Acute renal failure (ARF) is a syndrome characterized by an abrupt and reversible kidney dysfunction. The spectrum of inciting factors is broad: from ischemic and nephrotoxic agents to a variety of endotoxemic states and syndrome of multiple organ failure. The pathophysiology of ARF includes vascular, glomerular and tubular dysfunction which, depending on the actual offending stimulus, vary in the severity and time of appearance. Hemodynamic compromise prevails in cases when noxious stimuli are related to hypotension and septicemia, leading to renal hypoperfusion with secondary tubular changes (described in Chapter 13). Nephrotoxic offenders usually result in primary tubular epithelial cell injury, though endothelial cell dysfunction can also occur, leading to the eventual cessation of glomerular filtration. This latter effect is a consequence of the combined action of tubular obstruction and activation of tubuloglomerular feedback mechanism. In the following pages we shall review the existing concepts on the phenomenology of ARF including the mechanisms of decreased renal perfusion and failure of glomerular filtration, vasoconstriction of renal arterioles, how formed elements gain access to the renal parenchyma, and what the sequelae are of such an invasion by primed leukocytes.
Vasoactive Hormones

**FIGURE 14-1**
Pathophysiology of ischemic and toxic acute renal failure (ARF). The severe reduction in glomerular filtration rate (GFR) associated with established ischemic or toxic renal injury is due to the combined effects of alterations in intrarenal hemodynamics and tubular injury. The hemodynamic alterations associated with ARF include afferent arteriolar constriction and mesangial contraction, both of which directly reduce GFR. Tubular injury reduces GFR by causing tubular obstruction and by allowing backleak of glomerular filtrate. Abnormalities in tubular reabsorption of solute may contribute to intrarenal vasoconstriction by activating the tubuloglomerular (TG) feedback system. GPF—glomerular plasmaflow; P—glomerular pressure; Kf—glomerular ultrafiltration coefficient.

**FIGURE 14-2**
Vasoactive hormones that may be responsible for the hemodynamic abnormalities in acute tubule necrosis (ATN). A persistent reduction in renal blood flow has been demonstrated in both animal models of acute renal failure (ARF) and in humans with ATN. The mechanisms responsible for the hemodynamic alterations in ARF involve an increase in the intrarenal activity of vasoconstrictors and a deficiency of important vasodilators. A number of vasoconstrictor hormones have been implicated in the reduction in renal blood flow in ARF. The importance of individual vasoconstrictor hormones in ARF probably varies to some extent with the cause of the renal injury. A deficiency of vasodilators such as endothelium-derived nitric oxide (EDNO) and/or prostaglandin I2 (PGI2) also contributes to the renal hypoperfusion associated with ARF. This imbalance in intrarenal vasoactive hormones favoring vasoconstriction causes persistent intrarenal hypoxia, thereby exacerbating tubular injury and protracting the course of ARF.
The mesangium regulates single-nephron glomerular filtration rate (SN GFR) by altering the glomerular ultrafiltration coefficient ($K_f$). This schematic diagram demonstrates the anatomic relationship between glomerular capillary loops and the mesangium. The mesangium is surrounded by capillary loops. Mesangial cells (M) are specialized pericytes with contractile elements that can respond to vasoactive hormones. Contraction of mesangium can close and prevent perfusion of anatomically associated glomerular capillary loops. This decreases the surface area available for glomerular filtration and reduces the glomerular ultrafiltration coefficient.

The topography of juxtaglomerular apparatus (JGA), including macula densa cells (MD), extraglomerular mesangial cells (EMC), and afferent arteriolar smooth muscle cells (SMC). Insets schematically illustrate, B, the structure of JGA; C, the flow of information within the JGA; and D, the putative messengers of tubuloglomerular feedback responses. AA—afferent arteriole; PPC—peripolar cell; EA—efferent arteriole; GMC—glomerular mesangial cells. (Modified from Goligorsky et al. [1]; with permission.)
Acute Renal Failure

1. SNGFR increases causing increase in delivery of solute to the distal nephron.

2. The composition of filtrate passing the macula densa is altered and stimulates the JGA.

3. Renin is released from specialized cells of JGA and the intrarenal renin angiotensin system generates release of angiotensin II locally.

4. Afferent arteriolar and mesangial contraction reduce SNGFR back toward control levels.

Role of TG feedback in ARF

1. Renal epithelial cell injury reduces reabsorption of NaCl by proximal tubules.

2. The composition of filtrate passing the macula densa is altered and stimulates the JGA.

3. Local release of angiotensin II is stimulated.

4. Afferent arteriolar and mesangial contraction reduce SNGFR below normal levels.

The normal tubuloglomerular (TG) feedback mechanism

A. Normal TG feedback. In the normal kidney, the TG feedback mechanism is a sensitive device for the regulation of the single nephron glomerular filtration rate (SNGFR). Step 1: An increase in SNGFR increases the amount of sodium chloride (NaCl) delivered to the juxtaglomerular apparatus (JGA) of the nephron. Step 2: The resultant change in the composition of the filtrate is sensed by the macula densa cells and initiates activation of the JGA. Step 3: The JGA releases renin, which results in the local and systemic generation of angiotensin II. Step 4: Angiotensin II induces vasoconstriction of the glomerular arterioles and contraction of the mesangial cells. These events return SNGFR back toward basal levels.

B. TG feedback in ARF. Step 1: Ischemic or toxic injury to renal tubules leads to impaired reabsorption of NaCl by injured tubular segments proximal to the JGA. Step 2: The composition of the filtrate passing the macula densa is altered and activates the JGA. Step 3: Angiotensin II is released locally. Step 4: SNGFR is reduced below normal levels. It is likely that vasoconstrictors other than angiotensin II, as well as vasodilator hormones (such as PG12 and nitric oxide) are also involved in modulating TG feedback. Abnormalities in these vasoactive hormones in ARF may contribute to alterations in TG feedback in ARF.
**Osswald’s Hypothesis**

- Increased ATP hydrolysis (increased distal Na⁺ load)
- Increased generation of adenosine
- Activation of JGA
- Afferent arteriolar vasoconstriction

**Signal Transmission Mediator(s) Effects**

**FIGURE 14-6** Metabolic basis for the adenosine hypothesis. A, Osswald’s hypothesis on the role of adenosine in tubuloglomerular feedback. B, Adenosine metabolism: production and disposal via the salvage and degradation pathways. (A, Modified from Osswald et al. [2]; with permission.)
Endothelin (ET) is a potent renal vasoconstrictor. Endothelin (ET) is a 21 amino acid peptide of which three isoforms—ET-1, ET-2 and ET-3—have been described, all of which have been shown to be present in renal tissue. However, only the effects of ET-1 on the kidney have been clearly elucidated. ET-1 is the most potent vasoconstrictor known. Infusion of ET-1 into the kidney induces profound and long lasting vasoconstriction of the renal circulation. 

**A**

The appearance of the rat kidney during the infusion of ET-1 into the inferior branch of the main renal artery. The lower pole of the kidney perfused by this vessel is profoundly vasoconstricted and hypoperfused.

**B**

Schematic illustration of separate populations of glomeruli within the same kidney. The entire kidney underwent 25 minutes of ischemia 48 hours before micropuncture. Glomeruli I are nephrons not exposed to endothelin antibody; Glomeruli II are nephrons that received infusion with antibody through the inferior branch of the main renal artery. SNPFR—single nephron glomerular filtration rate; PFR—glomerular renal plasma flow rate. (From Kon et al. [4]; with permission.)
Pathophysiology of Ischemic Acute Renal Failure

**FIGURE 14-9**
Biosynthesis of mature endothelin-1 (ET-1). The mature ET-1 peptide is produced by a series of biochemical steps. The precursor of active ET is pre-pro ET, which is cleaved by dibasic pair-specific endopeptidases and carboxypeptidases to yield a 39- amino acid intermediate termed big ET-1. Big ET-1, which has little vasoconstrictor activity, is then converted to the mature 21-amino acid ET by a specific endopeptidase, the endothelin-converting enzyme (ECE). ECE is localized to the plasma membrane of endothelial cells. The arrows indicate sites of cleavage of pre-pro ET and big ET.

**FIGURE 14-10**
Regulation of endothelin (ET) action; the role of the ET receptors. Pre-pro ET is produced and converted to big ET. Big ET is converted to mature, active ET by endothelin-converting enzyme (ECE) present on the endothelial cell membrane. Mature ET secreted onto the basolateral aspect of the endothelial cell binds to two ET receptors (ETA and ETB); both are present on vascular smooth muscle (VSM) cells. Interaction of ET with predominantly expressed ETA receptors on VSM cells induces vasoconstriction. ETB receptors are predominantly located on the plasma membrane of endothelial cells. Interaction of ET-1 with these endothelial ETB receptors stimulates production of nitric oxide (NO) and prostacyclin by endothelial cells. The production of these two vasodilators serves to counterbalance the intense vasoconstrictor activity of ET-1. PGI2—prostaglandin I2.
**FIGURE 14-11**

Endothelin-1 (ET-1) receptor blockade ameliorates severe ischemic acute renal failure (ARF) in rats. The effect of an ET₄ receptor antagonist (BQ 123) on the course of severe postischemic ARF was examined in rats. BQ 123 (light bars) or its vehicle (dark bars) was administered 24 hours after the ischemic insult and the rats were followed for 14 days. **A**, Survival. All rats that received the vehicle were dead by the 3rd day after ischemic injury. In contrast, all rats that received BQ 123 post-ischemia survived for 4 days and 75% recovered fully. **B**, Glomerular filtration rate (GFR). In both groups of rats GFR was extremely low (2% of basal levels) 24 hours after ischemia. In BQ 123-treated rats there was a gradual increase in GFR that reached control levels by the 14th day after ischemia. **C**, Serum potassium. Serum potassium increased in both groups but reached significantly higher levels in vehicle-treated compared to the BQ 123-treated rats by the second day. The severe hyperkalemia likely contributed to the subsequent death of the vehicle treated rats. In BQ 123-treated animals the potassium fell progressively after the second day and reached normal levels by the fourth day after ischemia. (Adapted from Gellai et al. [5]; with permission.)

**FIGURE 14-12**

Production of prostaglandins. Arachidonic acid is released from the plasma membrane by phospholipase A₂. The enzyme cyclooxygenase catalyses the conversion of arachidonate to two prostanoid intermediates (PGH₂ and PGG₂). These are converted by specific enzymes into a number of different prostanoids as well as thromboxane (TXA₂). The predominant prostaglandin produced varies with the cell type. In endothelial cells prostacyclin (PGI₂) (in the circle) is the major metabolite of cyclooxygenase activity. Prostacyclin, a potent vasodilator, is involved in the regulation of vascular tone. TXA₂ is not produced in endothelial cells of normal kidneys but may be produced in increased amounts and contribute to the pathophysiology of some forms of acute renal failure (eg, cyclosporine A–induced nephrotoxicity). The production of all prostanoids and TXA₂ is blocked by nonsteroidal anti-inflammatory agents (NSAIDs), which inhibit cyclooxygenase activity.
**FIGURE 14-13**
Endothelin (ET) receptor blockade ameliorates acute cyclosporine-induced nephrotoxicity. Cyclosporine A (CSA) was administered intravenously to rats. Then, an ET receptor antagonist was infused directly into the right renal artery. Glomerular filtration rate (GFR) and renal plasma flow (RPF) were reduced by the CSA in the left kidney. The ET receptor antagonist protected GFR and RPF from the effects of CSA on the right side. Thus, ET contributes to the intrarenal vasoconstriction and reduction in GFR associated with acute CSA nephrotoxicity. (From Fogo et al. [6]; with permission.)

**FIGURE 14-14**
Prostacyclin is important in maintaining renal blood flow (RBF) and glomerular filtration rate (GFR) in “prerenal” states. A, When intravascular volume is normal, prostacyclin production in the endothelial cells of the kidney is low and prostacyclin plays little or no role in control of vascular tone. B, The reduction in absolute or “effective” arterial blood volume associated with all prerenal states leads to an increase in the circulating levels of a number of vasoconstrictors, including angiotensin II, catecholamines, and vasopressin. The increase in vasoconstrictors stimulates phospholipase A₂ and prostacyclin production in renal endothelial cells. This increase in prostacyclin production partially counteracts the effects of the circulating vasoconstrictors and plays a critical role in maintaining normal or nearly normal RBF and GFR in prerenal states. C, The effect of cyclooxygenase inhibition with nonsteroidal anti-inflammatory drugs (NSAIDs) in prerenal states. Inhibition of prostacyclin production in the presence of intravascular volume depletion results in unopposed action of prevailing vasoconstrictors and results in severe intrarenal vasoconstriction. NSAIDs can precipitate severe acute renal failure in these situations.
### A. Vasodilators used in experimental acute renal failure (ARF)

<table>
<thead>
<tr>
<th>Vasodilator</th>
<th>ARF Disorder</th>
<th>Time Given in Relation to Induction</th>
<th>Observed Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>Ischemic</td>
<td>Before, during, after</td>
<td>↓Scr, BUN if given before, during; no effect if given after</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>Toxic</td>
<td>Before, during, after</td>
<td>Prevented fall in RBF</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Ischemic</td>
<td>After</td>
<td>↓Scr, BUN</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Ischemic</td>
<td>Before, during</td>
<td>↑RBF, GFR</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Ischemic</td>
<td>Before, after</td>
<td>↑RBF; no change in GFR</td>
</tr>
<tr>
<td>Prostaglandin $E_1$</td>
<td>Ischemic</td>
<td>After</td>
<td>↑RBF; no change in GFR</td>
</tr>
<tr>
<td>Prostaglandin $E_2$</td>
<td>Ischemic</td>
<td>Before, after</td>
<td>↑RBF; no change in GFR</td>
</tr>
<tr>
<td>Prostaglandin $I_2$</td>
<td>Ischemic</td>
<td>Before, after</td>
<td>↑RBF; no change in GFR</td>
</tr>
<tr>
<td>Saralasin</td>
<td>Toxic, ischemic</td>
<td>Before</td>
<td>↑RBF; no change in Scr, BUN</td>
</tr>
<tr>
<td>Captopril</td>
<td>Toxic, ischemic</td>
<td>Before</td>
<td>↑RBF; no change in Scr, BUN</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Ischemic, toxic</td>
<td>Before, during, after</td>
<td>↑RBF, GFR in most studies</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Ischemic</td>
<td>Before, during, after</td>
<td>↑GFR</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>Toxic</td>
<td>Before, during, after</td>
<td>↑GFR</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Toxic</td>
<td>Before, during, after</td>
<td>↑GFR; recovery time</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Toxic</td>
<td>Before</td>
<td>↑GFR; recovery time</td>
</tr>
<tr>
<td>Atrial natriuretic peptide</td>
<td>Ischemic, toxic</td>
<td>After</td>
<td>↑RBF, GFR</td>
</tr>
</tbody>
</table>

**Remarks**
- Combined with furosemide
- Used with dopamine
- Used with NE
- Prophylactic use

**FIGURE 14-15**

Vasodilators used in acute renal failure (ARF). A, Vasodilators used in experimental acute ARF. B, Vasodilators used to alter the course of clinical ARF. (From Conger [7]; with permission.)

### B. Vasodilators used to alter course of clinical acute renal failure (ARF)

<table>
<thead>
<tr>
<th>Vasodilator</th>
<th>ARF Disorder</th>
<th>Observed Effect</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>Ischemic, toxic</td>
<td>Improved V, Scr if used early</td>
<td>Combined with furosemide</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>Ischemic, toxic</td>
<td>No change in V, RBF</td>
<td>Used with dopamine</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>Ischemic, toxic</td>
<td>No change in V, RBF</td>
<td>Used with NE</td>
</tr>
<tr>
<td>Prostaglandin $A_1$</td>
<td>Ischemic</td>
<td>No change in V, Scr</td>
<td></td>
</tr>
<tr>
<td>Prostaglandin $E_2$</td>
<td>Ischemic</td>
<td>↑RBF; no change v. C$_{cr}$</td>
<td></td>
</tr>
<tr>
<td>Dihydralazine</td>
<td>Ischemic, toxic</td>
<td>↑RBF; no change V, Scr</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>Ischemic</td>
<td>↑C$_{cr}$ or no effect</td>
<td>Prophylactic use</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Transplant, toxic</td>
<td>No effect</td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Radiocontrast</td>
<td>↑C$_{cr}$</td>
<td></td>
</tr>
<tr>
<td>Atrial natriuretic peptide</td>
<td>Ischemic</td>
<td>↑C$_{cr}$</td>
<td></td>
</tr>
</tbody>
</table>

**Remarks**
- C$_{cr}$—creatinine clearance; NE—noradrenaline; RBF—renal blood flow; Scr—serum creatinine; V—urine flow rate.
Pathophysiology of Ischemic Acute Renal Failure

A

NH₂ + NH₂ → O₂ + H₂O

L-arginine

N⁴-hydroxy-L-arginine

N⁴-oxy-L-arginine

N₂-hydroxy-L-arginine

L-citrulline

NO

Nitric oxide

B

Modular structure of nitric oxide synthases

nNOS

eNOS

iNOS

Target domain

Regulatory domain

Catalytic domain

Dimerization site

nNOS

eNOS

iNOS

Mammalian P450 Reductases

Bacterial Flavodoxins

DHF Reductases

Mammalian Syntrophins (GLGF Motif)

Plant Ferredoxin NADPH Reductases

FIGURE 14-16

Chemical reactions leading to the generation of nitric oxide (NO), A, and enzymes that catalyze them, B. (Modified from Gross [8]; with permission.)

FIGURE 14-17

Major organ, A, and cellular, B, targets of nitric oxide (NO). A, Synthesis and function of NO. B, Intracellular targets for NO and pathophysiological consequences of its action. C, Endothelium-dependent vasodilators, such as acetylcholine and the calcium ionophore A23187, act by stimulating eNOS activity thereby increasing endothelium-derived nitric oxide (EDNO) production. In contrast, other vasodilators act independently of the endothelium. Some endothelium-independent vasodilators such as nitroprusside and nitroglycerin induce vasodilation by directly releasing nitric oxide in vascular smooth muscle cells. NO released by these agents, like EDNO, induces vasodilation by stimulating the production of cyclic guanosine monophosphate (cGMP) in vascular smooth muscle (VSM) cells. Atrial natriuretic peptide (ANP) is also an endothelium-independent vasodilator but acts differently from NO. ANP directly stimulates a different mechanism of guanylyl cyclase (GC) distinct from soluble GC (called particulate GC) in VSM. CNS—central nervous system; GTP—guanosine triphosphate; NOS—nitric oxide synthase; PGC—particulate guanylyl cyclase; PNS—peripheral nervous system; ROI—reduced oxygen intermediates; SGC—soluble guanylyl cyclase. (A, From Reyes et al. [9], with permission; B, from Kim et al. [10], with permission.)
Impaired production of endothelium-dependent nitric oxide (EDNO) contributes to the vasoconstriction associated with established acute renal failure (ARF). Ischemia-reperfusion injury in the isolated erythrocyte-perfused kidney induced persistent intrarenal vasoconstriction. The endothelium-independent vasodilators (atrial natriuretic peptide [ANP] and nitroprusside) administered during the reflow period caused vasodilation and restored the elevated intrarenal vascular resistance (RVR) to normal. In marked contrast, two endothelium-dependent vasodilators (acetylcholine and A23187) had no effect on renal vascular resistance after ischemia-reflow. These data suggest that EDNO production is impaired following ischemic injury and that this loss of EDNO activity contributes to the vasoconstriction associated with ARF. (Adapted from Lieberthal [11]; with permission.)

Deleterious effects of nitric oxide (NO) on the viability of renal tubular epithelia. A, Hypoxia and reoxygenation lead to injury of tubular cells (filled circles); inhibition of NO production improves the viability of tubular cells subjected to hypoxia and reoxygenation (triangles in upper graph), whereas addition of L-arginine enhances the injury (triangles in lower graph). B, Amelioration of ischemic injury in vivo with antisense oligonucleotides to the iNOS: blood urea nitrogen (BUN), and creatinine (CR) in rats subjected to 45 minutes of renal ischemia after pretreatment with antisense phosphorothioate oligonucleotides (AS) directed to iNOS or with sense (S) and scrambled (SCR) constructs. C, Resistance of proximal tubule cells isolated from iNOS knockout mice to hypoxia-induced injury. LDH — lactic dehydrogenase. (A, From Yu et al. [12], with permission; B, from Noiri et al. [13], with permission; C, from Ling et al. [14], with permission.)
Proposed role of nitric oxide (NO) in radiocontrast-induced acute renal failure (ARF). A, Administration of iothalamate, a radiocontrast dye, to rats increases medullary blood flow. Inhibitors of either prostaglandin production (such as the NSAID, indomethacin) or inhibitors of NO synthesis (such as L-NAME) abolish the compensatory increase in medullary blood flow that occurs in response to radiocontrast administration. Thus, the stimulation of prostaglandin and NO production after radiocontrast administration is important in maintaining medullary perfusion and oxygenation after administration of contrast agents. B, Radiocontrast stimulates the production of vasodilators (such as prostaglandin [PGI₂] and endothelium-dependent nitric oxide [EDNO]) as well as endothelin and other vasoconstrictors within the normal kidney. The vasodilators counteract the effects of the vasoconstrictors so that intrarenal vasoconstriction in response to radiocontrast is usually modest and is associated with little or no loss of renal function. However, in situations when there is preexisting chronic renal insufficiency (CRF) the vasodilator response to radiocontrast is impaired, whereas production of endothelin and other vasoconstrictors is not affected or even increased. As a result, radiocontrast administration causes profound intrarenal vasoconstriction and can cause ARF in patients with CRF. This hypothesis would explain the predisposition of patients with chronic renal dysfunction, and especially diabetic nephropathy, to contrast-induced ARF. (A, Adapted from Agmon and Brezis [15], with permission; B, from Agmon et al. [16], with permission.)

Cellular calcium metabolism and potential targets of the elevated cytosolic calcium. A, Pathways of calcium mobilization. B, Pathophysiologic mechanisms ignited by the elevation of cytosolic calcium concentration. (A, Adapted from Goligorsky [17], with permission; B, from Edelstein and Schrier [18], with permission.)
14.14 Acute Renal Failure

**FIGURE 14-22**
Pathophysiologic sequelae of the elevated cytosolic calcium (Ca^{2+}).

A. The increase in cytosolic calcium concentration in hypoxic rat proximal tubules precedes the tubular damage as assessed by propidium iodide (PI) staining. B. Administration of calcium channel inhibitor verapamil before injection of norepinephrine (cross-hatched bars) significantly attenuated the drop in inulin clearance induced by norepinephrine alone (open bars). (A, Adapted from Kribben et al. [19], with permission; B, adapted from Burke et al. [20], with permission.)

**FIGURE 14-23**
Dynamics of heat shock proteins (HSP) in stressed cells. Mechanisms of activation and feedback control of the inducible heat shock gene. In the normal unstressed cell, heat shock factor (HSF) is rendered inactive by association with the constitutively expressed HSP70. After hypoxia or ATP depletion, partially denatured proteins (DP) become preferentially associated with HSC73, releasing HSF and allowing trimerization and binding to the heat shock element (HSE) to initiate the transcription of the heat shock gene. After translation, excess inducible HSP (HSP72) interacts with the trimerized HSF to convert it back to its monomeric state and release it from the HSE, thus turning off the response. (Adapted from Kashgarian [21], with permission.)
Cellular sources of reactive oxygen species (ROS) defense systems from free radicals. Superoxide and hydrogen peroxide are produced during normal cellular metabolism. ROS are constantly being produced by the normal cell during a number of physiologic reactions. Mitochondrial respiration is an important source of superoxide production under normal conditions and can be increased during ischemia-reflow or gentamycin-induced renal injury. A number of enzymes generate superoxide and hydrogen peroxide during their catalytic cycling. These include cyclooxygenases and lipoxygenes that catalyze prostanoid and leukotriene synthesis. Some cells (such as leukocytes, endothelial cells, and vascular smooth muscle cells) have NADH or NADPH oxidase enzymes in the plasma membrane that are capable of generating superoxide. Xanthine oxidase, which converts hypoxanthine to xanthine, has been implicated as an important source of ROS after ischemia-reperfusion injury. Cytochrome p450, which is bound to the membrane of the endoplasmic reticulum, can be increased by the presence of high concentrations of metabolites that are oxidized by this cytochrome or by injurious events that uncouple the activity of the p450. Finally, the oxidation of small molecules including free heme, thiols, hydroquinones, catecholamines, flavins, and tetrahydropterins, also contribute to intracellular superoxide production. (Adapted from [22]; with permission.)
Evidence suggesting a role for reactive oxygen metabolites in acute renal failure. The increased ROS production results from two major sources: the conversion of hypoxanthine to xanthine by xanthine dehydrogenase and the oxidation of NADH by NADH oxidase(s). During the period of ischemia, oxygen deprivation results in the massive dephosphorylation of adenine nucleotides to hypoxanthine. Normally, hypoxanthine is metabolized by xanthine dehydrogenase which uses NAD+ rather than oxygen as the acceptor of electrons and does not generate free radicals. However, during ischemia, xanthine dehydrogenase is converted to xanthine oxidase. When oxygen becomes available during reperfusion, the metabolism of hypoxanthine by xanthine oxidase generates superoxide. Conversion of NAD+ to its reduced form, NADH, and the accumulation of NADH occurs during ischemia. During the reperfusion period, the conversion of NADH back to NAD+ by NADH oxidase also results in a burst of superoxide production. (From Ueda et al. [23]; with permission.)

**EVIDENCE SUGGESTING A ROLE FOR REACTIVE OXYGEN METABOLITES IN ISCHEMIC ACUTE RENAL FAILURE**

Enhanced generation of reactive oxygen metabolites and xanthine oxidase and increased conversion of xanthine dehydrogenase to oxidase occur in vitro and in vivo models of injury.

Lipid peroxidation occurs in vitro and in vivo models of injury, and this can be prevented by scavengers of reactive oxygen metabolites, xanthine oxidase inhibitors, or iron chelators.

Glutathione redox ratio, a parameter of "oxidant stress" decreases during ischemia and markedly increases on reperfusion.

Scavengers of reactive oxygen metabolites, antioxidants, xanthine oxidase inhibitors, and iron chelators protect against injury.

A diet deficient in selenium and vitamin E increases susceptibility to injury.

Inhibition of catalase exacerbates injury, and transgenic mice with increased superoxide dismutase activity are less susceptible to injury.

**FIGURE 14-25**

FIGURE 14-26 Effect of different scavengers of reactive oxygen metabolites and iron chelators on, A, blood urea nitrogen (BUN) and, B, creatinine in gentamicin-induced acute renal failure. The numbers shown above the error bars indicate the number of animals in each group. Benz—sodium benzoate; Cont—control group; DFO—deferoxamine; DHB—2,3 dihydroxybenzoic acid; DMSO—dimethyl sulfoxide; DMTU—dimethylthiourea; Gent—gentamicin group. (From Ueda et al. [23]; with permission.)

**FIGURE 14-27**

Production of the hydroxyl radical: the Haber-Weiss reaction. Superoxide is converted to hydrogen peroxide by superoxide dismutase. Superoxide and hydrogen peroxide per se are not highly reactive and cytotoxic. However, hydrogen peroxide can be converted to the highly reactive and injurious hydroxyl radical by an iron-catalyzed reaction that requires the presence of free reduced iron. The availability of free "catalytic iron" is a critical determinant of hydroxyl radical production. In addition to providing a source of hydroxyl radical, superoxide potentiates hydroxyl radical production in two ways: by releasing free iron from iron stores such as ferritin and by reducing ferric iron and recycling the available free iron back to the ferrous form. The heme moiety of hemoglobin, myoglobin, or cytochrome present in normal cells can be oxidized to metheme (Fe³⁺). The further oxidation of metheme results in the production of an oxyferryl moiety (Fe⁴+=O), which is a long-lived, strong oxidant which likely plays a role in the cellular injury associated with hemoglobinuria and myoglobinuria.

Activated leukocytes produce superoxide and hydrogen peroxide via the activity of a membrane-bound enzyme NADPH oxidase. This superoxide and hydrogen peroxide can be converted to hydroxyl radical via the Haber-Weiss reaction. Also, the enzyme myeloperoxidase, which is specific to leukocytes, converts hydrogen peroxide to another highly reactive and injurious oxidant, hypochlorous acid.
Pathophysiology of Ischemic Acute Renal Failure

FIGURE 14-28
Cell injury: point of convergence between the reduced oxygen intermediates-generating and reduced nitrogen intermediates-generating pathways, A, and mechanisms of lipid peroxidation, B.

FIGURE 14-29
Detection of peroxynitrite production and lipid peroxidation in ischemic acute renal failure. A, Formation of nitrotyrosine as an indicator of ONOO⁻ production. Interactions between reactive oxygen species such as the hydroxyl radical results in injury to the ribose-phosphate backbone of DNA. This results in single- and double-strand breaks. ROS can also cause modification and deletion of individual bases within the DNA molecule. Interaction between reactive oxygen and nitrogen species results in injury to the ribose-phosphate backbone of DNA, nuclear DNA fragmentation (single- and double-strand breaks) and activation of poly-(ADP)-ribose synthase. B, Immunohistochemical staining of kidneys with antibodies to nitrotyrosine. C, Western blot analysis of nitrotyrosine. D, Reactions describing lipid peroxidation and formation of hemiacetal products. The interaction of oxygen radicals with lipid bilayers leads to the removal of hydrogen atoms from the unsaturated fatty acids bound to phospholipid. This process is called lipid peroxidation. In addition to impairing the structural and functional integrity of cell membranes, lipid peroxidation can lead to a self-perpetuating chain reaction in which additional ROS are generated.

(Continued on next page)
Leukocytes in Acute Renal Failure

A, The normal inflammatory response is mediated by the release of cytokines that induce leukocyte chemotaxis and activation. The initial interaction of leukocytes with endothelium is mediated by the selectins and their ligands both of which are present on leukocytes and endothelial cells.

(Continued on next page)
B. **LEUKOCYTE ADHESION MOLECULES AND THEIR LIGANDS POTENTIALLY IMPORTANT IN ACUTE RENAL FAILURE**

<table>
<thead>
<tr>
<th>Major Families</th>
<th>Cell Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectins</td>
<td></td>
</tr>
<tr>
<td>L-selectin</td>
<td>Leukocytes</td>
</tr>
<tr>
<td>P-selectin</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>E-selectin</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>Carbohydrate ligands for selectins</td>
<td></td>
</tr>
<tr>
<td>Sulphated polysaccharides</td>
<td>Endothelium</td>
</tr>
<tr>
<td>Oligosaccharides</td>
<td>Leukocytes</td>
</tr>
<tr>
<td>Integrins</td>
<td></td>
</tr>
<tr>
<td>CD11a/CD18</td>
<td>Leukocytes</td>
</tr>
<tr>
<td>CD11b/CD18</td>
<td>Leukocytes</td>
</tr>
<tr>
<td>Immunoglobulin G-like ligands for integrins</td>
<td></td>
</tr>
<tr>
<td>Intracellular adhesion molecules (ICAM)</td>
<td>Endothelial cells</td>
</tr>
</tbody>
</table>

**FIGURE 14-29** (Continued)

B. Selectin-mediated leukocyte-endothelial interaction results in the rolling of leukocytes along the endothelium and facilitates the firm adhesion and immobilization of leukocytes. Immobilization of leukocytes to endothelium is mediated by the β2-integrin adhesion molecules on leukocytes and their ICAM ligands on endothelial cells. Immobilization of leukocytes is necessary for diapedesis of leukocytes between endothelial cells into parenchymal tissue. Leukocytes release proteases, elastases, and reactive oxygen radicals that induce tissue injury. Activated leukocytes also elaborate cytokines such as interleukin 1 and tumor necrosis factor which attract additional leukocytes to the site, causing further injury.

**FIGURE 14-31**
Neutralizing anti–ICAM antibody ameliorates the course of ischemic renal failure with blood urea nitrogen, **A**, and plasma creatinine, **B**. Rats subjected to 30 minutes of bilateral renal ischemia or a sham-operation were divided into three groups that received either anti-ICAM antibody or its vehicle. Plasma creatinine levels are shown at 24, 48, and 72 hours. ICAM antibody ameliorates the severity of renal failure at all three time points. (Adapted from Kelly et al. [24]; with permission.)

**FIGURE 14-32**
Neutralizing anti–ICAM antibody reduces myeloperoxidase activity in rat kidneys exposed to 30 minutes of ischemia. *M* yeloperoxidase is an enzyme specific to leukocytes. Anti-ICAM antibody reduced myeloperoxidase activity (and by inference the number of leukocytes) in renal tissue after 30 minutes of ischemia. (Adapted from Kelly et al. [24]; with permission.)
Mechanisms of Cell Death: Necrosis and Apoptosis

**FIGURE 14-33**
Apoptosis and necrosis: two distinct morphologic forms of cell death. **A**, Necrosis. Cells undergoing necrosis become swollen and enlarged. The mitochondria become markedly abnormal. The main morphologic features of mitochondrial injury include swelling and flattening of the folds of the inner mitochondrial membrane (the cristae). The cell plasma membrane loses its integrity and allows the escape of cytosolic contents including lyzosomal proteases that cause injury and inflammation of the surrounding tissues. **B**, Apoptosis. In contrast to necrosis, apoptosis is associated with a progressive decrease in cell size and maintenance of a functionally and structurally intact plasma membrane. The decrease in cell size is due to both a loss of cytosolic volume and a decrease in the size of the nucleus. The most characteristic and specific morphologic feature of apoptosis is condensation of nuclear chromatin. Initially the chromatin condenses against the nuclear membrane. Then the nuclear membrane disappears, and the condensed chromatin fragments into many pieces. The plasma membrane undergoes a process of “budding,” which progresses to fragmentation of the cell itself. Multiple plasma membrane-bound fragments of condensed DNA called apoptotic bodies are formed as a result of cell fragmentation. The apoptotic cells and apoptotic bodies are rapidly phagocytosed by neighboring epithelial cells as well as professional phagocytes such as macrophages. The rapid phagocytosis of apoptotic bodies with intact plasma membranes ensures that apoptosis does not cause any surrounding inflammatory reaction.

**FIGURE 14-34**
Hypothetical schema of cellular events triggering apoptotic cell death. (From Kroemer et al. [25]; with permission.)
**FIGURE 14-35**
Phagocytosis of an apoptotic body by a renal tubular epithelial cell. Epithelial cells dying by apoptosis are not only phagocytosed by macrophages and leukocytes but by neighbouring epithelial cells as well. This electron micrograph shows a normal-looking epithelial cell containing an apoptotic body within a lysosome. The nucleus of an epithelial cell that has ingested the apoptotic body is normal (white arrow). The wall of the lysosome containing the apoptotic body (black arrow) is clearly visible. The apoptotic body consists of condensed chromatin surrounded by plasma membrane (black arrowheads).

**FIGURE 14-36**
DNA fragmentation in apoptosis vs necrosis. DNA is made up of nucleosomal units. Each nucleosome of DNA is about 200 base pairs in size and is surrounded by histones. Between nucleosomes are small stretches of DNA that are not surrounded by histones and are called linker regions. During apoptosis, early activation of endonuclease(s) causes double-strand breaks in DNA between nucleosomes. No fragmentation occurs in nucleosomes because the DNA is "protected" by the histones. Because of the size of nucleosomes, the DNA is fragmented during apoptosis into multiples of 200 base pair pieces (e.g., 200, 400, 600, 800). When the DNA of apoptotic cells is electrophoresed, a characteristic ladder pattern is found.

In contrast, necrosis is associated with the early release of lysosomal proteases, which cause proteolysis of nuclear histones, leaving "naked" stretches of DNA not protected by histones. Activation of endonucleases during necrosis therefore cause DNA cleavage at multiple sites into double- and single-stranded DNA fragments of varying size. Electrophoresis of DNA from necrotic cells results in a smear pattern.
Acute Renal Failure

**POTENTIAL CAUSES OF APOPTOSIS IN ACUTE RENAL FAILURE**

- Loss of survival factors
  - Deficiency of renal growth factors (e.g., IGF-1, EGF, HGF)
  - Loss of cell-cell and cell-matrix interactions
  - Receptor-mediated activators of apoptosis
  - Tumor necrosis factor
  - Fas/Fas ligand
- Cytotoxic events
  - Ischemia; hypoxia; anoxia
  - Oxidant injury
  - Nitric oxide
  - Cisplatin

**FIGURE 14-37**
Potential causes of apoptosis in acute renal failure (ARF). The same cytotoxic stimuli that induce necrosis cause apoptosis. The mechanism of cell death induced by a specific injury depends in large part on the severity of the injury. Because most cells require constant external signals, called survival signals, to remain viable, the loss of these survival signals can trigger apoptosis. In ARF, a deficiency of growth factors and loss of cell-substrate adhesion are potential causes of apoptosis. The death pathways induced by engagement of tumour necrosis factor (TNF) with the TNF receptor or Fas with its receptor (Fas ligand) are well known causes of apoptosis in immune cells. TNF and Fas can also induce apoptosis in epithelial cells and may contribute to cell death in ARF.

**FIGURE 14-38**
Apoptosis is mediated by a highly coordinated and genetically programmed pathway. The response to an apoptotic stimulus can be divided into a commitment and execution phases. During the commitment phase, the balance between a number of proapoptotic and anti-apoptotic mechanisms determine whether the cell survives or dies by apoptosis. The BCL-2 family of proteins consists of at least 12 isoforms, which play important roles in the commitment phase. Some of the BCL-2 family of proteins (e.g., BCL-2 and BCL-XL) protect cells from apoptosis whereas other members of the same family (e.g., BAD and Bax) serve proapoptotic functions. Apoptosis is executed by a final common pathway mediated by a class of cysteine proteases—caspases. Caspases are proteolytic enzymes present in cells in an inactive form. Once cells are committed to undergo apoptosis, these caspases are activated. Some caspases activate other caspases in a hierarchical fashion resulting in a cascade of caspase activation. Eventually, caspases that target specific substrates within the cell are activated. Some substrates for caspases that have been identified include nuclear membrane components (such as lamin), cytoskeletal elements (such as actin and fodrin) and DNA repair enzymes and transcription elements. The proteolysis of this diverse array of substrates in the cell occurs in a predestined fashion and is responsible for the characteristic morphologic features of apoptosis.
Pathophysiology of Ischemic Acute Renal Failure

FIGURE 14-39

Therapeutic approaches, both experimental and in clinical use, to prevent and manage acute renal failure based on its pathogenetic mechanisms. ETR—ET receptor; GFR—glomerular filtration rate; HGF—hepatocyte growth factor 1; IGF-1—insulin-like growth factor 1; K—glomerular ultrafiltration coefficient; NOS—nitric oxide synthase; PMN—polymorphonuclear leukocytes; RBF—renal blood flow; T4—thyroxine.

References