow is not established for certain. However, Tamm-Horsfall mucoprotein (THP), a normal constituent of urine, is apparently synthesized in ascending limb of loop of Henle cells, and in the early distal tubule (87,88). Experimentally, pigs with vesicoureteral reflux and pyelotubular backflow develop circulating antibodies to THP - suggesting a backleak into the circulation of THP directly or via lymphatics (84;89); antibodies to THP also occur in people. Indeed, THP has been visualized in the glomerular capsular space in renal biopsy material (90).

Moreover, large interstitial deposits of periodic acid-Schiff positive material have been detected in many cases of vesicoureteral reflux, obstructive uropathy, and tubulointerstitial nephritis (91,92); these deposits stain with antibodies specific for THP, suggesting that the deposits are sequestered THP caused by extravasation. The cellular infiltrates surrounding these deposits suggest that they may be primary foci of an immunologically mediated inflammatory response.

F. Drug reactions

Drug-induced TIN has been described most frequently as a complication of sulfonamide therapy, and as a reaction to penicillin derivatives and congeners, rifampin, and a miscellaneous group of drugs such as phenindione, phenytoin, phenylbutazone, and diuretics (93,94). The frequency of this clinical problem undoubtedly is underestimated, and the circumstances of its development are unpredictable. One of the most awkward aspects of drug reactions in general, and TIN specifically, is that affected patients often are on several drugs concomitantly or have exposure histories to several drugs which could be the sensitizing agent. Hence, incriminating a single agent may be based on suspicion only (59). It is important to be mindful of cross-sensitivity that may occur between related classes of drugs by virtue of the similarity or sharing of hapten groups.

1. Schrier and his associates (96) called attention to the nephropathy complicating use of penicillin and homologues; two of the four cases they reported had microscopic evidence of angiitis and glomerulonephritis. Recent reports have emphasized the TIN in absence of glomerular involvement.

Baldwin et al (97) reported 7 cases of apparent TIN complicating penicillin or methicillin usage; one case was studied immunopathologically and a humoral

mechanism was suggested. Kidney sections of one patient stained along GBM, TBM, and in the interstitium for IgG and dimethoxyphenylpenicilloyl (DPO), the major heptenic antigenic determinant of methicillin (97,98). The patient's serum contained BPO specific antibodies, and skin tests later were positive to penicilloyl-polylysine. They suggested that penicillin derivatives may couple normally to structural kidney proteins, and that TIN results from an unusual immune response in certain individuals. Alternatively, affected individuals may be uniquely predisposed to form hapten-kidney conjugates.

Border et al (99) reported studies from a patient who developed TIN, presumably secondary to methicillin. The patient's renal biopsy had linear TBM staining of cortical tubules for C'3 and IgG; methicillin hepten, presumably DPO, was similarly located. His serum contained TBM antibodies, but not methicillin antibodies. Among other possibilities, the investigators suggested that drug derivative (hapten) could bind to TBM and induce antibodies capable of binding to native or altered TBM.

Since then, at least 9 other patients with TIN have been discribed (97,99, 63,94,100-104) who had immunological studies that demonstrated TBM staining for IgG (4 cases), hapten localization to renal tissue (3 cases), and circulating TBM antibodies (5 cases); see Table 6. Numerous reports have described negative immunofluorescent tests of renal tissue during TIN associated with or complicating these same drugs, and no evidence of circulating TBM antibodies (99,105-107). Hence, although there clearly are cases in which humoral mechanisms appear to be implicated in drug-induced TIN, multiple mechanism may operate.

2. Other drug-associated TIN

Despite the frequent clinical use of diuretic agents, reported instances of alleged or suspected TIN are scant (108-112). Such reactions seem to be

reflected in deteriorating renal function, abnormality of urinary sediment, proteinuria or eosinophilia. There are no significant immunopathologic observations in this group which link TIN to recognized humoral mechanisms, such as those described in experimental animals.

Numerous other drugs have been implicated in hypersensitivity reactions characterized as TIN; few reports detail immunopathologic information that implicates humoral mechanisms to the clinical problem.

The patient studied by Hyman, Ballow, and Knieser (113), however, clearly implicated phenytoin to TIN: renal tissue showed IgG fixed to cortical TBM, and circulating TBM antibodies were detected in serum; DPH hapten was demonstrated by immunofluorescence along cortical TBM, in interstitium, and in walls of small arterioles. In addition, lymphocyte transformation was demonstrated to DPH by patient's lymphocytes cultured in vitro. The report by Gabow et al described IgG, IgA, and C'3 around renal tubules, but insufficient detail precludes interpretation in that patient, who had received rifampin.

Hence, TIN associated with drug reactions is a regular phenomenon, probably occurring more frequently than is reported. Relatively few of the reported cases have been studied immunopathologically.

Several comments are in order: (1) Although studies in the majority of reported cases of TIN complicating drug therapies have failed to demonstrate tissue-bound Ig and/or circulating TBM antibodies, nevertheless, several such cases have been documented. In view of the importance of timing in demonstrating the sequence of immunologic events in animal models of TIN, and the difficulties in some of those models in demonstrating tissue bound Ig late in the disease, the negative studies reported in some people may not be interpretable absolutely that humoral mechanisms are not operative. (2) The

pathogenicity of human TBM antibodies has not been demonstrated by transfer experiments, nor has their in vivo binding been quantified; moreover, few eluates have been studied. Such studies are necessary to define whether tissue-bound Ig is directed toward native TBM, or to TBM-hapten complexes. (3) The frequent association of markedly increased serum IgE concentrations (104,114) and eosinophilia in some of these TIN patients suggest that antibody mediation may play an important role by as yet undefined mechanisms.

Further, the central role by the kidney in excretion of at least some portion of the drugs or their metabolites may be a crucial determinant in the clinical expression of sensitivity reactions as TIN. Sulfonamide derivatives, penicillin and its congeners, diuretic agents such as thiazides, phenindione, and rifampin may be excreted through secretory sites within the renal tubule, and their net disposition modified by reabsorption. Additionally, many of these agents undoubtedly bind to active sites within the nephron where they have a defined locus of action. Such excretory routes and binding sites offer the potential for creating uniquely high concentrations of drug that facilitate drug-tissue binding and perhaps contribute to the pathophysiology of TIN in the sensitized recipient. The degree to which other homeostatic derangements such as drug-drug interactions and inhibition of prostaglandin synthesis within the kidney may also contribute to these overall events has not been defined.

## VII. Local experience with tubulointerstitial nephritis

It is difficult to estimate what our local experience with TIN comprises. Renal biopsy in Dallas and in our own institution is done in a sporadic, unsystematic manner, which makes general inferences impossible.

Nevertheless, I have examined by immunofluorescent techniques renal

biopsy specimens of native kidneys from 138 patients during the past 2 years. Important - in some cases predominant - evidence of tubulointerstitial nephritis with immunoglobulin deposits was seen in 12%. Ten of the 17 patients had SLE; however, 7 had primary or complicating TIN not related to SLE, associated with renal failure.

I have not discussed renal allografts in this presentation. TIN unassociated with the cellular infiltrates characteristic of renal rejection, may occur in renal grafts. It usually has been marked by TBM immunoglobulin deposits (63) characteristic of TBM antibodies. My own studies, performed in collaboration with Dr. Peter Stastny, indicate that other circulating antibodies operate in some of these patients, in addition to TBM antibodies, and probably contribute to organ damage.

In summary, tubulointerstitial nephritis is an important cause of renal disease and renal failure in people. Experimental work has established several animal models of immunologically mediated TIN: the principal mechanisms are consequent to TBM antibodies or immune complex disposition. In many cases the immune complexes appear to form locally from antibody binding to soluble cellular components or products. Immunologic and histopathologic techniques have documented that these same mechanisms apparently also are operative in people. Delayed type hypersensitivity executed by cellular mechanisms can be induced in animal kidneys, but it is not clear whether spontaneous TIN in animals and TIN in the course of certain diseases in people are operative by this mechanism.

Drug reactions cause TIN in many patients. The mechanisms by which this occurs are not clear, although some patients have definite evidence of circulating autoantibodies and tissue immunoglobulin deposits. Because of

frequent eosinophilia, eosinophilic renal infiltrates, and elevated serum IgE concentrations, undocumented mechanisms, including reaginic antibodies, may participate.

TABLE 1

ETIOLOGIC FACTORS OF INTERSTITIAL NEPHRITIS IN 101 PATIENTS

| FACTORS | PRIMARY | SECONDARY |
|---|---|---|
| ANATOMIC ABNORMALITIES | 31 | 0 |
| ANALGESIC ABUSE | 20 | 0 |
| HYPERURICEMIA | 11 | 0 |
| NEPHROSCLEROSIS | 10 | 7 |
| STONES | 9 | 3 |
| SICKLE CELL DISEASE | 1 | 1 |
| RENAL TUBERCULOSIS | 1 | 0 |
| BACTERIAL URINARY TRACT INFECTION | 0 | 27 |
| MULTIPLE | 7 | |
| INDETERMINATE | 11 | |

From Murray & Goldberg

TABLE 2

CAUSES OF TUBULOINTERSTITIAL RENAL DISEASE

(Suki & Eknoyan)

1. PHYSICAL FACTORS: RADIATION NEPHRITIS
2. ENVIRONMENTAL: BALKAN NEPHRITIS
3. IMMUNOLOGICAL FACTORS: TRANSPLANT REJECTION
4. HYPERSENSITIVITY: SULFONAMIDES
5. TOXIC FACTORS: ANALGESIC ABUSE
6. METABOLIC FACTORS: HYPERCALCEMIA
7. DISORDERS DUE TO NEOPLASMS: LEUKEMIA
8. VASCULAR FACTORS: ARTERIOLAR NEPHROSCLEROSIS
9. OBSTRUCTION: OCCLUSIVE
10. HEREDITARY DISORDERS: HEREDOFAMILIAL NEPHRITIS
11. INFECTIOUS DISORDERS: PYELONEPHRITIS

TABLE 3

EXPERIMENTAL IMMUNOPATHOGENETIC MECHANISMS OF TUBULO-INTERSTITIAL NEPHRITIS

I. ANTIBODY-MEDIATED

- A) TUBULAR BASEMENT MEMBRANE ANTIBODY
  - 1. AS PRIMARY MECHANISM
  - 2. AS SECONDARY MECHANISM
- B) CIRCULATING IMMUNE COMPLEXES
- C) IMMUNE COMPLEX FORMATION, IN SITU
  - 1. AGAINST FIXED ANTIGEN
  - 2. AGAINST DIFFUSIBLE ANTIGEN
- D) CYTOTOXIC ANTIBODY
- E) LOCALLY-PRODUCED ANTIBODY

II. CELL-MEDIATED

- A) DELAYED TYPE HYPERSENSITIVITY
  - 1. AUTOLOGOUS ANTIGENS
  - 2. EXOGENOUS ANTIGENS
- B) TRANSPLANTATION

III. UNCERTAIN

- A) CYTOMEGALOVIRUS, LCM VIRUS INFECTIONS
- B) E. COLI WITH ADJUVANT

TABLE 4

TUBULOINTERSTITIAL NEPHRITIS IN EXPERIMENTAL MODELS

| | | IMMUNOPATHOGENETIC MECHANISM OF | |
|---|---|---|---|
| | IMMUNOGEN USED | GLOMERULAR DISEASE | TUBULOINTERSTITIAL DISEASE |
| I. GLOMERULONEPHRITIS WITH TIN | | | |
| 1. | GBM | GBM ANTIBODY | TBM ANTIBODY |
| 2. | KIDNEY SUSP IN RAT | IMMUNE COMPLEX | IMMUNE COMPLEX; CYTOTOXIC |
| 3. | KIDNEY SUSP IN RAT | (IMMUNE COMPLEX) | TBM ANTIBODY |
| 4. | SOLUBLE ANTIGEN | IMMUNE COMPLEX | IMMUNE COMPLEX: CIRCULATING |
| II. PRIMARY TUBULOINTERSTITIAL NEPHRITIS | | | |
| 5. | KIDNEY SUSP IN RABBIT | | IMMUNE COMPLEX: IN SITU |
| 6. | TBM IN GUINEA PIG | (ANTI GBM) | TBM ANTIBODY |
| 7. | TBM IN RAT | | TBM ANTIBODY |
| 8. | THP | | IMMUNE COMPLEX: SECRETORY PRODUCTS |

TABLE 5

COMPARATIVE TUBULOINTERSTITIAL DISEASE IN THREE GROUPS OF PATIENTS WITH KIDNEY DISEASE (BRENTJENS)

| | | |
|---|---|---|
| SYSTEMIC LUPUS ERYTHEMATOSUS | | |
| FOCAL PROLIFERATIVE | 9/17 | |
| MEMBRANOUS | 5/10 | |
| DIFFUSE PROLIFERATIVE | 16/18 | |
| OVERALL | | 30/45 |
| IDIOPATHIC MEMBRANOUS GLOMERULOPATHY | | 3/34 |
| MINIMAL GLOMERULAR DISEASE | | 8/80 |

TABLE 6

IMMUNOPATHOLOGIC STUDIES IN TIN OF PENICILLIN CONGENERS

| | | RENAL BIOPSY: IMMUNOFLUORESCENT LOCALIZATION OF | | CIRCULATING ANTIBODIES | | SKIN |
|---|---|---|---|---|---|---|
| AUTHOR | PATIENTS | Ig | HAPTEN | TBM | PENICILLIN | TESTS |
| BALDWIN | 1 | + | + | ND | + | + |
| BORDER | 1 | + | + | + | - | + |
| LEHMAN | 1 | + | + | - | | - |
| COLVIN | 1 | + | + | | | |
| MAYAUD | 1 | (INADEQUATE BIOPSY) | | + | | |
| COGAN | 1 | + | + | ND | ND | ND |
| APPEL | 1 | + | - | - | | |
| MÉRY | 1 | - | ND | + | | |
| | 2 | - | ND | + | | |
| OOI | 1 | - | ND | + | | |
| | 2 | + | ND | + | | |
| | 11 | 7/10 | 5/11 | 6/7 | 1/3 | |

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