**Toxic Responses of the Kidney:**

Body homeostasis is related to functional integrity of the kidney because of the kidney's role in the excretion of metabolic wastes, synthesis and release of the hormones renin and erythropoietin, and regulation of extracellular fluid volume, electrolyte composition, and acid–base balance.

***Functional Anatomy:***

Kidney gross examination reveals three clearly fixed anatomic areas: the cortex, medulla, and papilla. The cortex receives about 90% of blood flow, compared with the medulla (6-10%) and the papilla (1-2%). The functional unit of the kidney, the nephron, may be divided into three portions: the vascular element, the glomerulus, and the tubular element.

***Pathophysiologic Responses of the Kidney***

**Acute Renal Failure** (ARF)

It is a common signs of nephrotoxic damage, characterized by an abrupt decline in glomerular filtration rate (GFR) with resulting azotemia or nitrogenous wastes in the blood.

After exposure to a nephrotoxicant, many mechanisms may lead to a reduction in GFR. These mechanisms include prerenal vasoconstriction resulting in prerenal azotemia and obstruction caused by precipitation of a drug or endogenous compound within the capillaries before entering the glomerulus. Intrarenal factors include direct tubular obstruction and dysfunction resulting in tubular back leak and increased tubular pressure.

Tubular obstruction also may occur, the maintenance of tubular integrity is dependent on cell-to-cell and cell-to-matrix adhesion. After a chemical or hypoxic insult, adhesion of non–lethally damaged cells to the basement membrane will cause gaps in the epithelial cell lining and resulting in back leak of filtrate and diminished GFR. These detached cells also may aggregate in the tubular lumen and/or adhere or reattach to adherent epithelial cells downstream, resulting in tubular obstruction.

Alterations in the levels of a variety of vasoactive mediators may result in decreased renal perfusion pressure and renal blood flow.

**Adaptation after a Toxic Insult**

After unilateral nephrectomy or damage, GFR of the remnant kidney increases by approximately 40-60% (compensatory mechanism) and accompanied by proportionate increases in proximal tubular water and solute reabsorption. The overall renal function appears normal on standard clinical tests. These changes may not be detected until the compensatory mechanism is affected by obvious nephron loss and/or damage.

There are a number of cellular and molecular responses to a nephrotoxic insult. After exposure to a toxicant, a fraction of the cells will be severely injured and undergo cell death by apoptosis or necrosis. Cells with nonlethal injuries may undergo cell repair and/or adaptation, which contribute to the structural and functional recovery of the nephron. In addition, there is a population of uninjured cells that may undergo compensatory hypertrophy, cellular adaptation, and cellular proliferation. Which contribute to the structural and functional recovery of the nephron.

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| **Chronic Renal Failure**  Progressive deterioration of renal function may occur with long-term exposure to various chemicals. With time, the adaptation of remnant viable nephrons will changed to maladaptation, and glomerulosclerosis eventually develops that may lead to tubular atrophy, interstitial fibrosis and a mechanical damage characterized by altered permeability. |

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| **Susceptibility of the Kidney to Toxic Injury**  Many drugs, environmental chemicals, and metals can cause site-specific nephrotoxicity. The intensity of ARF vary from recovery to permanent renal damage, which may require dialysis or renal transplantation.  **Reasons for the Susceptibility of the Kidney to Toxicity**  Kidneys constitute only 0.5% of total body mass, they receive about 20-25% of the cardiac output. Consequently, any drug or chemical in the systemic circulation is delivered to these organs in relatively high amounts. The processes involved in forming concentrated urine also serve to concentrate potential toxicants in the tubular fluid, thus driving passive diffusion of toxicants into tubular cells. So, a nontoxic concentration of a chemical in the plasma may reach toxic concentrations in the kidney. Finally, renal transport, accumulation, and metabolism of xenobiotics contribute significantly to the susceptibility of the kidney to toxic injury.  In addition to intrarenal factors, the incidence and/or severity of chemically induced nephrotoxicity may be related to the sensitivity of the kidney to circulating vasoconstrictors (angiotensin II or vasopressin), whose actions normally are counterbalanced by the actions of increased vasodilatory prostaglandins. When prostaglandin synthesis is suppressed by nonsteroidal anti-inflammatory drugs (NSAIDs), renal blood flow (RBF) declines markedly and ARF ensues as a result of the unopposed actions of vasoconstrictors. Another example of predisposing risk factors relates to the clinical use of angiotensin-converting enzyme (ACE) inhibitors. Glomerular filtration pressure is dependent on angiotensin II–induced efferent arteriolar constriction. ACE inhibitors block this vasoconstriction, resulting in a precipitous decline in filtration pressure and ARF.  **Glomerular Injury**  The glomerulus is a complex, specialized capillary bed that serves as the first stage in the filtering process of the [blood](https://en.wikipedia.org/wiki/Blood) and urine formation. The glomerulus is characterized by its high permeability to water and small solutes and an almost complete impermeability to large molecules. Since the glomerulus is the initial site of chemical exposure in the nephron, a number of nephrotoxicants can alter glomerular permeability to proteins.  Cyclosporine, amphotericin B, and gentamicin impair glomerular ultrafiltration without a significant loss of structural integrity and decreased GFR. Amphotericin B decreases GFR by causing renal vasoconstriction. Gentamicin interacts with the anionic sites on the endothelial cells, decreasing GFR. Finally, cyclosporine not only causes renal vasoconstriction and vascular damage but is injurious to the glomerular endothelial cell.  Heavy metals, hydrocarbons, penicillamine, and captopril can produce certain type of glomerular injury (glomerulonephritis). A chemical may function as a hapten attached to a native protein or as a complete antigen and may elicit an antibody response. Antibody reactions with cell-surface antigens lead to immune deposit formation within the glomeruli, mediator activation, and subsequent injury to glomerular tissue.  **Proximal Tubular Injury**  The proximal tubule is the most common site of toxicant-induced renal injury. Approximately 60-80 % of solute and water filtered at the glomerulus are rebsorbed. The proximal tubule also reabsorbs almost all the filtered low-molecular-weight proteins. The nephrotoxic potential of xenobiotics depends on the intrinsic reactivity of the drug with subcellular or molecular targets. Cytochrome P450 and other enzymes are localized almost exclusively in the proximal tubule, which may contribute in bioactivation of chloroform. Proximal tubular cells are more susceptible to ischemic injury than distal tubular cells.  **Loop of Henle/Distal Tubule/Collecting Duct Injury**  Approximately 25% of the filtered Na+ and K+ and 20% of the filtered water are reabsorbed by the segments of the loop of Henle.  Functional abnormalities at these sites manifest primarily as impaired concentrating ability and/or acidification defects. Amphotericin B, cisplatin, and methoxyflurane induce an ADH-resistant polyuria.  **Papillary Injury**  The initial target of abusive consumption of analgesics is the medullary interstitial cells, followed by degenerative changes in the medullary capillaries, loops of Henle, and collecting ducts. High papillary concentrations of potential toxicants and inhibition of vasodilatory prostaglandins compromise renal blood flow to the renal medulla/papilla and result in tissue ischemia. |

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| **Biochemical Mechanisms/Mediators of Renal Cell Injury**  **Cell Death**  Cell death may occur through either necrosis or apoptosis. Apoptosis is a tightly controlled, organized process that usually affects scattered individual cells. Ultimately, the cell breaks into small fragments that are phagocytosed by adjacent cells or macrophages without producing an inflammatory response. In contrast, necrosis often affects many contiguous cells; the cells rupture, releasing cellular contents, and inflammation follows. With many toxicants, lower but injurious concentrations produce cell death through apoptosis. As the concentration of the toxicant increases, necrosis plays a predominant role.  **Mediators of Toxicity**  A chemical can initiate cell injury by various mechanisms. The chemical may initiate toxicity because of its reactivity with cellular macromolecules, may require renal or extrarenal bioactivation to a reactive intermediate, or may initiate injury indirectly by inducing oxidative stress through increased production of reactive oxygen species (ROS) which can attack proteins, lipids, and DNA to induce toxicity. |

**Specific Nephrotoxicants**

**Mercury**

The kidneys are the primary target organs for the accumulation of Hg2 +. Changes in mitochondrial morphology and function are very early events after HgCl2 administration, supporting the hypothesis that mitochondrial dysfunction is an early and important contributor to inorganic mercury-induced cell death along the proximal tubule.

Early markers of HgCl2-induced renal dysfunction include an increase in the urinary excretion of brush-border enzymes such as alkaline phosphatase, when tubular injury becomes severe, intracellular enzymes such as lactate dehydrogenase and aspartate aminotransferase increase in the urine. As injury progresses, tubular reabsorption of solutes and water decreases.

**Cadmium**

Cadmium has a half-life of more than 10 years in humans and thus accumulates in the body over time. Approximately 50% of the body burden of cadmium can be found in the kidney. Cadmium produces proximal tubule dysfunction and injury that may progress to a chronic interstitial nephritis.

**Halogenated Hydrocarbons**

Humans are exposed to halogenated hydrocarbons in the workplace and in the environment.

**Chloroform**

The primary cellular target of chloroform is the proximal tubule, with no primary damage to the glomerulus or the distal tubule. Proteinuria, glucosuria, and increased blood urea nitrogen levels are all characteristic of chloroform-induced nephrotoxicity. The nephrotoxicity produced by chloroform is linked to its metabolism by renal cyt-P450, which biotransforms chloroform to trichloromethanol, which is unstable and releases HCl to form phosgene, which reacts injuriously with cellular macromolecules.

**Bromobenzene**

Biotransformation of bromobenzene and other halogenated benzenes is critical for their nephrotoxicity. Hepatic cyt-P450 metabolizes bromobenzene, conjugates it to glutathione, and then releases it in a form that can cause nephrotoxicity. The diglutathione conjugate of the hydroquinone is approximately a thousand fold more potent than is bromobenzene in causing nephrotoxicity, leading to an increase in the amount of protein, glucose, and cellular enzymes in the urine.

**Therapeutic Agents**

**Acetaminophen**

Acetaminophen (APAP) nephrotoxicity is characterized by proximal tubular necrosis; decreases in GFR; increases in the fractional excretion of water, sodium, and potassium; and increases in urinary glucose, protein, and brush-border enzymes. Renal cyt-P450 plays a role in APAP activation and nephrotoxicity, and glutathione conjugates of APAP also may contribute to APAP nephrotoxicity.

**Nonsteroidal Anti-Inflammatory Drugs**

At least three different types of nephrotoxicity have been associated with NSAID administration. ARF may occur within hours after a large dose of a NSAID, is usually reversible upon withdrawal of the drug, and is characterized by decreased GFR. When the normal production of vasodilatory prostaglandins is inhibited by NSAIDs, vasoconstriction induced by circulating catecholamines and angiotensin II is unopposed, resulting in ischemia.

In contrast, chronic consumption of NSAIDs and/or APAP (>3 years) results in an often irreversible nephrotoxicity. The primary lesion in this nephropathy is papillary necrosis with chronic interstitial nephritis. The mechanism by which NSAIDs produce analgesic nephropathy is not known, but the process may result from chronic medullary/papillary ischemia secondary to renal vasoconstriction or from the genesis of a reactive intermediate that in turn initiates an oxidative stress or binds covalently to critical cellular macromolecules.

The third, rare, type of nephrotoxicity associated with NSAIDs is an interstitial nephritis.

If NSAIDs are discontinued, renal function improves in 1 to 3 months.

**Amphotericin B**

Amphotericin B nephrotoxicity is characterized by antidiuretic hormone–resistant polyuria, renal tubular acidosis, hypokalemia, and acute or chronic renal failure. The functional integrity of the glomerulus and of the proximal and distal portions of the nephron is impaired due to renal arteriolar vasoconstriction or activation of tubuloglomerular feedback.

**Cyclosporine**

Cyclosporine-induced nephrotoxicity may manifest as (1) acute reversible renal dysfunction, (2) acute vasculopathy, and (3) chronic nephropathy with interstitial fibrosis.

**Cisplatin**

Cisplatin nephrotoxicity includes acute and chronic renal failure, renal magnesium wasting, and polyuria. ARF is observed, the primary cellular target associated with ARF is the proximal tubule. The chronic renal failure observed with cisplatin is due to prolonged exposure and is characterized by focal necrosis in numerous segments of the nephron without a significant effect on the glomerulus. Cisplatin may produce nephrotoxicity through its ability to inhibit DNA synthesis as well as transport functions.