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Tubulo-interstitial Nephropathies—A Pathophysiologic Approach

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, CA 94143.

DR. SCHMID: **This grand rounds' presentation will focus on interstitial renal disease. Dr. Martin Cogan from the Division of Nephrology is the discussant.*

DR. COGAN:† Interstitial diseases of the kidney have assumed increased importance for internists as three facts have emerged in recent years. First, it has been estimated that as many as a third of all patients with end-stage renal disease have a primary chronic interstitial process as a major pathologic factor in their loss of renal function.[1] As the complexity and cost of caring for patients with end-stage renal disease continue to escalate, it would behoove us to augment our efforts to identify and treat these chronic interstitial diseases. This is especially important because many types of interstitial kidney disease, such as analgesic abuse nephropathy, are preventable. Second, as opposed to glomerulonephritis, it is now firmly established that many forms of interstitial nephritis can be easily and quickly treated. Compared with the controversy surrounding the efficacy of various treatment programs for lupus or membranous glomerulonephritis, there is no doubt that many forms of interstitial nephritis can be dramatically reversed by corticosteroid therapy or by simply removing an offending toxic or immunologic agent. Third, there has been an increasing awareness that particular acid-base and electrolyte disorders accompany interstitial but not glomerular diseases of the kidney. Such tubular dysfunction seems inevitable if one looks at the pathologic features—interstitial involvement of the kidney almost always involves pronounced tubular destruction. Conversely, a primary tubular insult can evoke an interstitial inflammatory response. Because of this close pathologic and physiologic association, I prefer the somewhat more cumbersome term of tubulo-interstitial nephropathy, to emphasize the functional (tubular) aspects of the disease process.

In this review, we will consider the general immunologic mechanisms mediating injury in the tubulo-interstitial nephropathies. We will then move briefly through a summary of the specific acute and chronic tubulo-interstitial nephropathies. Finally, before emphasizing the treatment aspects, we will concentrate on the various fluid, acid-base and electrolyte abnormalities that characterize these disorders and propose a new classification system based on these pathophysiologic

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ABBREVIATIONS USED IN TEXT
GFR = glomerular filtration rate
RTA = renal tubular acidosis

features. Recognition that such electrolyte derangements exist may be the tip-off that a renal disease, specifically a tubulo-interstitial nephropathy, is present. On the other hand, if the diagnosis of a tubulo-interstitial nephropathy has already been made clinically or by biopsy, one should be on the lookout for such electrolyte disorders so that treatment can begin before the patient is in jeopardy.

Immunologic Pathogenesis

Most tubulo-interstitial nephropathies have as a pathogenetic basis one of two fundamental immunologic mechanisms. In both, immunoglobulin deposition evokes cellular infiltration of the kidney parenchyma, with lymphocytes, monocytes and eosinophils. Some of these cells, especially eosinophils, find their way into tubule lumens and can be recovered in the urine. Examination of urine specimens for eosinophils should always be done in cases of suspected tubulo-interstitial nephropathy. Fever and rash likewise are commonly part of the allergic response.

The two forms of immunologic process that cause tubulo-interstitial disease are very similar to the immunologic processes that cause glomerulonephritis: (1) direct attack of antibodies against the basement membrane and (2) deposition of antigen-antibody complexes near basement membranes.[2-4]

The first type is the antitubular basement membrane form. If the immunoglobulins were to be directed against pulmonary or glomerular basement membranes, Goodpasture disease would ensue. Instead, the immunoglobulins, especially IgG, are formed against renal tubular basement membranes. The prototype for this process is methicillin-induced tubulo-interstitial nephropathy.[5] In this case, antibodies are formed against part of the methicillin molecule, the dimethoxyphenyl penicilloyl moiety. These antibodies then cross-react with the renal tubule basement membrane and evoke a round cell infiltration. A linear immunofluorescent pattern is observed. Specific attack on either proximal or distal tubule basement membranes has been described.

The second type of immunologic injury can be evoked if an antigen combines with antibody and then becomes deposited alongside the renal basement membrane.[2-4] This is the tubulo-interstitial equivalent of some forms of glomerulonephritis.

TABLE 1.—*Causes of Tubulo-interstitial Nephropathies*

ACUTE TUBULO-INTERSTITIAL NEPHRITIDES	
Associated with drugs:	Associated with infection:
Methicillin	Bacterial
Penicillin and derivatives	Granulomatous
Cephalosporins	Tuberculosis and leprosy
Sulfa derivatives	Sarcoid
Antitubercular drugs	Leptospirosis
Antiepileptic drugs	Toxoplasmosis
Allopurinol	Syphilis
Phenacetin	Mycetoma
	Viral (especially mononucleosis)
Associated with immunologic diseases:	Secondary to interstitial inflammation:
Transplant rejection	Pyelonephritis
Sjögren syndrome	Acute tubular necrosis
Lupus	Toxic
Idiopathic	Secondary to primary glomerular disease or vasculitis
CHRONIC TUBULO-INTERSTITIAL NEPHROPATHIES	
Metabolic	Immunologic
Hypercalcemia	Sjögren syndrome
Hyperuricemia	Lupus
Sickle cell	Transplant rejection
Paroxysmal nocturnal hemoglobinuria	Toxic
Hyperoxaluria	Analgesic
Neoplastic	Balkan
Multiple myeloma	Hereditary
Leukemia	Polycystic
Lymphoma	Medullary cystic

In those kinds of glomerulonephritis, an immunofluorescent pattern of granular immune complex deposition occurs, such as in poststreptococcal, membranous or lupus glomerulonephritis. When such immune complexes are deposited by unknown determinants in the interstitium rather than in the glomerulus, a monocellular infiltration arises. The prototype of this form of tubulo-interstitial nephropathy is lupus, in which proximal and distal basement membrane immune complex deposition can uncommonly be as severe as in the glomerulus.[6]

Causes

With this brief background for the immunological basis of tubulo-interstitial nephropathies, let us examine some of the agents that provoke such a response. Because tubulo-interstitial nephropathies may be either acute or chronic, we will separate them and consider the acute forms first. *Acute tubulo-interstitial nephritis* usually occurs from one to three weeks after an agent is introduced.[7-9] It is characterized by a decrease in glomerular filtration rate (GFR) that may be mild to severe. Typically, if the process is mild and slower, the patient will be nonoliguric. If the process is more rapid, the GFR will decline quickly, the patient will be oliguric, and the acute renal failure may have to be treated with dialysis. Processes that can evoke acute interstitial nephritis are listed in Table 1[7,9] and basically can be divided into those associated with drug administration, immunologic disorders, an idiopathic form, infections, inflammatory processes, and those secondary to other renal or vasculitic processes. The most common of these is the tubulo-interstitial nephritis caused by penicillin and its derivatives, especially methicillin.[5,10,11] With acute methicillin tubulo-interstitial nephritis there are frequently associated eosinophilia, sterile pyuria, hematuria, fever and rash that occur due to the allergic response to the drug. A recrudescence of fever after an infection has been treated, associated with a decline in renal function, can be a sign that a drug reaction is occurring.

To summarize, the typical clinical features in a patient with acute tubulo-interstitial nephropathy are the development, after a week or two of drug treatment or in association with an infection or collagen disease, of oliguric or nonoliguric acute renal failure along with a fever, rash, eosinophilia and sterile pyuria with hematuria. There are never red cell casts and only minimal proteinuria, however; both of these are markers of glomerulonephritis, not tubulo-interstitial nephritis.

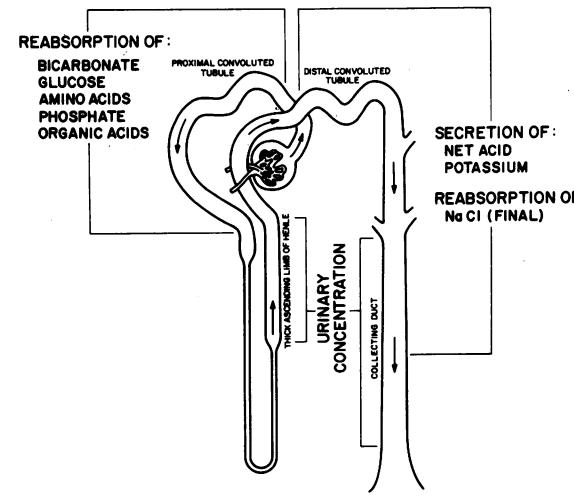

Figure 1.—Segmental physiologic aspects of nephron function. Schematically represented are the principal nephron segments and transport properties that can be individually affected by tubulo-interstitial nephropathies: the proximal nephron, which reabsorbs the bulk of bicarbonate, glucose, amino acids, phosphate and organic acids following glomerular filtration; the distal nephron, which is responsible for reabsorbing the final quantity of luminal sodium, for secreting hydrogen ions to generate net acid excretion as well as for secreting potassium; and the medullary and papillary structures, the loops of Henle and collecting ducts, which abstract water to concentrate the urine.

The presentation of patients with *chronic tubulo-interstitial nephropathy,* on the other hand, does not usually include the pronounced allergic features seen in the acute form. The various metabolic, neoplastic, immunologic, toxic and hereditary causes of chronic interstitial nephritis are shown in Table 1.[1,7] They lead to slowly progressive renal insufficiency that is indistinguishable from chronic glomerulonephritis except that normotension is more commonly present and except for some of the electrolyte abnormalities discussed later. Of particular importance in this group of disorders, however, is the recent recognition that chronic analgesic abuse can cause progressive renal interstitial damage that can potentially lead to an end-stage condition.[1] Phenacetin is usually present in the ingested analgesic combinations, but need not be. Withdrawal of analgesic drugs can halt the renal damage. The older conception that chronic infections are a common cause of chronic tubulo-interstitial disease has yielded to the notion that only infections associated with obstructive processes of the

urinary tract cause chronic damage. The diagnosis of chronic pyelonephritis as a cause of significant renal dysfunction should be reserved only for these unusual conditions associated with chronic obstruction. More specific metabolic or toxic causes of a chronic interstitial process must be sought, rather than assuming an unidentified chronic infectious condition exists.

Pathophysiologic Features

Having briefly surveyed the clinical spectrum of acute and chronic tubulo-interstitial nephropathies, let us turn to some of the functional consequences associated with them. Although a decrease in glomerular filtration rate commonly occurs in these diseases, there are frequently electrolyte disturbances that are disproportionately severe for the level of GFR reduction. I will approach these disorders according to nephron geography; that is, according to which segment of the nephron is more seriously affected.

There are two purposes for the physiologic classification of these diseases. First, attention is called to the disease-specific acid-base and electrolyte derangements that can aid in diagnosis or call for therapy after a diagnosis has been reached. Second, it is hoped that the grouping of diseases in this way will stimulate the search for the pathogenetic factors that make the destruction of a single nephron segment so selective and so prominent.

The functional abnormalities can be divided into those that are caused primarily by disruption of proximal nephron function, distal nephron function, and loop of Henle and collecting duct function as illustrated in Figure 1. This categorization clearly is oversimplified because more than one segment may be involved. Also, renal physiologists are increasingly aware of functional subdivisions of nephron segments. For instance, there are now recognized to be three distinct subsegments of the proximal tubule and at least three morphologic subsegments of the distal tubule. Nevertheless, a first approximation of the important functional aspects of the tubulo-interstitial nephropathies can be gained when the electrolyte dysfunctions are ordered in this way. A concise diagnostic and therapeutic classification system emerges.

There are some interstitial processes that affect almost exclusively the *proximal nephron,* either by cellular infiltration or by glomerular filtration of presumably toxic substances. The proximal tubule is responsible for 80 percent of the total renal bicarbonate reabsorption. Bicarbonate reabsorption is accomplished by hydrogen ion secretion accompanied by sodium reabsorption. Other sodium co-transported solutes reabsorbed in the proximal nephron include glucose, amino acids, phosphate and organic anions, including uric acid (Figure 1). Therefore, a patient with a tubulo-interstitial nephropathy that affects the proximal tubule will have the bicarbonate-wasting or proximal form of renal tubular acidosis (RTA) and inappropriate glycosuria, amino aciduria, phosphaturia and uricosuria, together known as the Fanconi syndrome.

TABLE 2.—*Patterns of Renal Dysfunction in Tubulo-interstitial Nephropathies: Primarily Affecting Proximal Tubule**

Multiple myeloma (± distal)
Paroxysmal nocturnal hemoglobinuria
Heavy metals
? Antitubular basement membrane idiopathic tubulo-interstitial nephritis
? Lupus
? Acute myelogenous leukemia

*Proximal RTA with or without Fanconi syndrome.

As seen in Table 2, a patient with the proximal form of RTA with or without the Fanconi syndrome must be considered to have multiple myeloma until proved otherwise.[12] Other tubulo-interstitial nephropathies responsible for this syndrome include paroxysmal nocturnal hemoglobinuria,[13] heavy metals[14,15] and, less well documented, an antitubular basement membrane idiopathic form,[8,16] lupus,[7] and acute myelogenous and myelomonocytic leukemic[17] forms of tubulo-interstitial nephropathy. It should be mentioned that in caring for a patient with multiple myeloma, the development of proximal RTA or the Fanconi syndrome should be considered in the spectrum of myeloma renal disease.

The *distal nephron* is mainly concerned with the regulation and conservation of the final quality of sodium in the tubular fluid and the secretion of potassium and hydrogen ions (Figure 1). The hydrogen ions titrate the small amount of bicarbonate escaping proximal reabsorption, lower the urinary pH, and titrate ammonia and other buffers to effect urinary net acid excretion. A defect in distal nephron function will result, therefore, in the distal form of renal tubular acidosis characterized by high urinary pH, with or without clinical salt wasting or hyperkalemia.

There are numerous examples of the selective

disruption of distal nephron function sometimes accompanied by a defect in urinary concentrating ability but with normal proximal tubule function. As seen in Table 3, these disorders include amyloidosis,[18] methicillin,[19] states with hypercalcemia or nephrocalcinosis (or both),[20,21] medullary cystic disease,[22] hypergammaglobulinemic states (especially the Sjögren syndrome),[23] chronic obstructive uropathy,[24] renal transplantation,[25] granulomatous infections[26] and Balkan nephropathy.[27]

An example of how the mononuclear cell infiltrate of the kidney can selectively affect distal tubules is seen in Figure 2, which shows a renal biopsy specimen from a patient with methicillin tubulo-interstitial nephropathy.[19] Here the glomeruli and the proximal tubules are well preserved, but the distal tubules (arrows) have been invaded.

TABLE 3.—*Patterns of Renal Dysfunction in Tubulo-interstitial Nephropathies: Primarily Affecting Distal Tubule**

Amyloid
Methicillin
Hypercalcemic/nephrocalcinosis states
Primary hyperparathyroidism
Milk alkali syndrome
Idiopathic hypercalciuria
Medullary cystic disease
Hypergammaglobulinemic states
Sjögren syndrome (± proximal)
Chronic active hepatitis
Lupus
Chronic obstructive uropathy
Renal transplantation (± proximal)
Granulomatous infections
Balkan

*(Distal renal tubular acidosis ± salt wasting ± elevated potassium levels) ± collecting duct dysfunction (decreased concentrating ability).

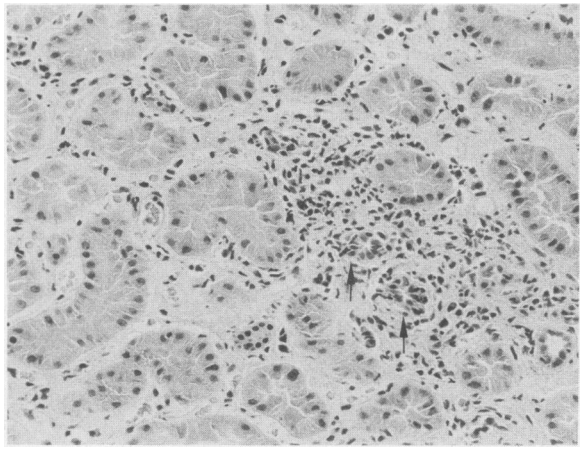

Figure 2.—Photomicrograph of a renal biopsy specimen from a patient with methicillin tubulo-interstitial nephropathy. Glomerulus (not shown) and proximal tubules are relatively spared but distal tubules (arrows) are surrounded by dense mononuclear infiltration. Reduced from original ×80. (Reproduced with permission from Cogan MG and Am J Med.[19])

As illustrated in Figure 3, this patient presented clinically with azotemia without oliguria, accompanied by dehydration, acidosis and hyperkalemia.[19] The elevated blood urea nitrogen (BUN) and creatinine could be appreciably lowered when salt was given back (period I). The hyperkalemia and acidosis were corrected as well, but after correction of the salt depletion, acidosis and hyperkalemia these electrolyte disturbances recurred when a low salt diet was instituted (period II). Salt wasting was shown to be present. Proximal nephron function was intact.

Intermediate forms of distal nephron damage by tubulo-interstitial nephropathies also exist in which normal dietary acid, potassium and salt loads are tolerated. However, stressful situations from acid-loading,[20,21] potassium loading[28] or salt restriction[29] cannot be normally handled by the kidney. Such tubulo-interstitial nephropathies can thus be categorized as displaying incomplete renal tubular acidosis, potassium intolerance or subclinical salt wasting.

In summary, the presentation of a patient with dehydration due to renal salt wasting or with hyperkalemia and acidosis disproportionate to the degree of renal insufficiency should alert one to the possibility of this distal nephron group of tubulo-interstitial nephropathies being present. Conversely, in a patient with these disorders follow-up studies should be done to check for the possible development of overt salt wasting, acidosis or hyperkalemia. Concurrent or isolated hypoaldosteronism can mimic these disorders and should also be sought because therapy differs. In the tubulo-interstitial nephropathies that affect the distal nephron, there is aldosterone resistance (period IV in Figure 3) so that renin and aldosterone levels are high. On the other hand, in the primary or the secondary (hyporeninemic) forms of hypoaldosteronism, aldosterone levels are low.

Finally, there are many diseases that primarily involve the medulla and papilla of the kidney and, therefore, disproportionately affect the *loops of Henle* and the *collecting ducts* (Figure 1). These medullary structures are responsible for water conservation. The ascending limb of Henle generates steep solute gradients in the interstitium using the countercurrent multiplication system.

The collecting ducts allow water to flow out of the tubule lumen when antidiuretic hormone is present. Disruption of these structures can lead, therefore, to polyuria due to mild nephrogenic diabetes insipidus, which occasionally can be severe.

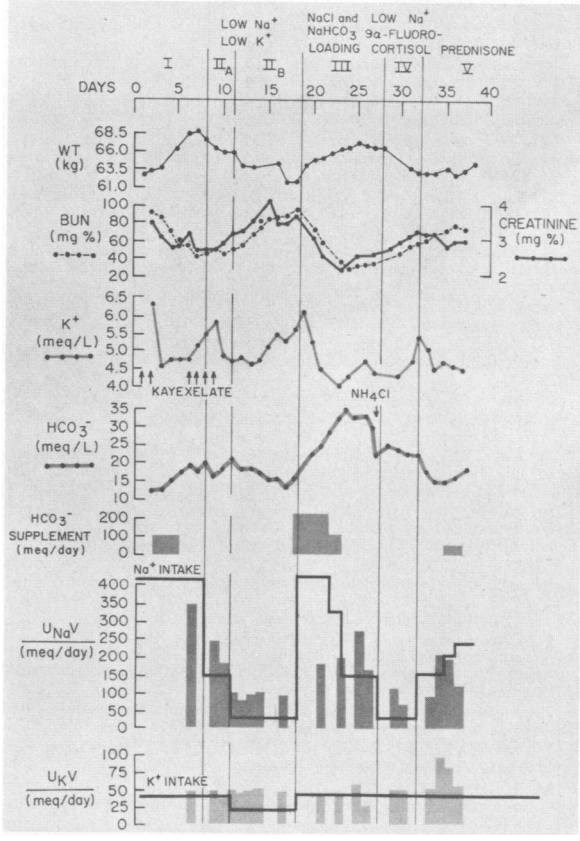

Figure 3.—Metabolic testing of a patient with methicillin acute tubulo-interstitial nephropathy (renal biopsy specimen is shown in Figure 2). The weight loss, azotemia, hyperkalemia and metabolic acidosis on admission were repaired in period I, but recurred during salt restriction in period II accompanied by pronounced renal salt wasting. The response to salt and bicarbonate loading, mineralocorticoid and prednisone administration are shown in periods III to V. See text for further discussion. (Reproduced with permission from Cogan MG and Am J Med.[19])

TABLE 4.—*Patterns of Renal Dysfunction in Tubulo-interstitial Nephropathies: Primarily Affecting Medullary Structures**

Drugs: analgesic nephropathy
Acute pyelonephritis
Sickle cell disease (± distal)
Hyperuricemic and hyperoxaluric obstructive nephropathies (± distal)
Medullary sponge kidney (± distal)
Polycystic kidney disease (± distal)
Sarcoidosis
? Hypokalemic nephropathy

*Decreased concentrating ability.

TABLE 5.—*Clinical Tip-offs That Renal Failure Is Due to Interstitial Rather Than Glomerular Process*

General
History of drug exposure (especially penicillin derivatives)
Fever, rash
Blood
Normal blood pressure
Eosinophilia
"Inappropriate" acidosis and hyperkalemia
Urine
Normal urine output
Nonspecific sediment (no red blood cell casts); pyuria and eosinophiluria
Mild ("tubular") proteinuria
Isosthenuria; high urine pH; glycosuria or amino aciduria (Fanconi)

A partial list of the tubulo-interstitial nephropathies mainly affecting the medulla and papilla of the kidney and consequently impairing water conservation is given in Table 4. These include analgesic nephropathy,[7] acute pyelonephritis,[30] sickle cell disease,[31] hyperuricemic and hyperoxaluric obstructive nephropathies,[32] medullary sponge and polycystic kidney diseases,[33] sarcoidosis,[34] and perhaps hypokalemic nephropathy.[35]

These diseases have a predilection for the papilla and medulla more because of the physicochemical properties of this area of the kidney, being relatively hypertonic and anaerobic, rather than due to immunologic properties. Proximal and distal nephron functions are usually intact, however.

To summarize the immunologic basis for the tubulo-intersitial nephropathies and to emphasize some of the electrolyte abnormalities that are peculiar to them, it is useful to review the characteristics of acute interstitial processes that distinguish them from glomerular processes (Table 5). The allergic basis for many acute tubulo-interstitial nephropathies suggests that fever, rash and eosinophilia may exist. The disproportionate effect on tubules, rather than on the glomerular filtration rate, means that a patient may be normotensive, nonoliguric, and acidotic or hyperkalemic out of proportion to the degree of renal insufficiency present. The urine is also more likely to contain white cells, and especially eosinophils, but not red cell casts or heavy proteinuria. When these features are present, an astute internist can make a presumptive diagnosis of a tubulo-

interstitial nephropathy. Of course, a renal biopsy is necessary for definitive description.

Treatment

The diagnosis of a tubulo-interstitial nephropathy is of more than academic concern because many types are treatable. If a drug is at fault in acute cases, simple withdrawal of the drug is usually sufficient to halt the renal damage. The prognosis is excellent for full return of renal function. The treatment of an underlying infection or collagen vascular disease also causes the renal interstitial disease to abate. In chronic tubulo-interstitial nephropathies, treatment of the underlying disease is often sufficient to cause regression of the renal lesion. It is very important to question patients closely about analgesic consumption because cessation of drug ingestion will halt the renal damage.

Prednisone acts promptly to accelerate the healing process in moderate doses, such as 1 mg per kg of body weight.[10] In general, treatment should not be attempted unless the renal pathologic condition is known from biopsy results. However, if clinical suspicion is high enough because of the historical, immunologic and functional characteristics we have discussed, and if the patient is too ill to tolerate a biopsy safely, I think a brief course of steroids can be recommended. The response is usually observed quickly, within a week, before chronic adverse effects of the steroids become evident.

In conclusion, I hope this emphasis on the pathophysiologic characteristics of the tubulo-interstitial nephropathies, in conjunction with the immunologic and treatment aspects, has served to heighten awareness and stimulate interest in this group of diseases. Certainly, the interrelationships of structure and function are nowhere more elegantly exemplified in nephrology than in these disorders.

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