As a rule, diseases of the kidney primarily affect the glomeruli, vasculature, or remainder of the renal parenchyma that consists of the tubules and interstitium. Although the interstitium and the tubules represent separate functional and structural compartments, they are intimately related. Injury initially involving either one of them inevitably results in damage to the other. Hence the term tubulointerstitial diseases is used. Because inflammatory cellular infiltrates of variable severity are a constant feature of this entity, the terms tubulointerstitial diseases and tubulointerstitial nephritis have come to be used interchangeably. The clinicopathologic syndrome that results from these lesions, commonly termed tubulointerstitial nephropathy, may pursue an acute or chronic course. The chronic course is discussed here. The abbreviation TIN is used to refer synonymously to chronic tubulointerstitial nephritis and tubulointerstitial nephropathy.

TIN may be classified as primary or secondary in origin. Primary TIN is defined as primary tubulointerstitial injury without significant involvement of the glomeruli or vasculature, at least in the early stages of the disease. Secondary TIN is defined as secondary tubulointerstitial injury, which is consequent to lesions initially involving either the glomeruli or renal vasculature. The presence of secondary TIN is especially important because the magnitude of impairment in renal function and the rate of its progression to renal failure correlate better with the extent of TIN than with that of glomerular or vascular damage.

Renal insufficiency is a common feature of chronic TIN, and its diagnosis must be considered in any patient who exhibits renal insufficiency. In most cases, however, chronic TIN is insidious in onset, renal insufficiency is slow to develop, and earliest manifestations of the disease are those of tubular dysfunction. As such, it is important to maintain a high
6.2 Tubulointerstitial Disease

index of suspicion of this entity whenever any evidence of tubular dysfunction is detected clinically. At this early stage, removal of a toxic cause of injury or correction of the underlying systemic or renal disease can result in preservation of residual renal function. Of special relevance in patients who exhibit renal insufficiency caused by primary TIN is the absence or modest degree of the two principal hallmarks of glomerular and vascular diseases of the kidney: salt retention, manifested by edema and hypertension; and proteinuria, which usually is modest and less than 1 to 2 g/d in TIN. These clinical considerations notwithstanding, a definite diagnosis of TIN can be established only by morphologic examination of kidney tissue.

Structure of the Interstitium

![Diagram](image)

**FIGURE 6-1**
Diagram of the approximate relative volume composition of tissue compartments at different segments of the kidney in rats. The interstitium of the kidney consists of peritubular and periarterial spaces. The relative contribution of each of these two spaces to interstitial volume varies, reflecting in part the arbitrary boundaries used in assessing them, but increases in size from the cortex to the papilla. In the cortex there is little interstitium because the peritubular capillaries occupy most of the space between the tubules. The cortical interstitial cells are scattered and relatively inconspicuous. In fact, a loss of the normally very close approximation of the cortical tubules is the first evidence of TIN. In the medulla there is a noticeable increase in interstitial space. The interstitial cells, which are in greater evidence, have characteristic structural features and an organized arrangement. The ground substance of the renal interstitium contains different types of fibrils and basementlike material embedded in a glycosaminoglycan-rich substance. (From Bohman [1]; with permission.)

Cortex

![Electron micrograph](image)

**FIGURE 6-2**
A, Electron micrograph of a rat kidney cortex, where C is the cortex. B, Schematic rendering, where the narrow interstitium is shown in black and the wide interstitium is shown by dots. The relative volume of the interstitium of the cortex is approximately 7%, consisting of about 3% interstitial cells and 4% extracellular space. The vasculature occupies another 6%; the remainder (ie, some 85% or more) is occupied by the tubules. The cortical interstitial space is unevenly distributed and has been divided into narrow and wide structural components. The tubules and peritubular capillaries either are closely apposed at several points, sometimes to the point of sharing a common basement membrane, or are separated by a very narrow space.

This space, the so-called narrow interstitium, has been estimated to occupy 0.6% of cortical volume in rats. The narrow interstitium occupies about one-half to two-thirds of the cortical peritubular capillary surface area. The remainder of the cortical interstitium consists of irregularly shaped clearly discernible larger areas, the so-called wide interstitium. The wide interstitium has been estimated to occupy 3.4% of cortical volume in rats. The capillary wall facing the narrow interstitium is significantly more fenestrated than is that facing the wide interstitium. Functional heterogeneity of these interstitial spaces has been proposed but remains to be clearly defined. (From Bohman [1]; with permission.)
Renal Interstitium and Major Features of Chronic Tubulointerstitial Nephritis

Medulla

FIGURE 6-3
Scanning electron micrograph of the inner medulla, showing a prominent collecting duct, thin wall vessels, and abundant interstitium. A gradual increase in interstitial volume from the outer medullary stripe to the tip of the papilla occurs. In the outer stripe of the outer medulla, the relative volume of the interstitium is slightly less than that of the cortex. This volume has been estimated to be approximately 5% in rats. It is in the inner stripe of the outer medulla that the interstitium begins to increase significantly in volume, in increments that gradually become larger toward the papillary tip.

The inner stripe of the outer medulla consists of the vascular bundles and the interbundle regions, which are occupied principally by tubules. Within the vascular bundles the interstitial spaces are meager, whereas in the interbundle region the interstitial spaces occupy some 10% to 20% of the volume. In the inner medulla the differentiation into vascular bundles and interbundle regions becomes gradually less obvious until the two regions merge. A gradual increase in the relative volume of the interstitial space from the base of the inner medulla to the tip of the papilla also occurs. In rats, the increment in interstitial space is from 10% to 15% at the base to about 30% at the tip. In rabbits, the increment is from 20% to 25% at the base to more than 40% at the tip.

Cell types

FIGURE 6-4
A, High-power view of the medulla showing the wide interstitium and interstitial cells, which are abundant, varied in shape, and arranged as are the rungs of a ladder. B, Renal interstitial cells. The interstitium contains two main cell types, whose numbers increase from the cortex to the papilla. Type I interstitial cells are fibroblastic cells that are active in the deposition and degradation of the interstitial matrix. Type I cells contribute to fibrosis in response to chronic irritation. Type II cells are macrophage-derived mononuclear cells with phagocytic and immunologic properties. Type II cells are important in antigen presentation. Their cytokines contribute to recruitment of infiltrating cells, progression of injury, and sustenance of fibrogenesis.

In the cortex and outer zone of the outer medulla, type I cells are more common than are type II cells. In the inner zone of the medulla, some type I cells form pericytes whereas others evolve into specialized lipid-laden interstitial cells. These specialized cells increase in number toward the papillary tip and are a possible source of medullary prostaglandins and of production of matricellular glycosaminoglycans. A characteristic feature of these medullary cells is their connection to each other in a characteristic arrangement, similar to the rungs of a ladder. These cells have a distinct close and regular transverse apposition to their surrounding structures, specifically the limbs of the loop of Henle and capillaries, but not to the collecting duct cells.

<table>
<thead>
<tr>
<th>Cell types</th>
<th>Cortex</th>
<th>Outer medulla</th>
<th>Inner medulla</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroblastic cells</td>
<td>Fibroblastic cells</td>
<td>Pericytes</td>
<td></td>
</tr>
<tr>
<td>Mononuclear cells</td>
<td>Mononuclear cells</td>
<td>Lipid-laden cells</td>
<td></td>
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<td></td>
<td></td>
<td>Mononuclear cells</td>
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