Case - Acute Renal Failure

- 73 yo diabetic F w hx of mild HBP but normal renal function develops infection of R foot. Over 1 week fever, chills, inflammation swelling of her R foot and leg . She takes Motrin for pain. For 4 d low urine output.
- Admitted to hosp with BP 82/60 T102 P88 Confused disoriented Cor –Chest wnl Ext severe cellulitis of R foot and leg.
- BUN 106 mg/dl (nl 10-20) Pcreatinine 6.6 mg/dl (nl 0.6-1.2) .
- She is treated with fluids, antibiotics and dialysis.

Acute Renal Failure

- How do we know the patient has ARF?
- What are the possible etiologies of the acute renal failure?
- What are the pathophysiologic mechanisms that cause the ARF?
- How can you use knowledge of the mechanisms for Diagnosis and Treatment?

Clinical Significance of ARF

- Occurs in 5-10% of hospitalized pts
- Occurs in up to 25% of ICU pts
- Mortality rate is high especially for severe ARF (20-40%)
- Contributes to morbidity of critically ill pts
- Correct Dx and treatment depend upon knowledge of pathophysiology.

Hospital Acquired Renal Insufficiency

- Study of 4,622 consecutive pts admitted to medicine and surgery service of large urban tertiary care center
- Acute renal Insufficiency in > 7%
- Over-all mortality almost 20%
- For severe ARF (serum creatinine > 3mg/dl) mortality 38%

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Hospital Acquired Renal Insufficiency

Major Causes of Acute Renal Insufficiency

- Decreased renal perfusion 44%
- Medications 18%
- Radiographic Contrast Agents 13%
- Post-operative 17%
- Sepsis 8%

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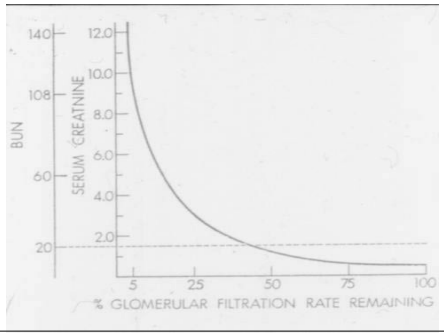
Relationship between Serum Creatinine and Renal Function (% GFR remaining)



Hospital Acquired ARF

Mortality versus Severity of ARF

Increase in S Creatinine	Mortality
<1	10%
1-2	22%
2-3	31%
>3	38%

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Acute Renal Failure

- A rapid deterioration of renal function (GFR) associated with the accumulation of normally excreted nitrogenous and other waste products.
- All forms of ARF typically have an elevated blood level of creatinine and BUN

Three major patterns:

- Post-renal Azotemia (Obstruction)
- Pre-renal Azotemia (Perfusion problem)
- Intrinsic Renal Failure (ATN, AIN, AGN, vascular disease)

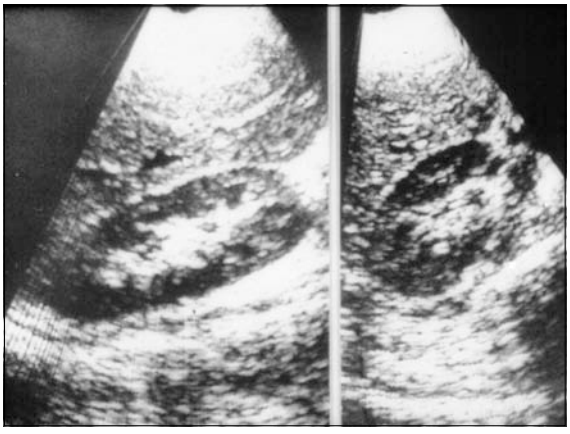
Post-renal Azotemia

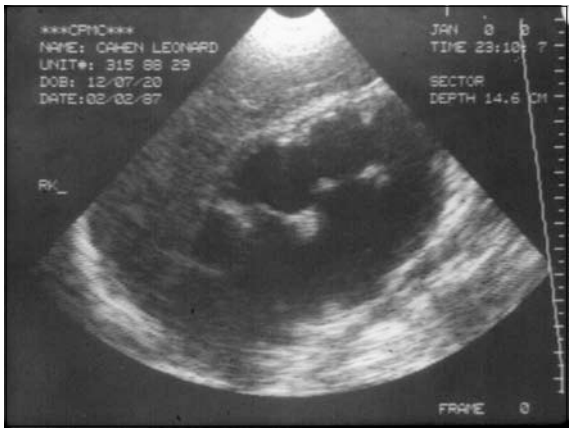
- ARF caused by obstruction to the outflow of urine.
- Blockage can occur at any level from the urethra to the pelvis of the kidneys.
- Common causes are prostatic enlargement due to benign hypertrophy or cancer, gynecologic malignancies, kidney stones.
- Anuria (<100cc/day)suggests obstruction.

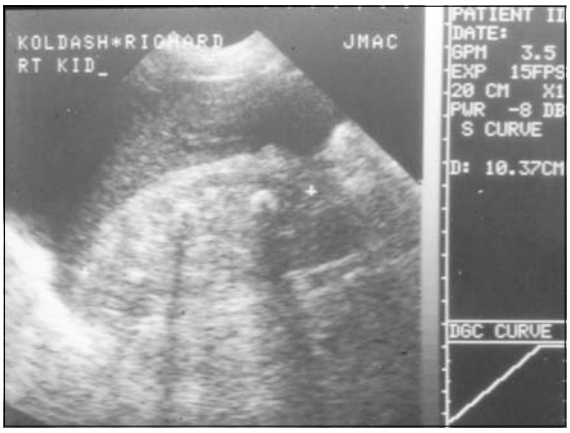
3 Rules about Post-renal Azotemia

- Exclude obstruction in every case of ARF
- Radiologic tests (IVP, CAT scan , etc.) can show there is no blockage.

  In most cases use ultrasonogram (USG) – bounces sound waves off kidney to take picture – fast, cheap, safe, no contrast.
- Unilateral obstruction does not cause progressive severe ARF.







Pre-Renal Azotemia

An Oliguric condition, associated with decreased GFR and retention of nitrogenous wastes, caused by decreased perfusion of the kidney

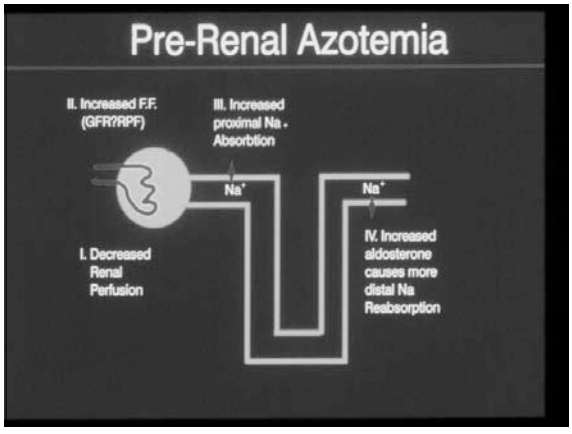
- Volume depletion
- Volume over-load

Potentially rapidly reversible

Urinary Findings in Pre-renal Azotemia

- Low urinary Na+ concentration (<20 mEq/L) and low FeNa+ (<1%)
- Large increase in BUN - High BUN/Pcreat ratio (>20:1)
- Increased Urine Osmolality (>400 mOsm/L) and urinary specific gravity.

Pre-Renal Azotemia



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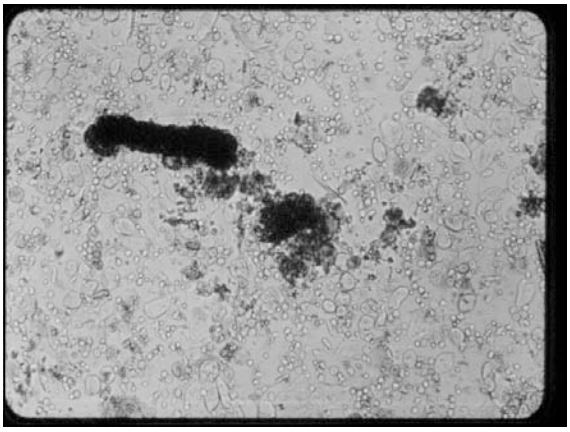
Acute Tubular Necrosis

- Most Common Pattern of Intrinsic ARF
- Physiologic Syndrome not Morphologic Etiologies
  - Ischemic
  - Nephrotoxins
- Classic Oliguric and Diuretic Phases
- Non-Oliguric ATN



Urinary Findings in Acute Tubular Necrosis

- High urinary Na+ concentration (>40 mEq/L) and high FeNa+ (>1%)
- Unchanged BUN/ plasma creatinine ratio in blood (10-15/1)
- Fixed urine osmolality (300mOsm/L) and urinary specific gravity (1.010)

Urinary Findings in Acute Renal Failure

	Pre-renal	ATN
UNa+	low (<20 mEq/L)	high (>40 mEq/L)
FE Na+	low (<1%)	high (>1%)
BUN/Pcreat	>20/1	10-15/1
Urine Osm	>400 mOsm/L	300 mOsm/L

Problem Conditions in Using FE Na+ in ARF

- Potent Diuretics
- Osmotic Diuretics
- Cirrhosis
- Chronic Renal Insufficiency

Non-Oliguric Acute Tubular Necrosis

- Increased Incidence
- Common with Nephrotoxins
- Difficult to Recognize
- Lower morbidity and mortality

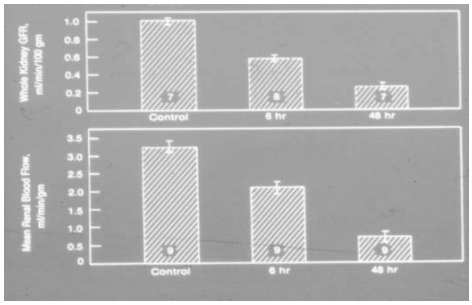
Mechanisms of Acute Tubular Necrosis

- Ischemic Animal Models of ATN
  (renal artery clamping, infuse intra-arterial vasoconstrictor).
- Nephrotoxic Animal Models
  (HgCl2, Uranyl Nitrate, Gentamicin, Cisplatinum, Cyclosporine).
- Not all models have the same pathogenesis.
- More than one mechanisms may be involved in each model of ARF.

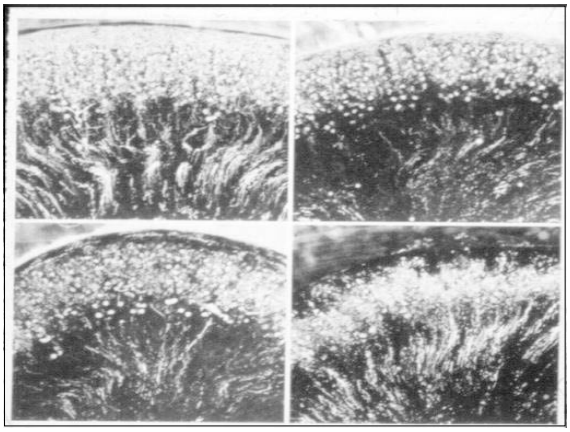
Why Is the GFR Reduced in Acute Tubular Necrosis?

- Vasoconstriction
- Back Leak of tubular fluid
- Intratubular Obstruction
- Altered Glomerular Permeability

Role of Renal Blood Flow in ARF



Changes in GFR and RBF over time in nephrotoxic rat model (UN) of ARF



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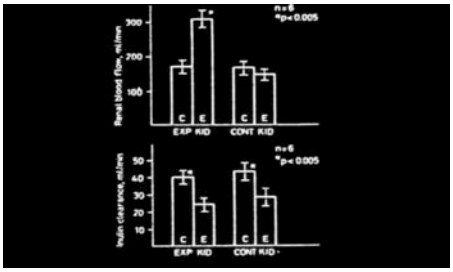
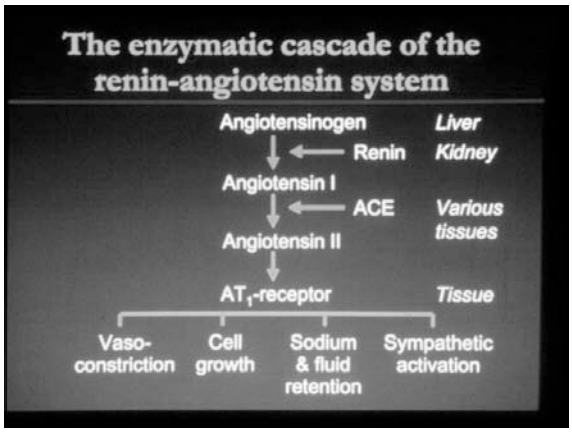
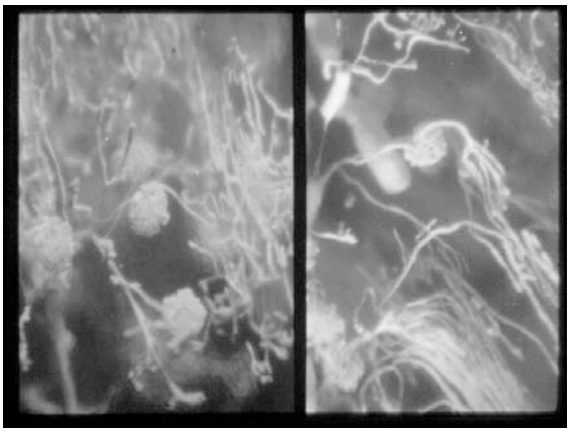


Restoration of RBF to high levels at 3 hrs does not correct the decrease in GFR after ARF is established in UN model.

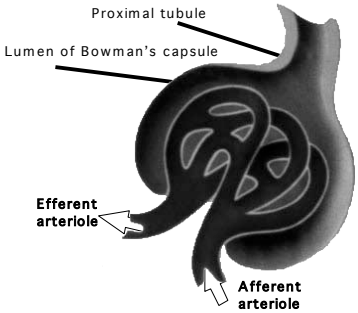
Role of Renin-Angiotensin System in ARF

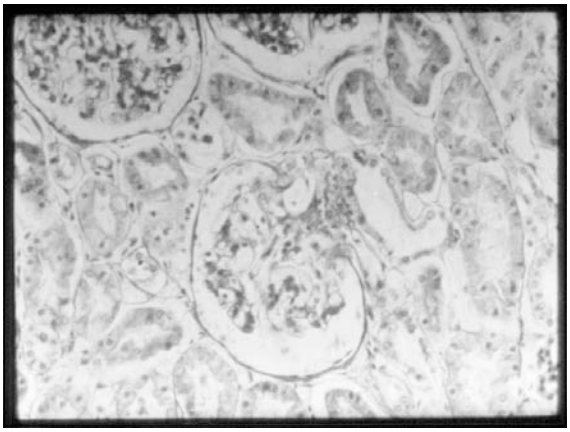
- Early studies - JGA hyperplasia.
- Increased plasma Renin and A II levels in ARF.
- Experiments with blockers of Renin-A II system.
- Tubulo glomerular Feedback Theory.





The Glomerulus

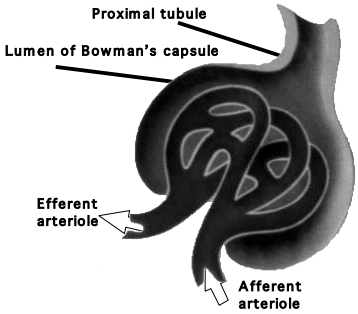




Tubulo-glomerular Feedback in ATN

Increased delivery of Cl- to the macula densa of the distal tubule leads to local vasoconstriction of the afferent arteriole of the same glomerulus.

The Glomerulus



Why Is the GFR Reduced in Acute Tubular Necrosis?

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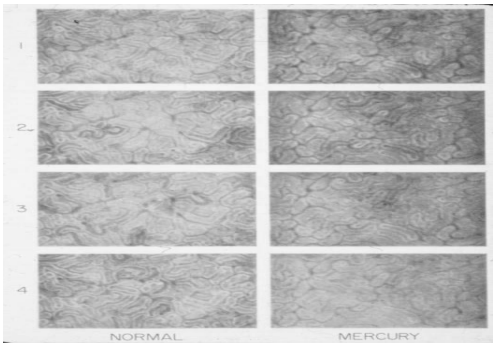
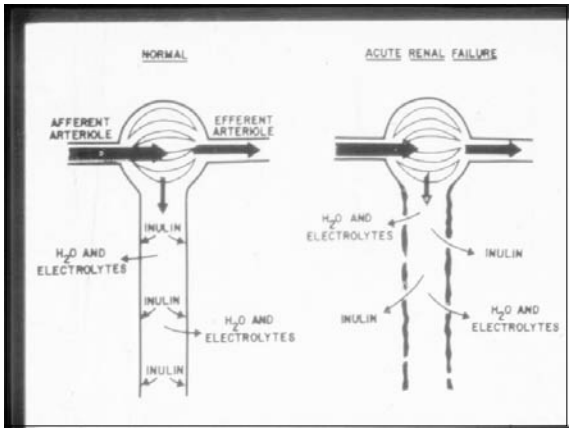
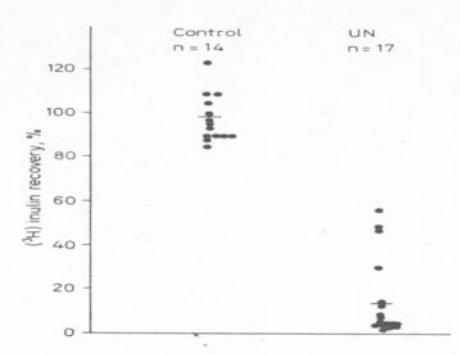


Injection of non-reabsorbable lisamine green dye into renal artery showing progressive concentration in tubules of normal animal as opposed to ATN HgCl2 model Bank et al. JCI 1967





Injection of radiolabeled inulin into proximal tubule and % recovery in urine – showing loss of recovery and back-leak in uranyl nitrate ATN model

Why Is the GFR Reduced in Acute Tubular Necrosis?

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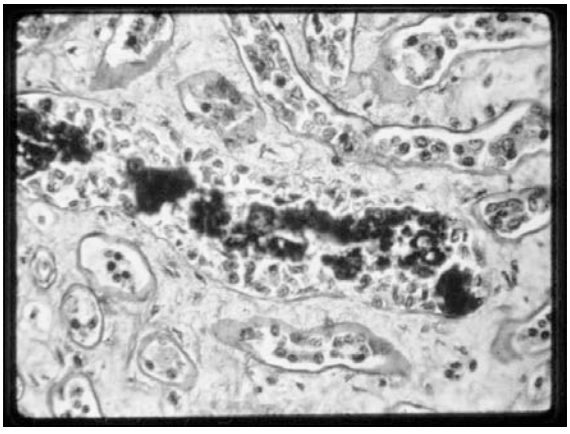

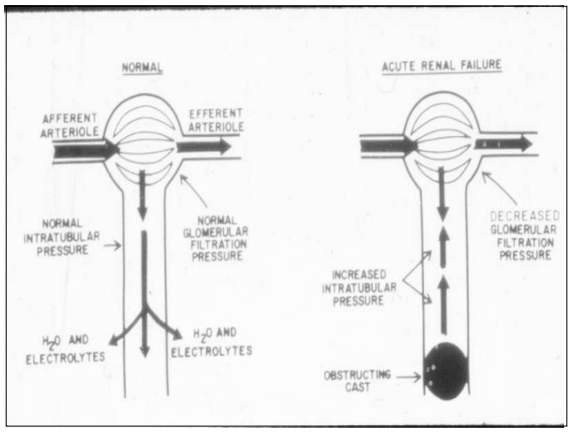

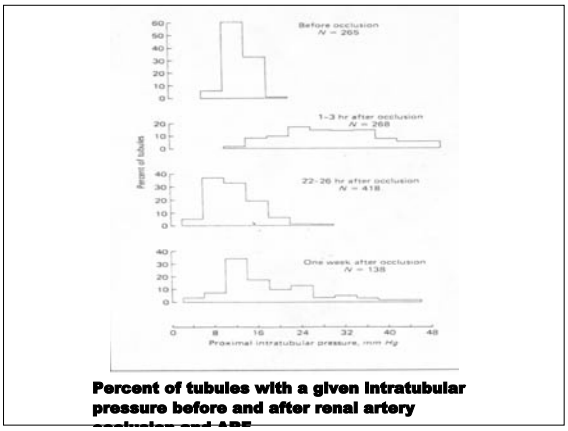

Percent of tubules with a given intratubular pressure before and after renal artery

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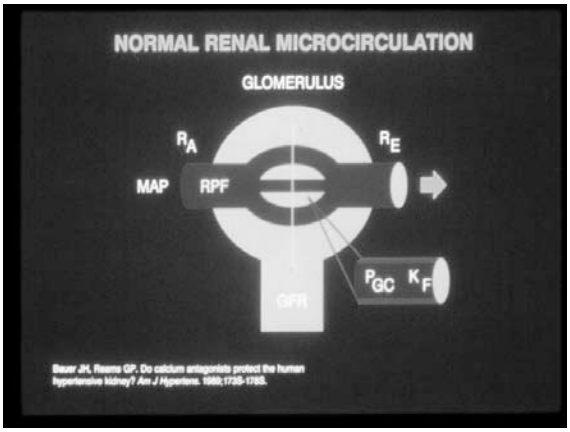

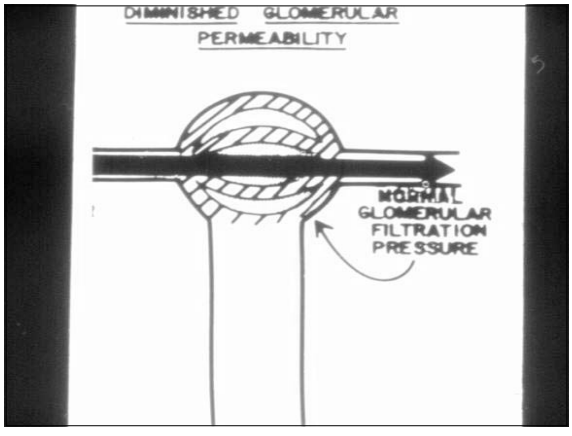

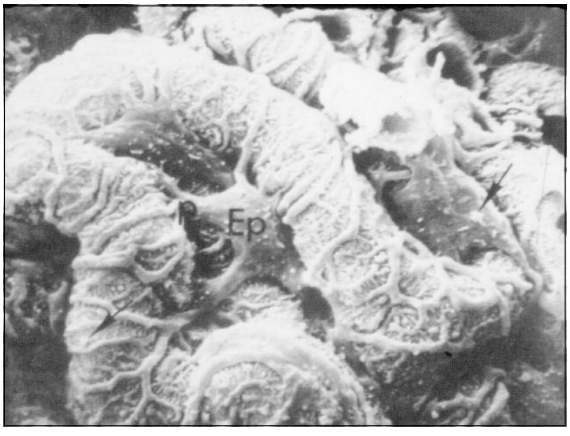


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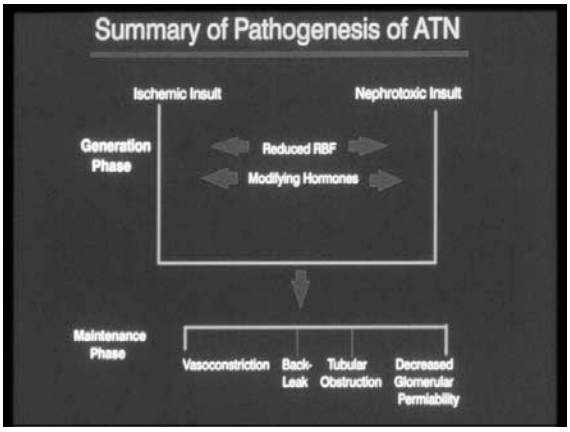
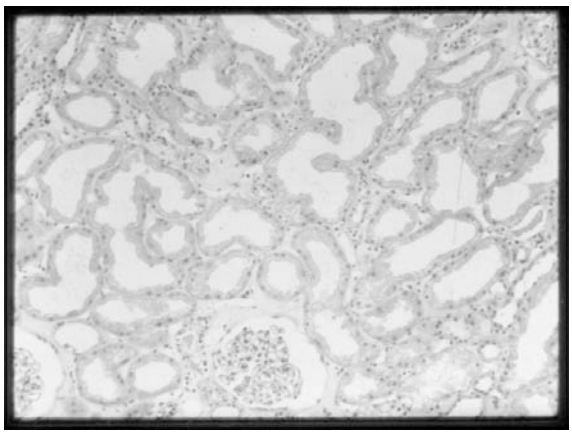
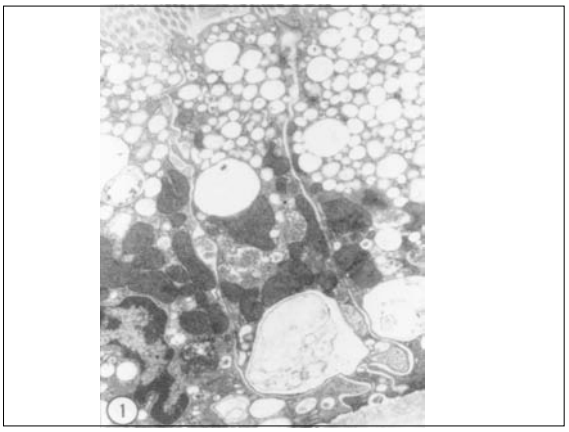

Summary of Pathogenesis of ATN
Ischemic Insult
Nephrotoxic Insult
Generation Phase
Reduced RBF
Modifying Hormones
Maintenance Phase
Vasoconstriction
Back-Leak
Tubular Obstruction
Decreased Glomerular Permiability

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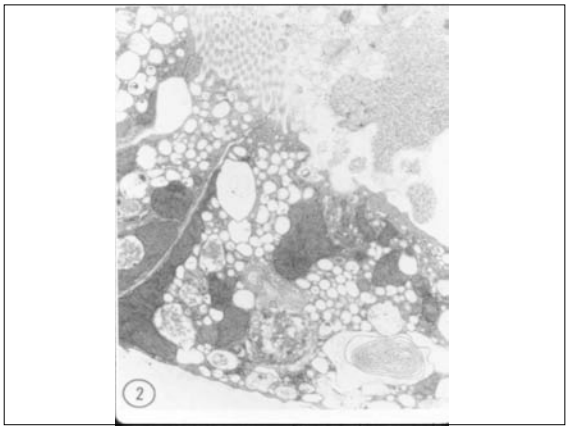
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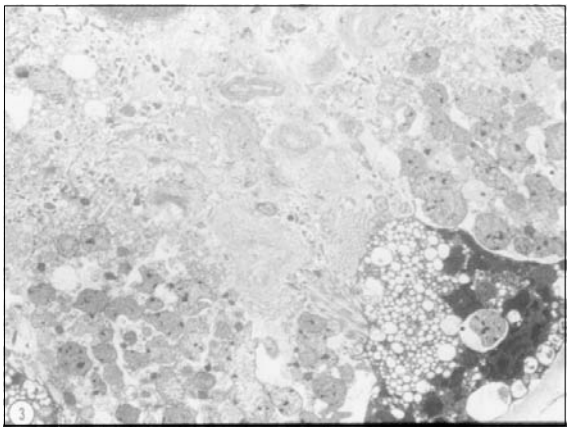
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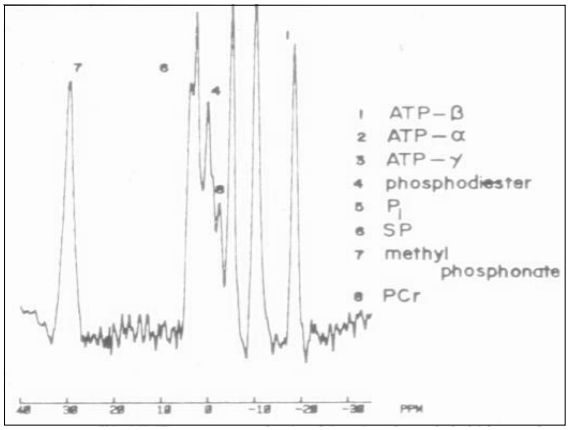
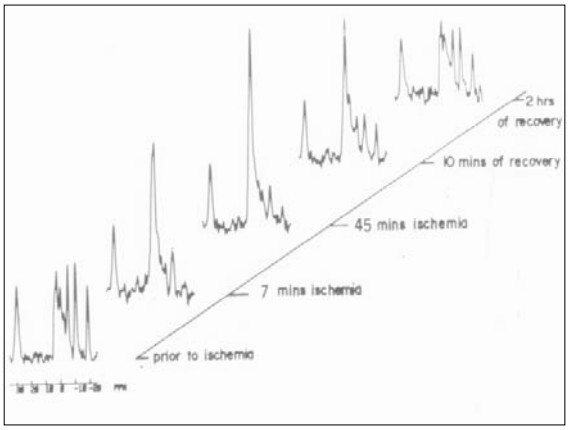
Biochemical Markers of Cell Injury

Function	Response
Mitochondria	
Basal O2 consumption	decreased
Max O2 consumption	decreased
Phospholipases	activated
Reactive Oxygen species	increased
Plasma Membrane	
Cellular potassium	decreased
Cellular calcium	increased
Adenine Nucleotides	
ATP levels	decreased
AMP levels	increased





Possible Mechanisms of Tubular Cell Injury and Necrosis

Ischemia — Nephrotoxic Insult

↓

Reduction of Cell ATP and ADP levels

↓

Inability to regulate intracellular ions (Na+ and Ca++)

↓

Swelling of Cytosol - Mitochondrial Damage - Activation Enzymes

↓

Organelle damage & increased membrane permeability

Molecular Responses to Renal Ischemia

- Increased gene expression
  - Genes involved in cell fate determinations: regeneration, apoptosis
  - Genes involved in inflammation
- Decreased gene expression – Loss of mature phenotype

Targets of Treatment ARF

- Offset vasoconstriction
  - Calcium channel blockage
  - Atrial natriuretic factor
  - Endothelin blockade
  - Adenosine-receptor blockade
  - Nitric oxide regulation
- Limit inflammation
  - α-MSH
  - Antiadhesion strategies, Anti-ICAM, Anti-integrins
  - Biocompatible membranes
  - Cytokine absorbing biomembranes
- Alter cell outcome
  - Growth factors & "survival" factors
- Change of dialysis prescription

Hospital Acquired Renal Insufficiency

Outcomes of Hospital Acquired ARF

- Partial recovery renal function 23%
- Discharged w increasing Pcreat 17%
- Discharged on chr. Hemodialysis 3%
- Death 20%

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