Acute Interstitial Nephritis - Reappraised

13th Congress of BANTAO

Sarajevo, 8 October 2017

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Renal Section, Department of Medicine
Baylor College of Medicine
Houston, TX

Overview of Presentation

- Historical Background
- Pathology
- Kidney Function
- Etiology
- Clinical & Laboratory Manifestations
- Diagnosis
- Treatment and Outcomes
- Take Home Messages

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- **Historical Background**
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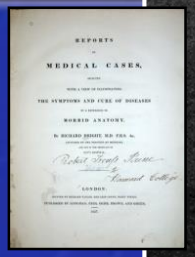
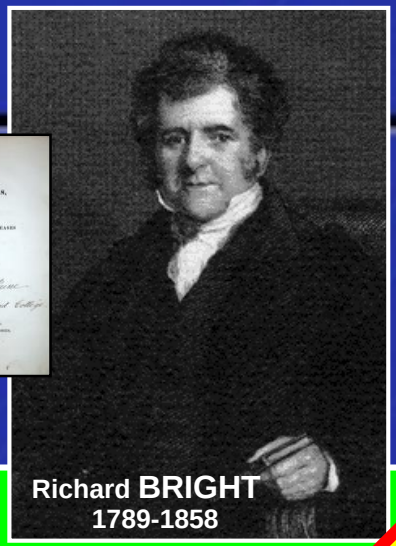
Origins of NEPHROLOGY …


REPORTS
OF
MEDICAL CASES,
LONDON.


Richard BRIGHT
1789-1858

19th Century

1827

Bright's Disease

1961

1961 ISN
1966 ASN
1993 BANTAO

NEPHROLOGY

Kidney Function Studies

Shock, Diuretics

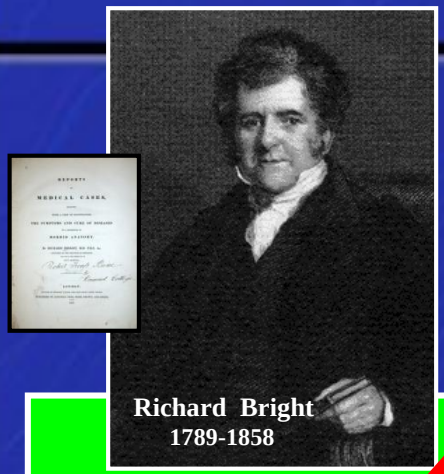
Technical Advances

Kidney Biopsy

Dialysis

Auto-analyzer

Origins of NEPHROLOGY … and AIN



Bright's Disease

*nephritis**

1873: **Acute**

Chronic

1827

1961

BANTAO
1993

ISN

NEPHROLOGY
Kidney Function Studies
SHOCK , Diuretics
Technical Advances
Kidney Biopsy
Dialysis
Autoanalyzer

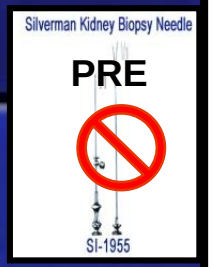
*'nephritis', 1580
'inflammation of the kidnies'

Am J Nephrol 2002;22:225-230
Adv Chron Kidney Dis 2008; 15:308-313

Histological Beginnings and the KIDNEY

CKD Classification

1850 - 1950



Rudolph VIRCHOW ("Cellular Pathology")

(1821-1902)

1858 **NEPHRITIS**

1. **Tubules** ***Parenchymatous Nephritis***

   (tubular, desquamative, catarrhal, croupous, diffuse, **Large White kidney**)

2. **Interstitium** ***Interstitial Nephritis***

   (cirrhotic, hobnail, non-desquamative, gouty, gin-drinker kidney, **Red Granular kidney**)

3. **Vessels** ***Amyloid*** (waxy, lardaceous)

William Bowman ***1847 Glomerulus***

(1816-1892)

Axel Key **1864 Glomerular** 'Mesangial' and Epithelial cells

(1832-1901)

Edwin KLEBS **1869 Glomerular Nephritis, Glomerulitis**

(1834-1912)

KLEBS' DISEASE ICD-9: 583.9

Diseases of the Kidney ~ 1890

- Glomeruli ± ?
- Vascular ± ?
- Parenchyma
  - A. Tubules
  - B. Interstitium

Councilman WT. ACUTE INTERSTITIAL NEPHRITIS

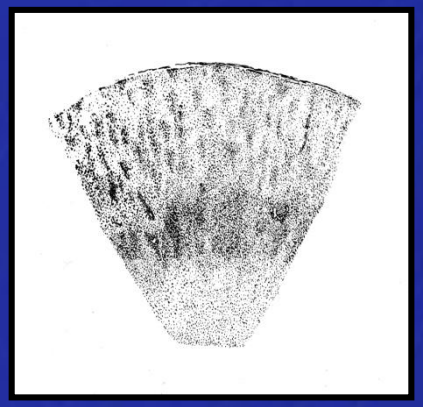
J Exp Med **1898**; *3:393- 422*

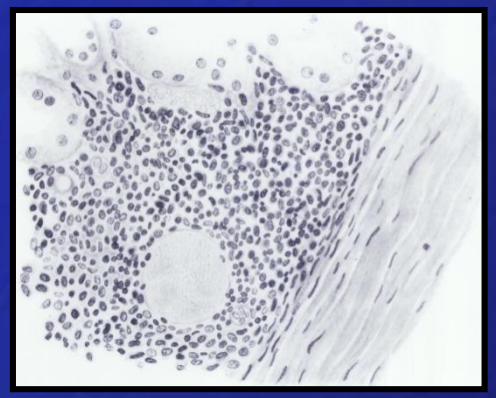
ACUTE INTERSTITIAL NEPHRITIS.

By W. T. COUNCILMAN, M. D.

(From the Sears Pathological Laboratory of Harvard University.)

Definition.—An acute inflammation of the kidney characterized by cellular and fluid exudation in the interstitial tissue, accompanied by, but not dependent on, degeneration of the epithelium; the exudation is not purulent in character, and the lesions may be both diffuse and focal.





INFECTION	#	AIN
Diphtheria	103	24
Scarlet Fever	20	5
Dipht.+Scarl. Fev.	23	5
Dipht.+Measles	5	2
Whooping Cough		1
Lobar Pneumonia		2
Meningitis		1
Empyema		1
AGN*		1
Post-abortion		1
TOTAL		**42**

The changing profile of AIN

1. ETIOLOGY

Antiquity **Infections** (?)

1890s *Infections*

1940s **Sulfonamides**

1950s **Antibiotics- Penicillin**

1960s **"*RENAISSANCE of AIN*"**

***Methicillin** 1959; **Ibuprofen** 1960*

1970s **Drugs – *Penicillins; NSAIDs***

Systemic Diseases

Idiopathic

2000s **DRUGS – *PPIs; Amoxicillin; Cipro***

KIDNEY BIOPSY

"Acute Renal Failure"

Hemodialysis

(Auto-analyzer)

ACUTE INTERSTITIAL NEPHRITIS DUE TO DRUG SENSITIVITY

BY

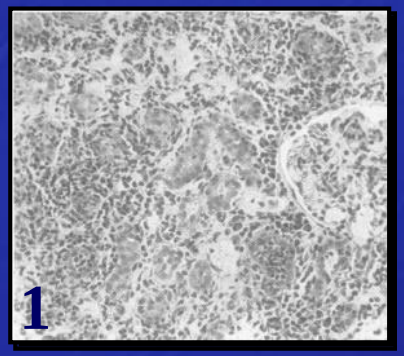
S. B. de C. BAKER, M.D. R. T. WILLIAMS, M.B., B.Ch., M.R.C.P.

From the Departments of Pathology and Medicine, University of Manchester

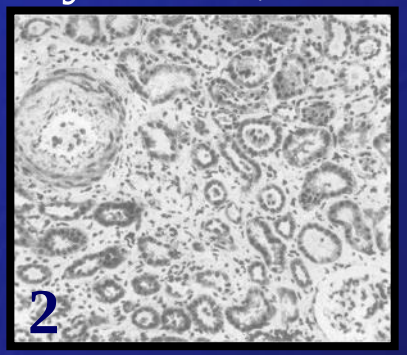
BMJ 1963; 1:1655-1658

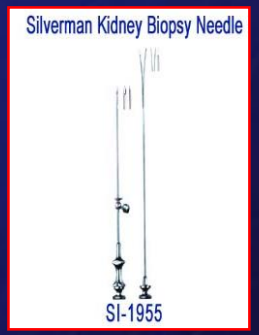
47 year old man on phenindione (post-MI anticoagulation), skin rash, hematuria, jaundice, anuria. Dialysis x 2, recovered.

Biopsied x2:



1 month





Baker SB, Williams RT: **Acute Interstitial Nephritis**

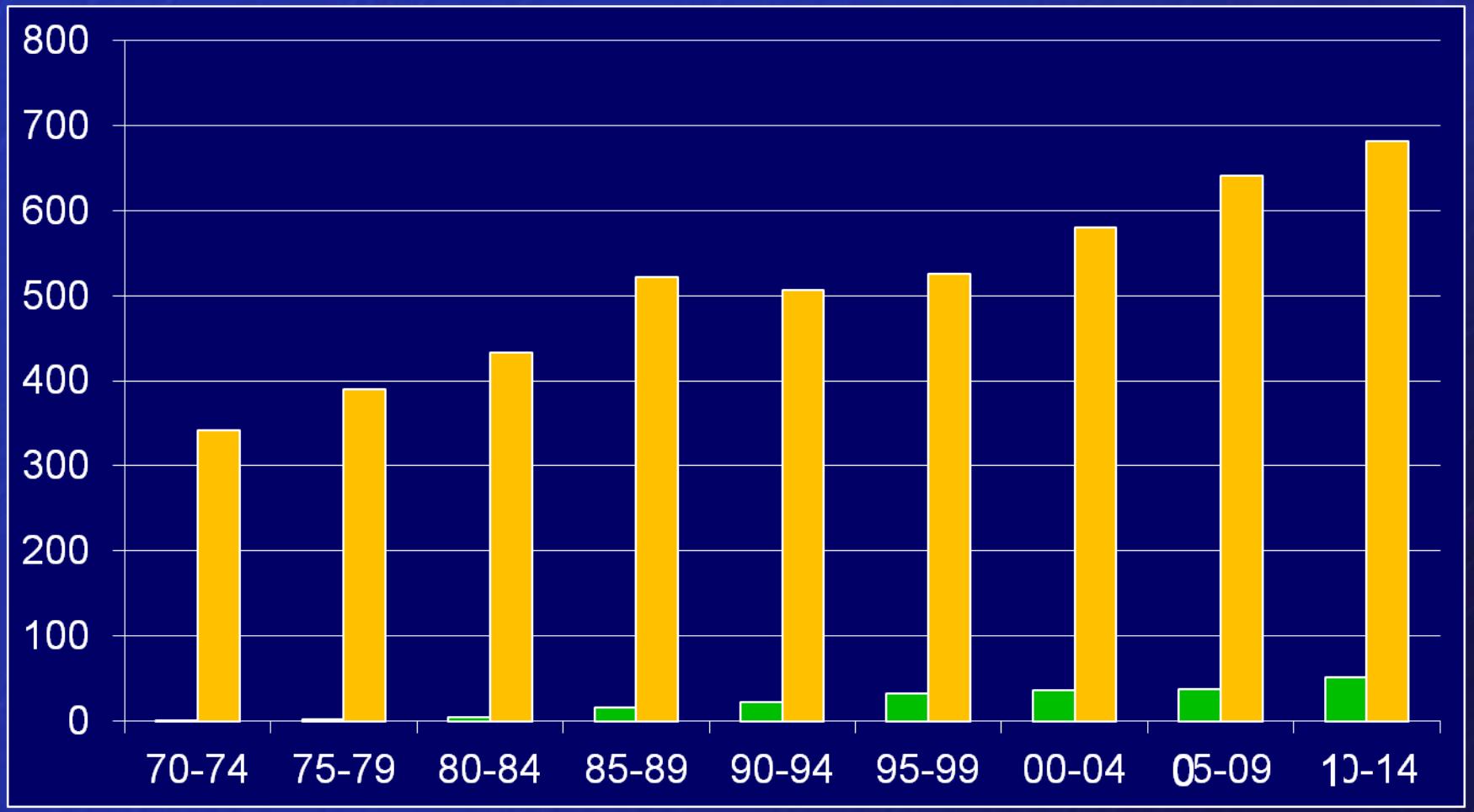
Am Heart J 1964; 68: 281-282

The RENAISSANCE of AIN 1960s

The changing profile of AIN
2. NOMENCLATURE

1. Acute Interstitial Nephritis
2. Acute Tubulo-Interstitial Nephropathy
3. Acute Tubulo-Interstitial nephritis
4. Tubulo-interstitial nephritis

Number of PubMed entries for AIN and ATIN



Clin Nephrol 2014; 82:149-162

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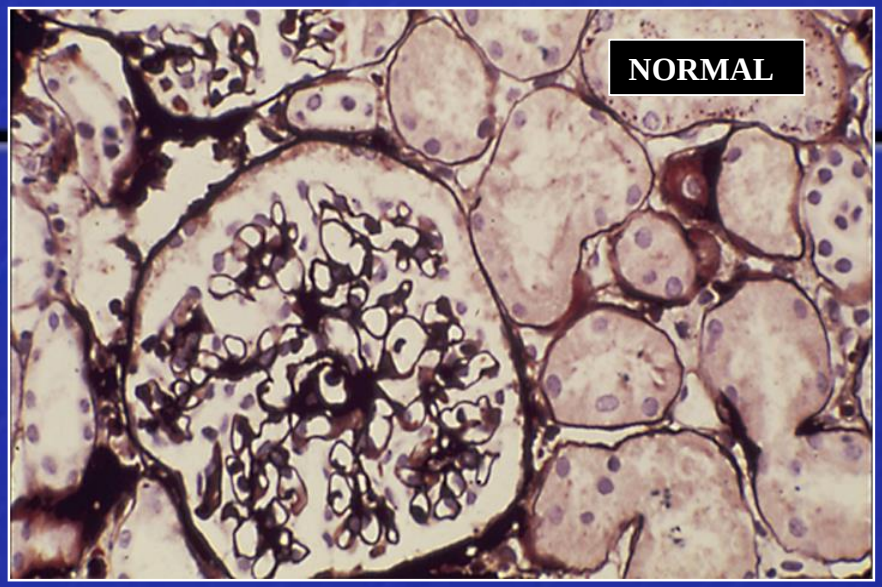
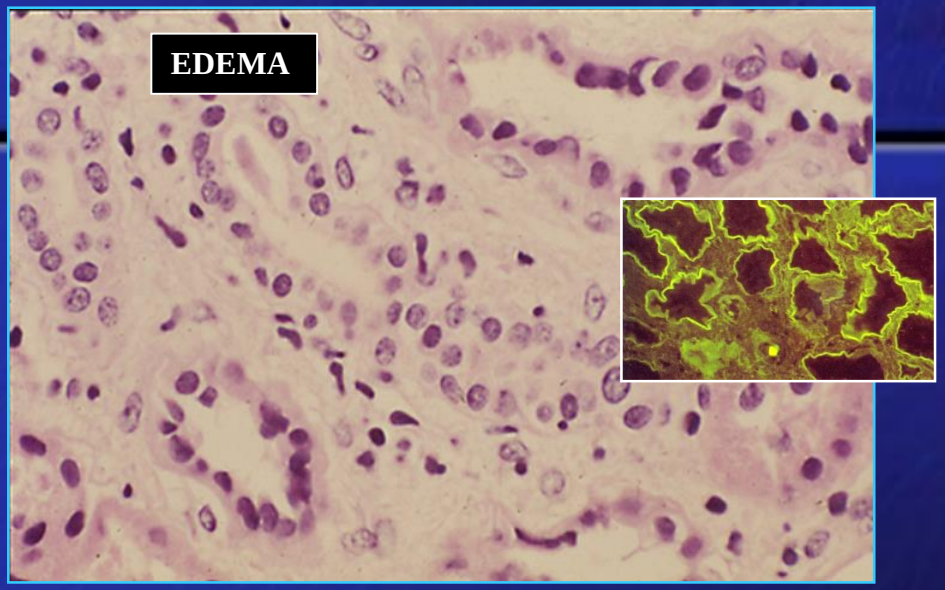
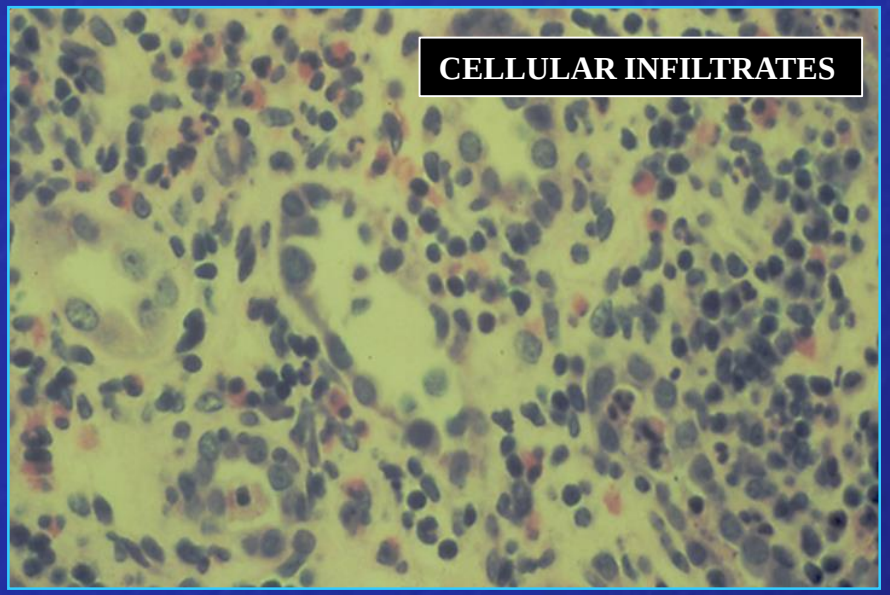
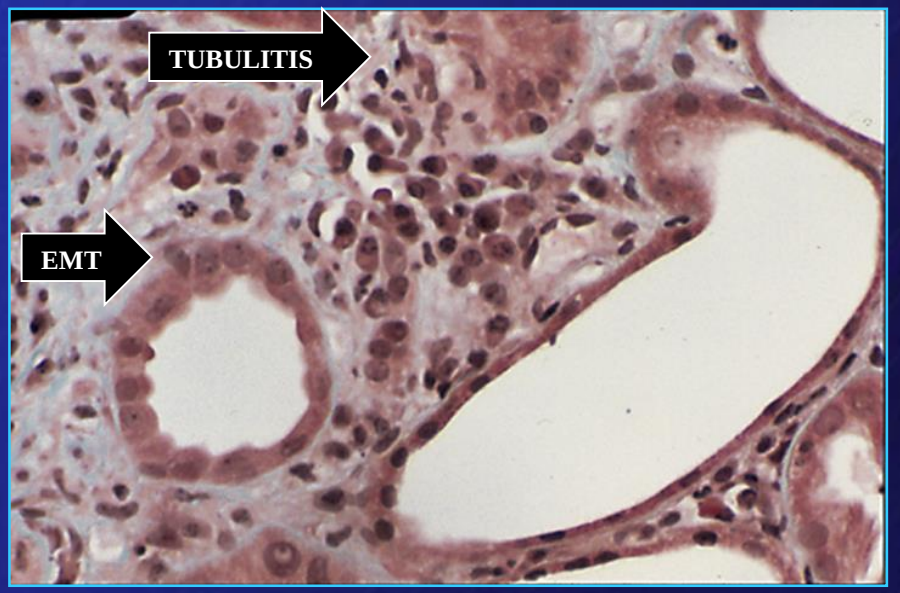








(Temporal !) **Variable!**

AIN - MORPHOLGY

FOCAL → **DIFFUSE**

I. INTERSTITIUM

- **Cellular Infiltrate** : + → ++++
- **Edema** : + → ++++
- **Fibrosis** : 0 → ±

II. TUBULES

- **Epithelium** : Periubular Injury → Necrosis
- **Basement membrane** : Peritubular Injury → Disruption
- **Shape** : Preserved

III. GLOMERULI

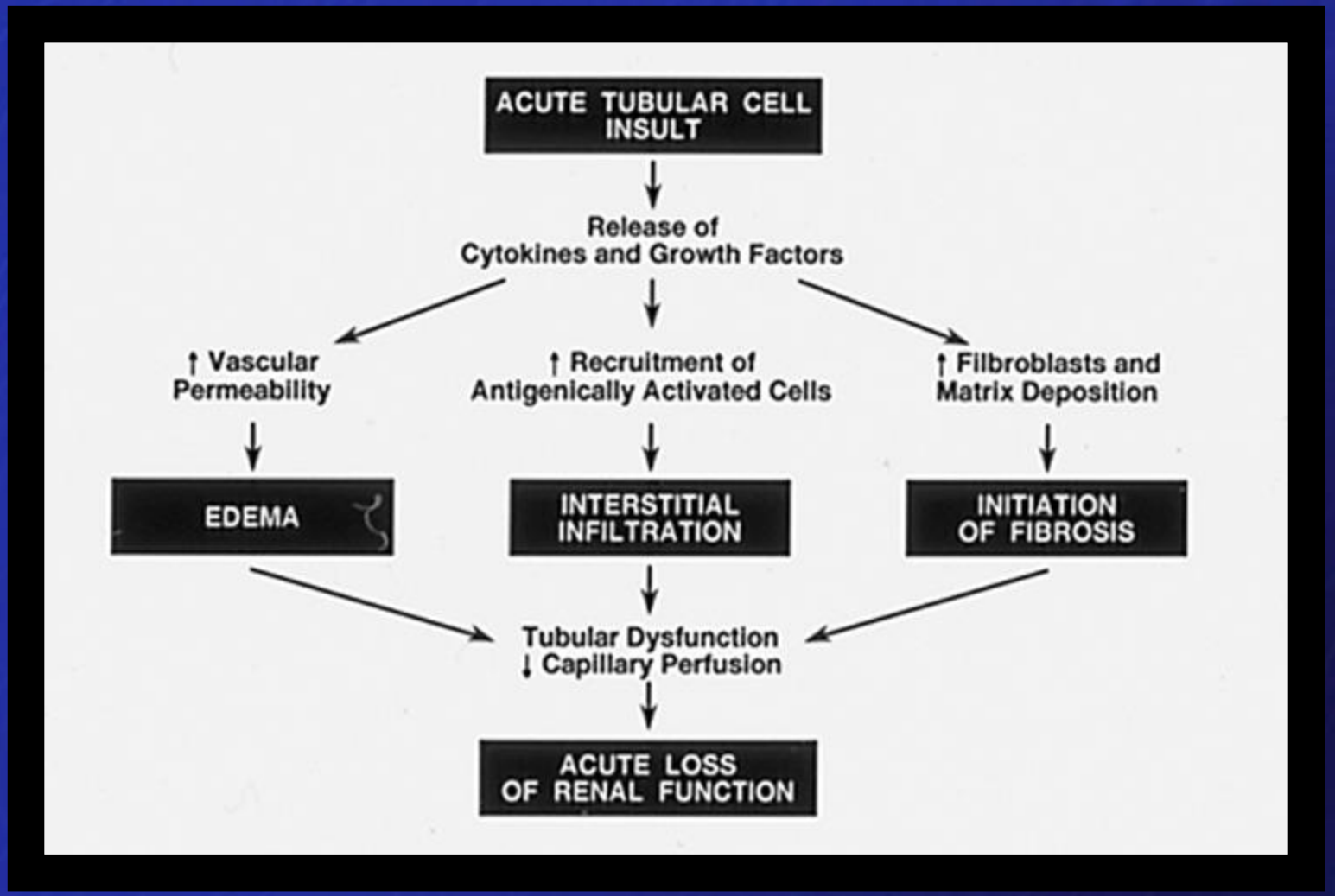
- **Structure** : 0 → M.C.D.
- **Function** : Acute renal failure / AKI

IV. VASCULATURE

Minimal / Reversible

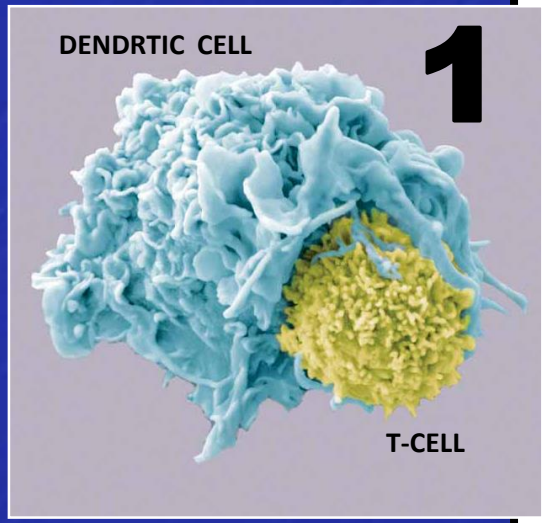
(Temporal !) **Variable Severity?**

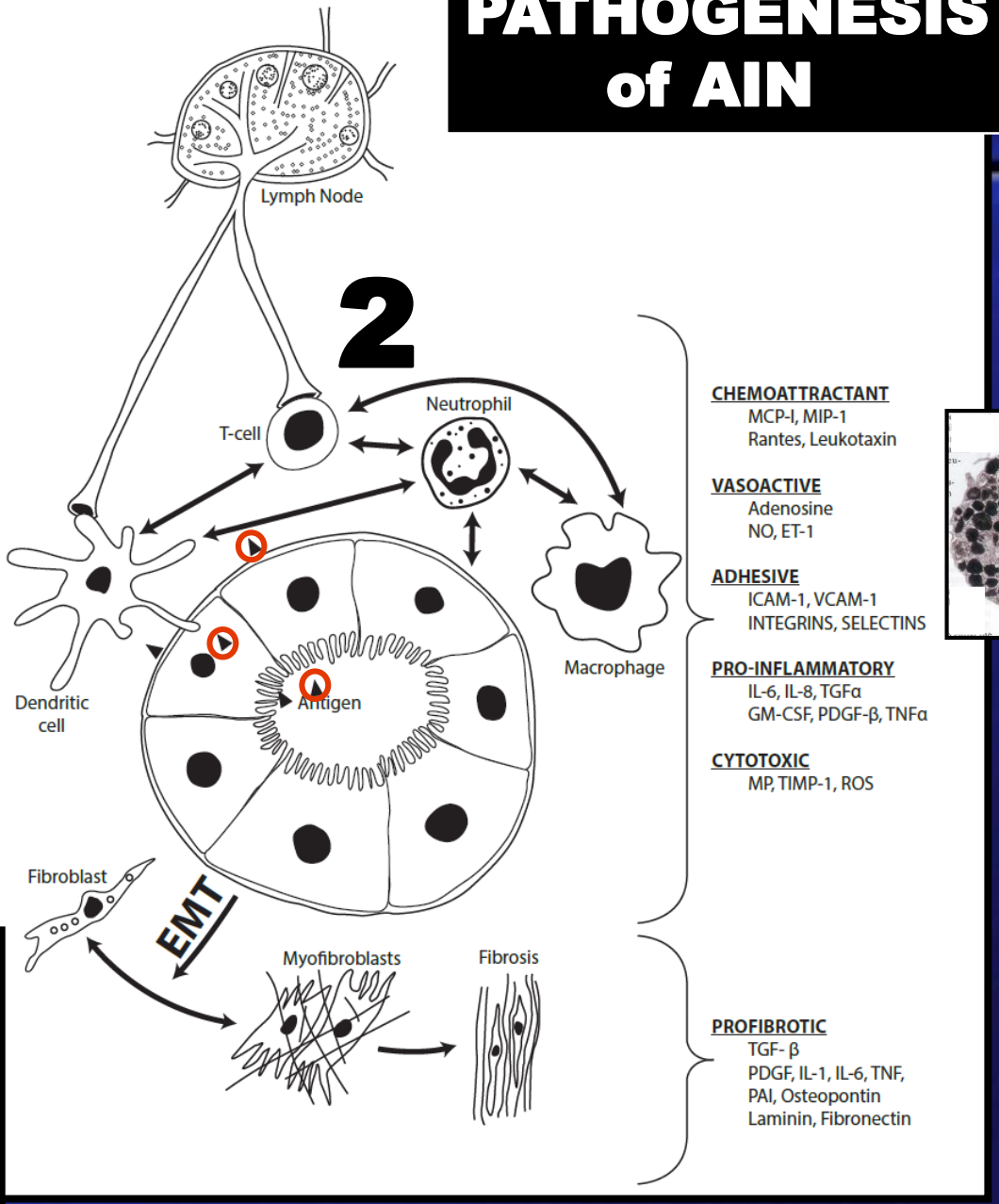
AIN - MECHANISMS OF INJURY



PATHOGENESIS of AIN

1. Activation
2. Signaling
3. Fibrogenic
4. Destructive





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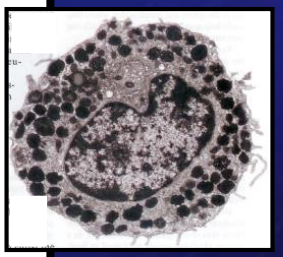
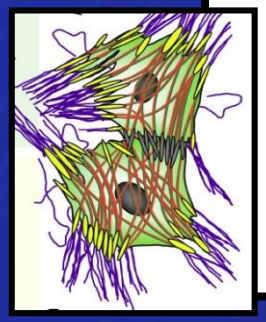


MACROPHAGE

4



MYOFIBROBLAST

Clin Nephrol 2014; 82:149-162

AIN – Outcomes

Recovery

GOOD

ACUTE

Edema
Infiltration
Tubular Injury

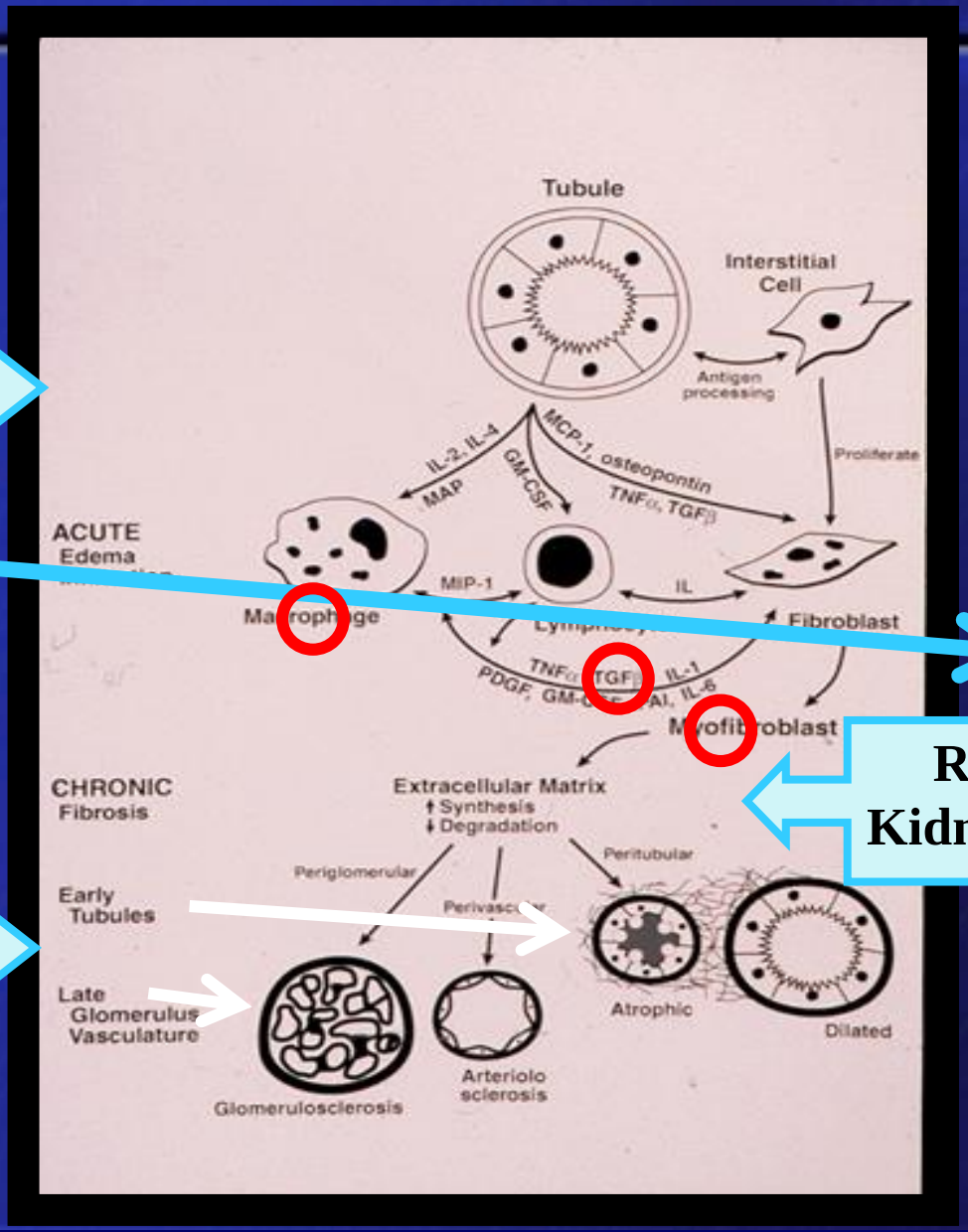
BAD

2

CHRONIC

Fibrosis
Tubular atrophy
and dilatation

ESRD



1

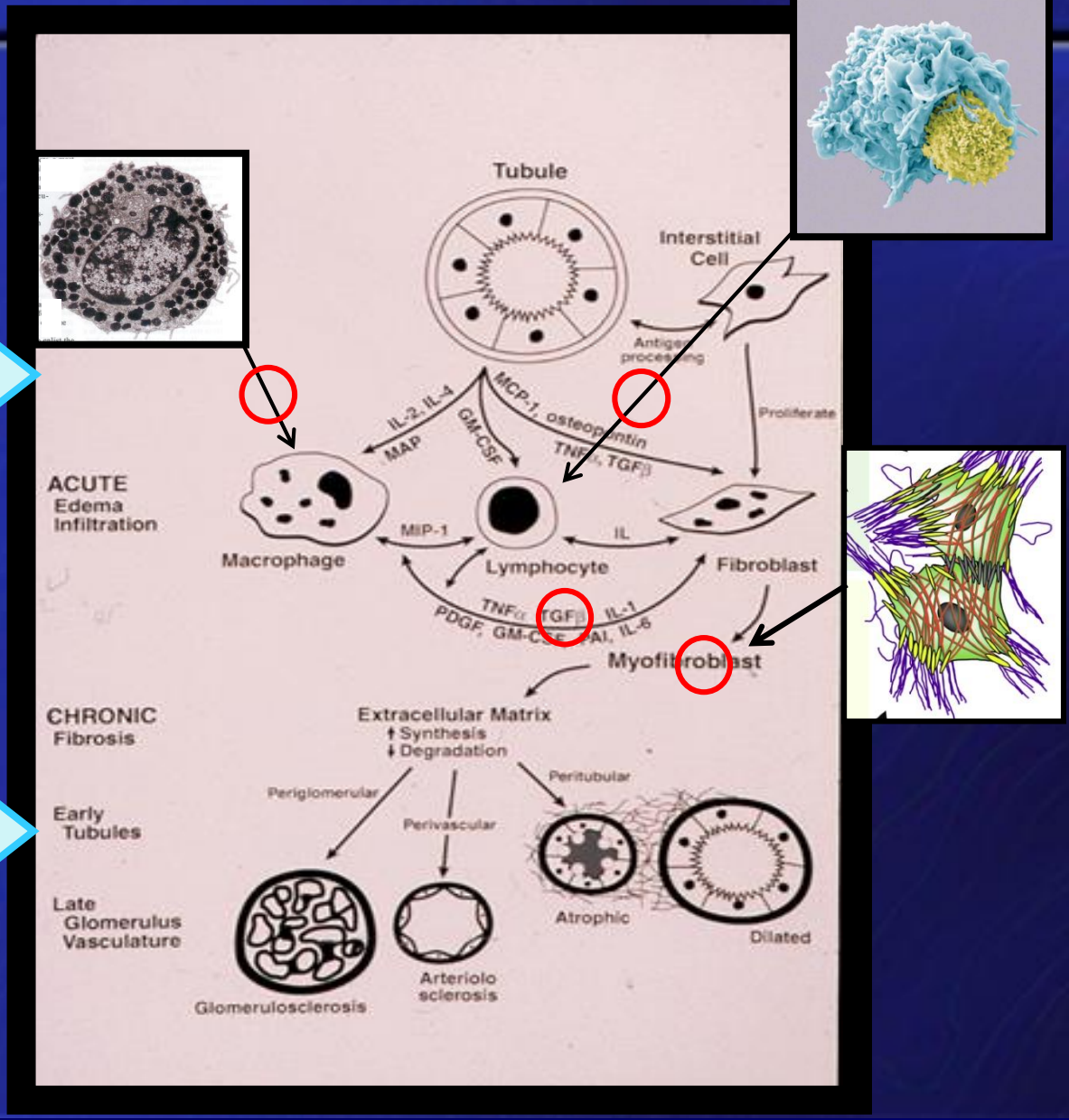
Residual Kidney Injury

CKD

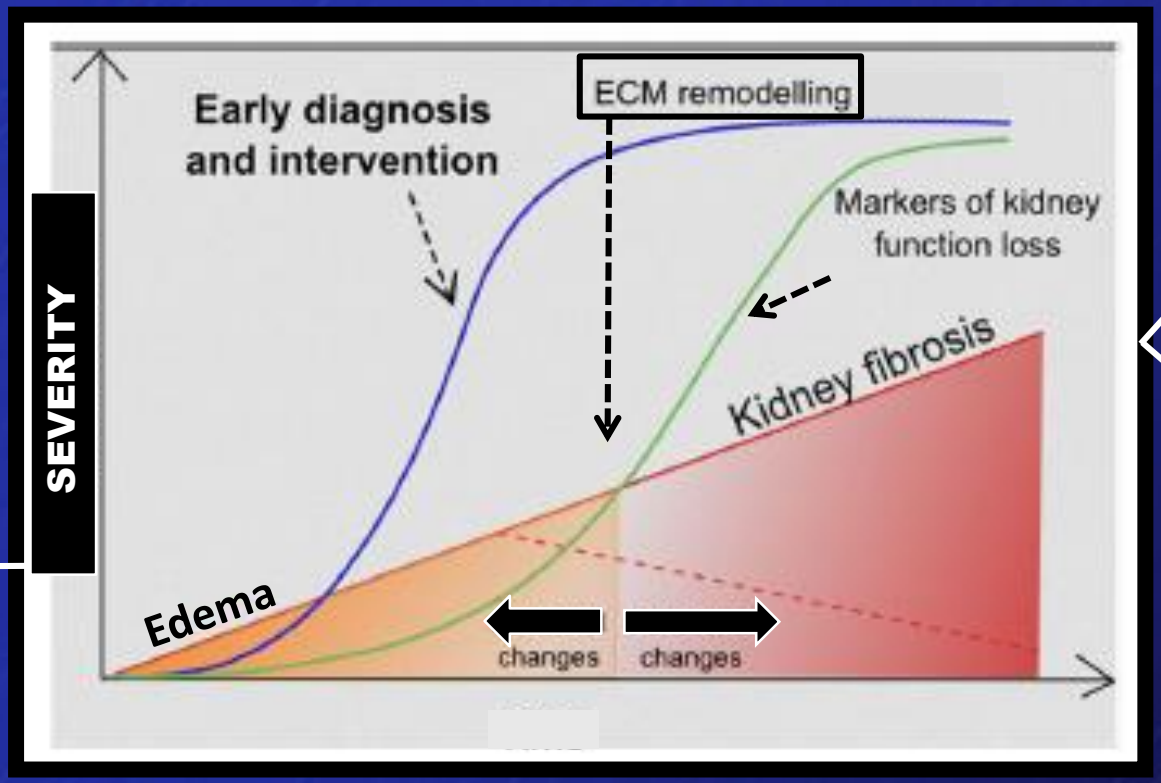
All Chronic INs begin as Acute IN

ACUTE IN
Edema
Infiltration
Tubular Injury

CHRONIC IN
Fibrosis
Tubular atrophy and dilatation

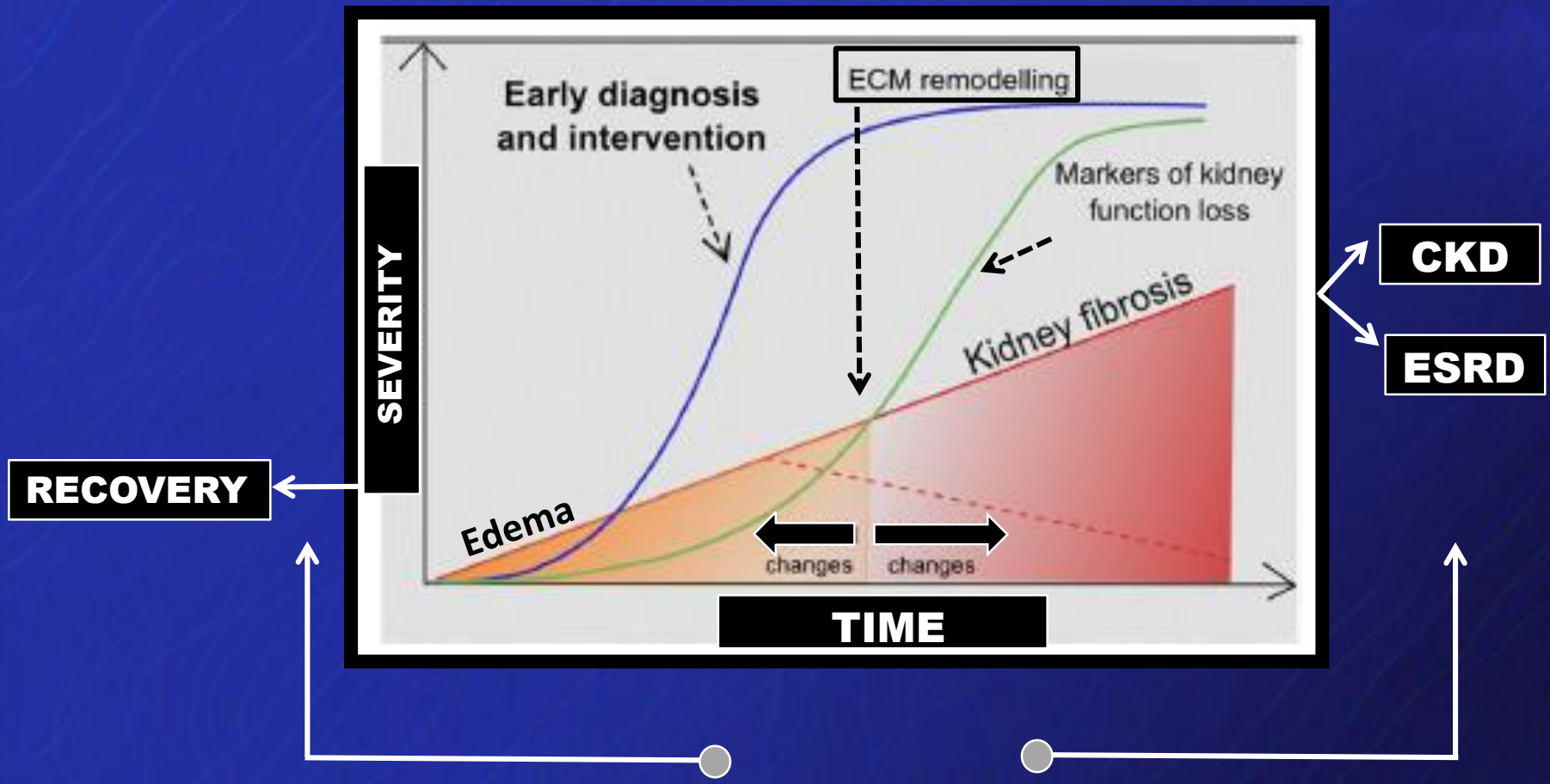


Progression of AIN
Correlates of Outcome



1. Severity of pathology

Progression of AIN
Correlates of Outcome



2. Time to diagnosis

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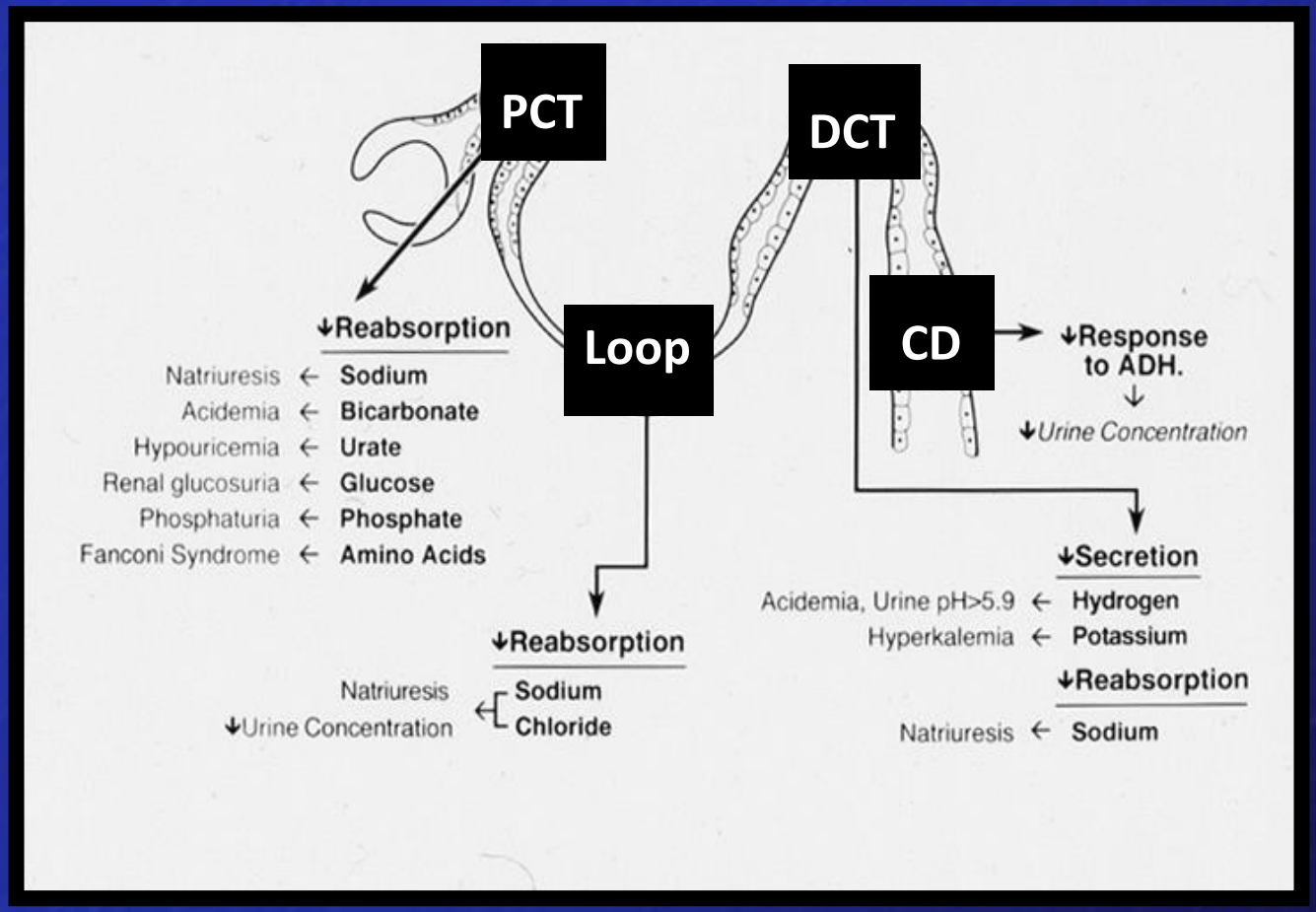
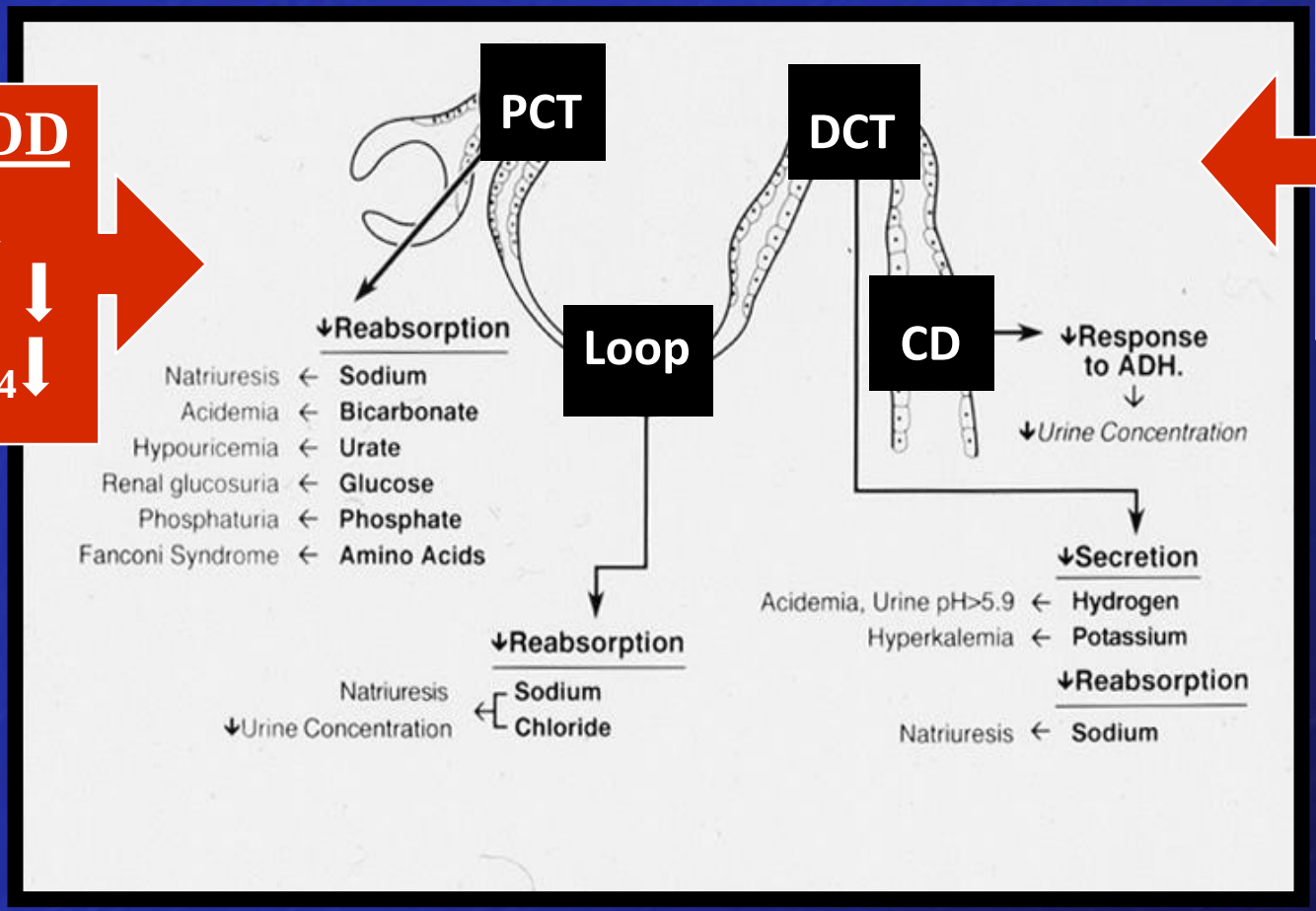
AIN is a disease of Tubular Dysfunction…



AIN is a disease of Tubular Dysfunction…

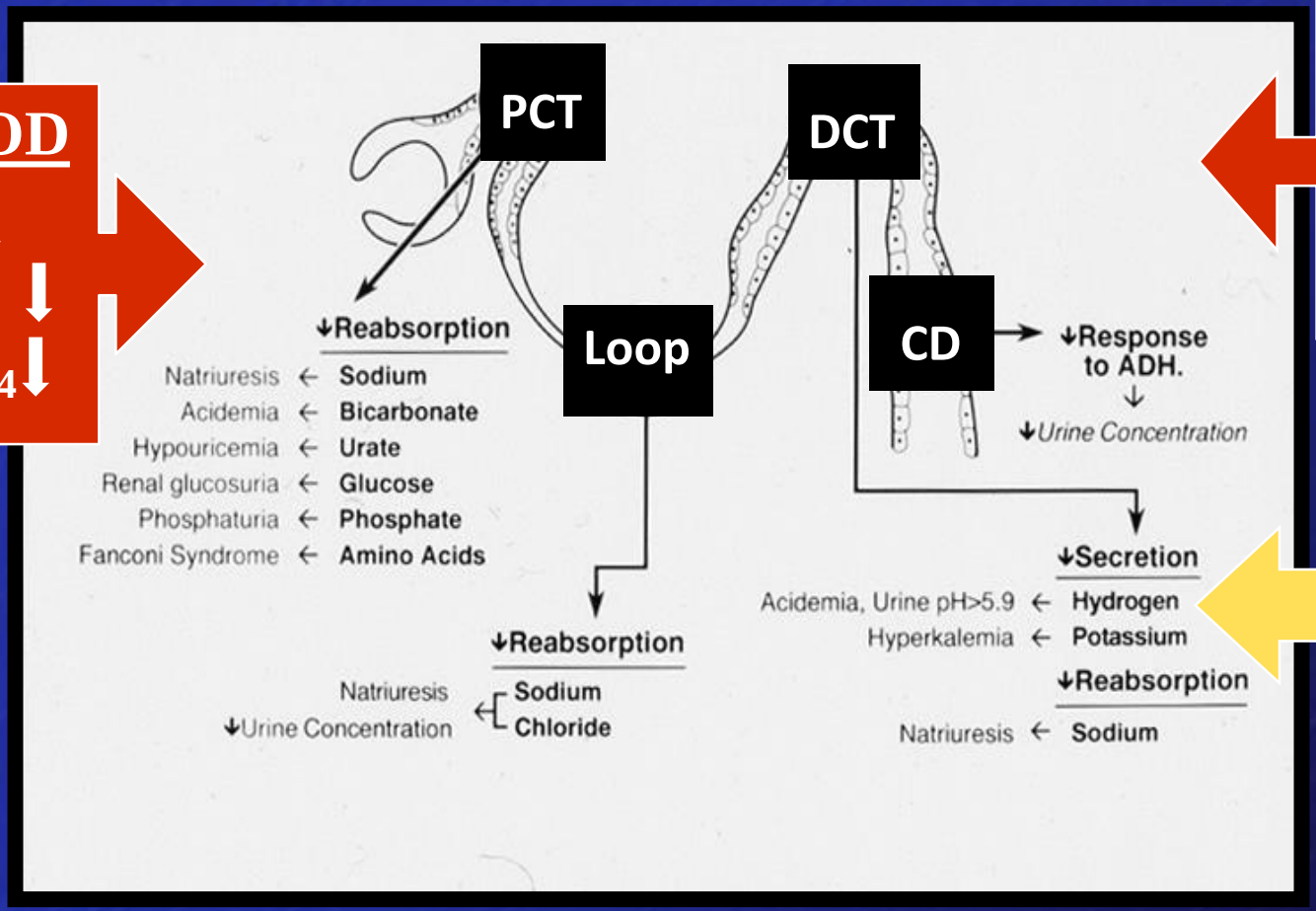
BLOOD
CO_2 ↓
Urate ↓
± PO_4 ↓



BLOOD
K^+ ↑
Disproportionate
CO_2 ↓

AIN is a disease of Tubular Dysfunction…

BLOOD
CO_2 ↓
Urate ↓
± PO_4 ↓



BLOOD
K^+ ↑
Disproportionate
CO_2 ↓

URINE
↑ VOLUME
↓ Sp. Gr.
Glucose ±
↑ FE_{Na}
pH > 5.9

AIN – KIDNEY FUNCTION

A. TUBULAR DYSFUNCTION

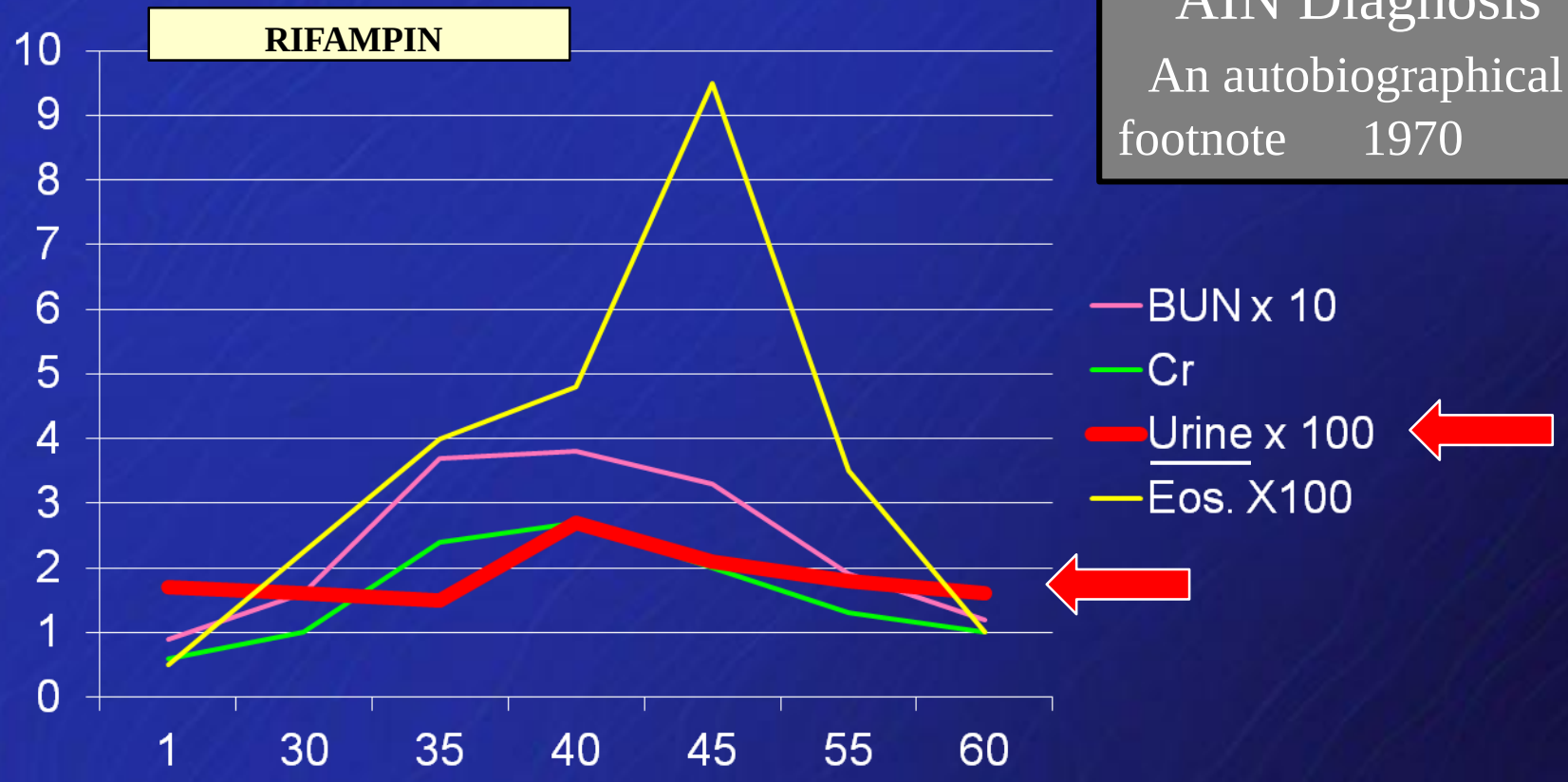
1. Proximal: U.A., H^+, Glucose, PO_4^-, β_2 microglobulin
2. Distal: K+, H+
3. Medulla: ↓ Tonicity

B. GLOMERULAR DYSFUNCTION

1. Non-Oliguric ARF
2. Oliguric ARF
3. Proteinuria + → ++++ (NS)

AIN during continuous Rifampin therapy

West J Med 1980; 73:791-792

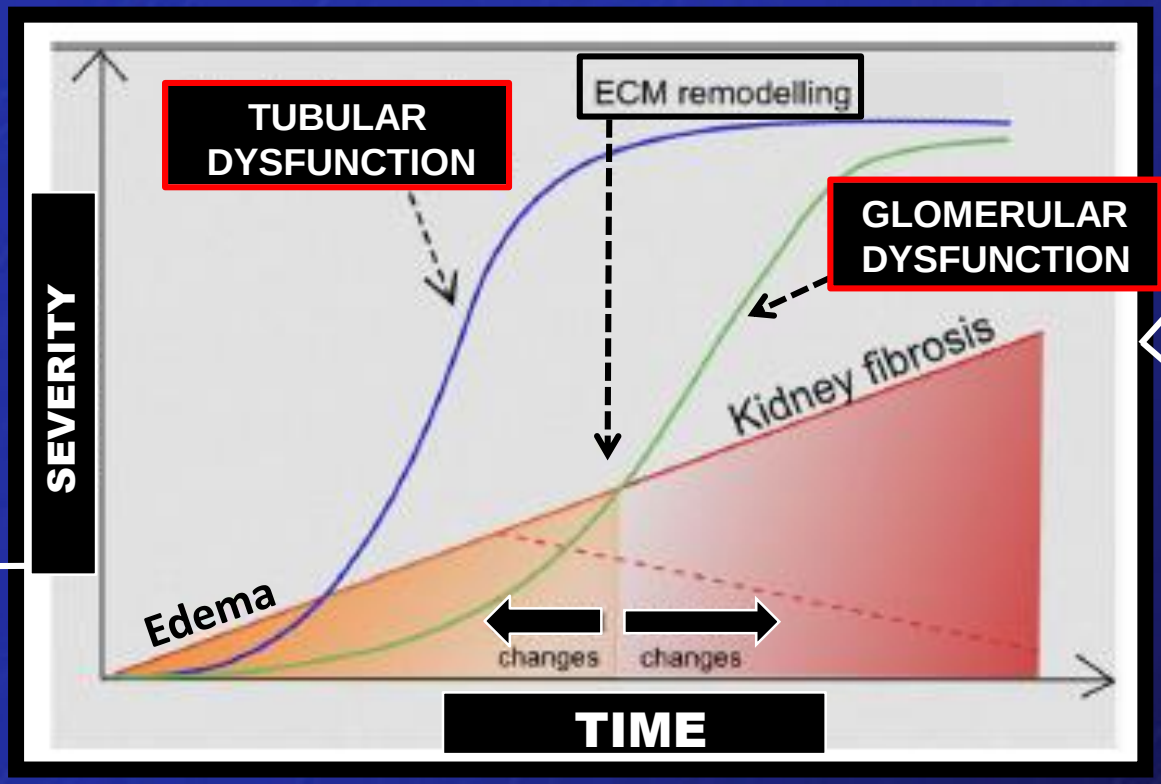


AIN Diagnosis

An autobiographical footnote 1970

Proteinuria	**Neg.**	**Neg.**			**1.6 g/d**	**0.9 g/d**	**Neg.**
Glycosuria *	**Neg.**	**Neg.**	**2+**	**3+**	**1+**	**Neg.**	**Neg.**
Uosm		**305**	**303**	**285**		**540**	
Urine Eos.				**+**			
FE Uric Acid *				**30% (3.5)**			

Progression of AIN
Correlates of Outcome

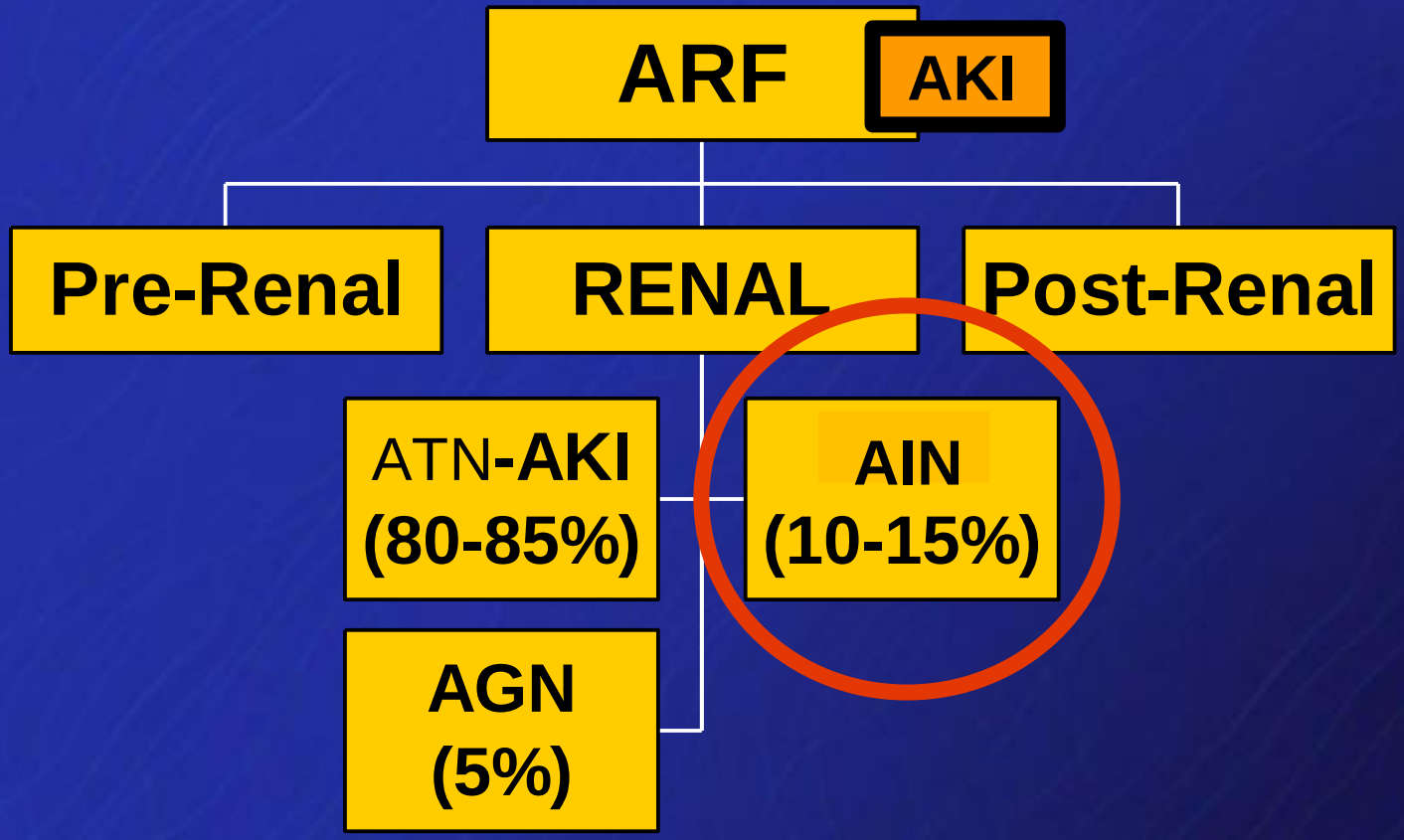


CONTRIBUTORS to OUTCOME

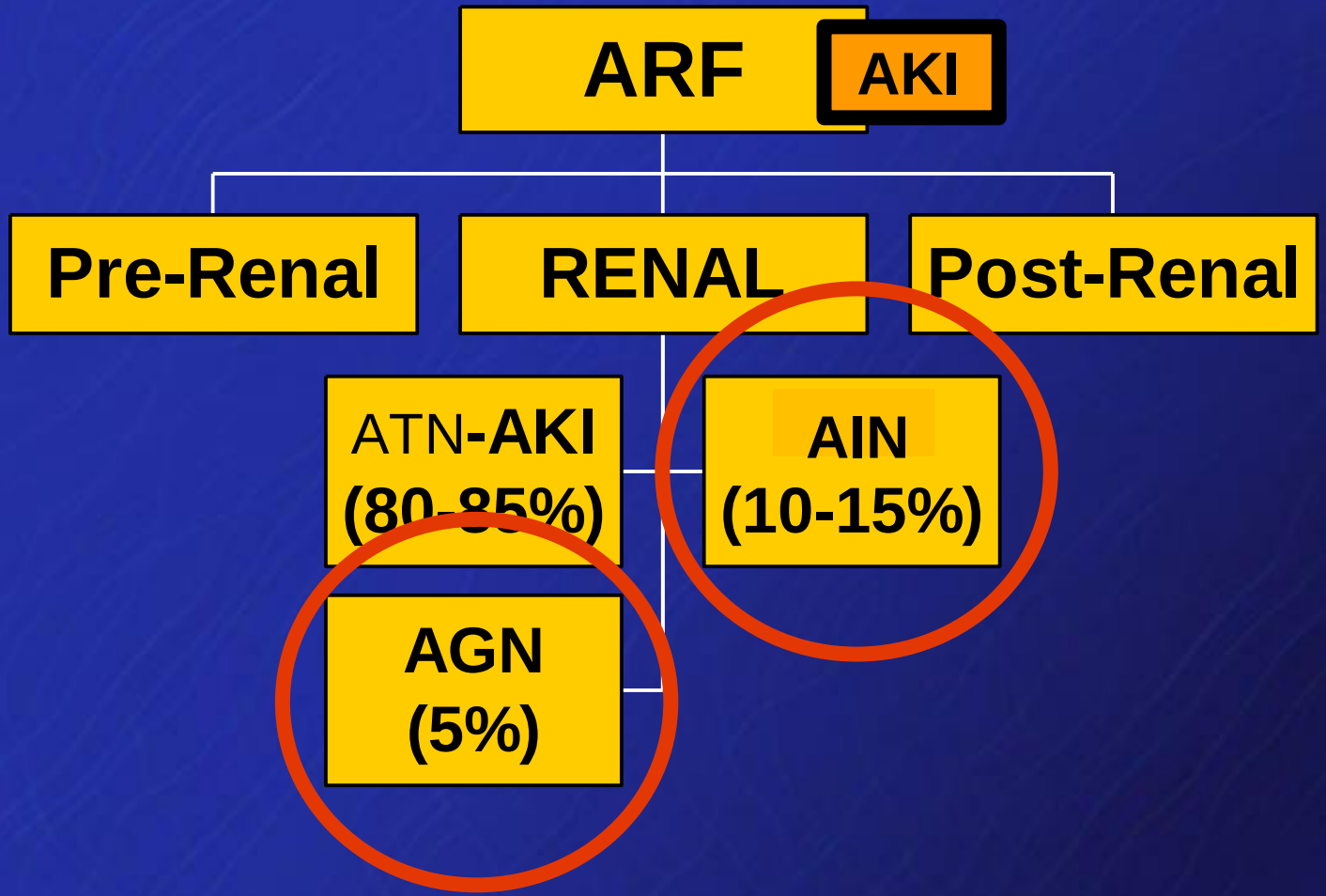
1. Severity of pathology 2. Time to diagnosis **3. Kidney function**

The problem with ARF

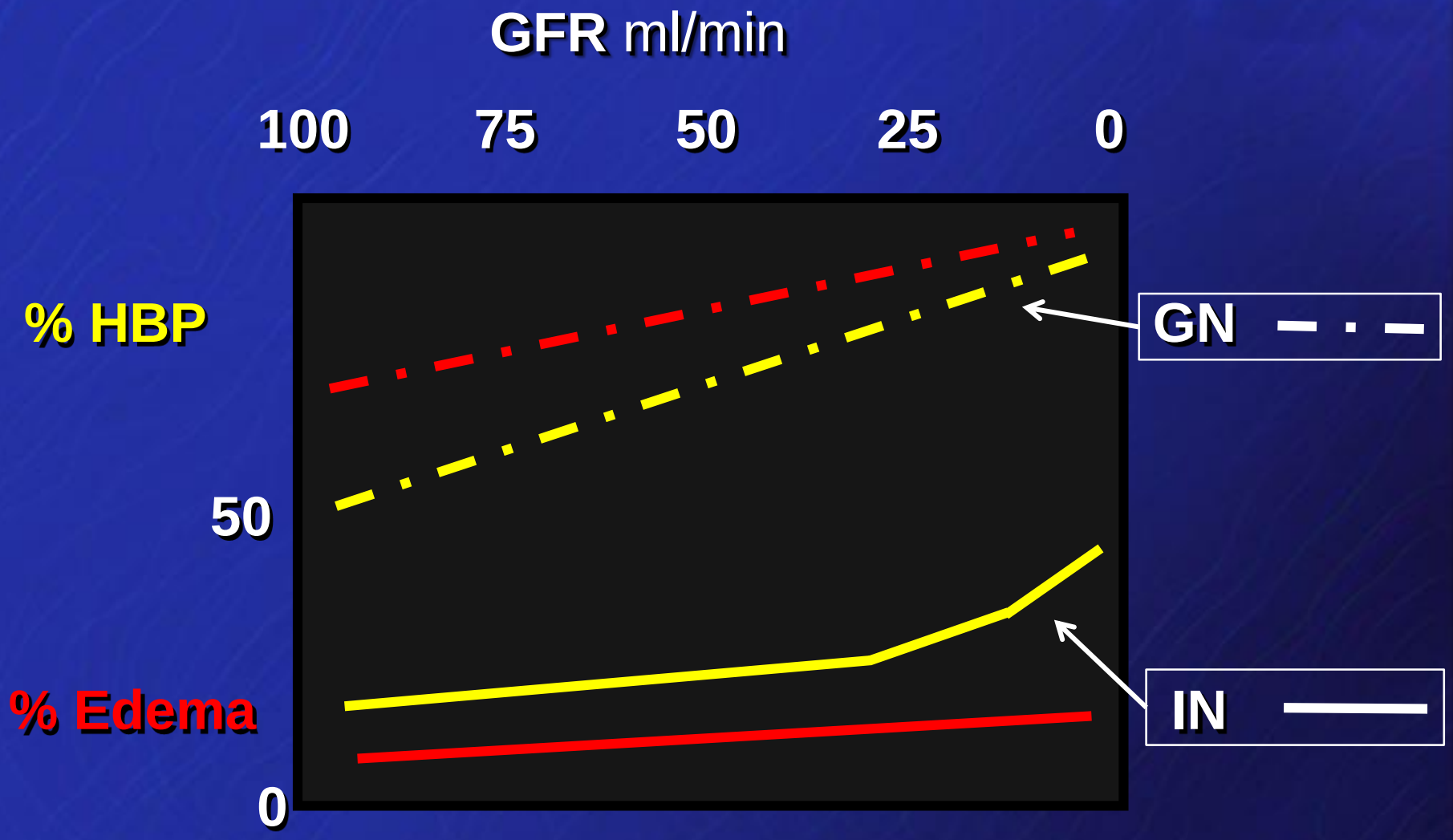
… and now with AKI



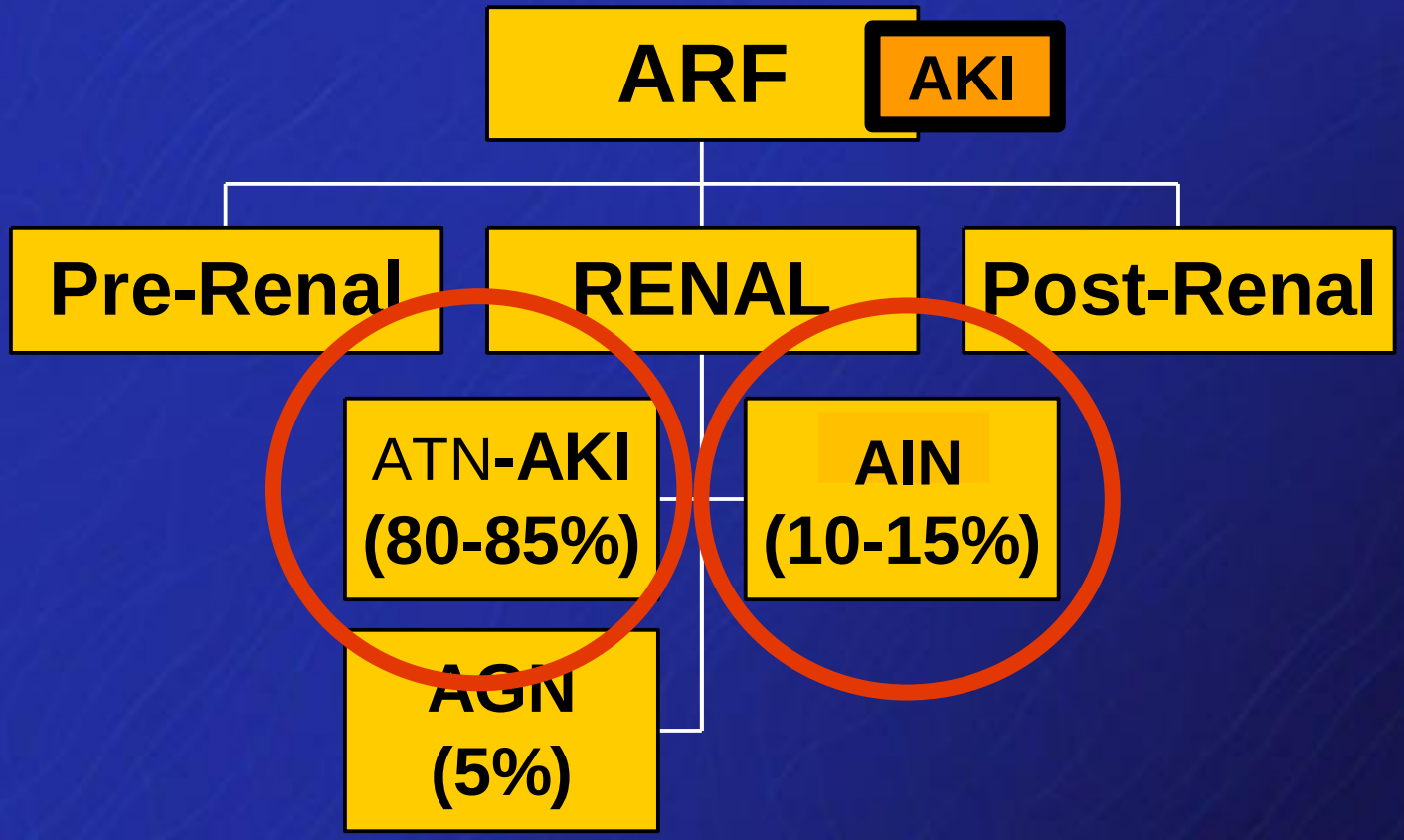
Differential of AIN from AGN



Hypertension and Edema
in Glomerular vs Interstitial Diseases



Differential of ARF(AKI) from AIN



Distinguishing features of **ATN** from **AIN**

	Acute Tubular Necrosis (**ATN**)	Acute Interstitial Nephritis (**AIN**)
Onset following injury	Hours to days	Days to weeks
Urine volume	Oliguria < 500 mL/d	Polyuria (> 2,000 mL/d)
Clinical features	Hemodynamic instability	Rash (25 – 40%), fever (35 – 70%), back pain (25 – 40%), arthralgia (25 – 40%)
Histology	Tubular epithelial cell injury	Interstitial cellular infiltrates, edema, tubulitis
Eosinophilia	Absent	Present (35 – 60%)
Tubular dysfunction†	Rare	Very common
FE_{Na}#	> 1%	> 1%
Urine microscopy	Epithelial cell and broad granular casts	Hematuria (70 – 90%), pyuria (75 – 85%), eosinophiliuria* (variable)
Treatment	Hemodynamic resuscitation, withdrawal of nephrotoxic agent, supportive care	Withdrawal of offending agent, supportive care, limited trial steroids
Prognosis	Recovery (65%), CKD (~ 35%)	Recovery (65%), CKD (~ 35%)

Clin Nephrol 2014; 82:149-162

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AIN - ETIOLOGY

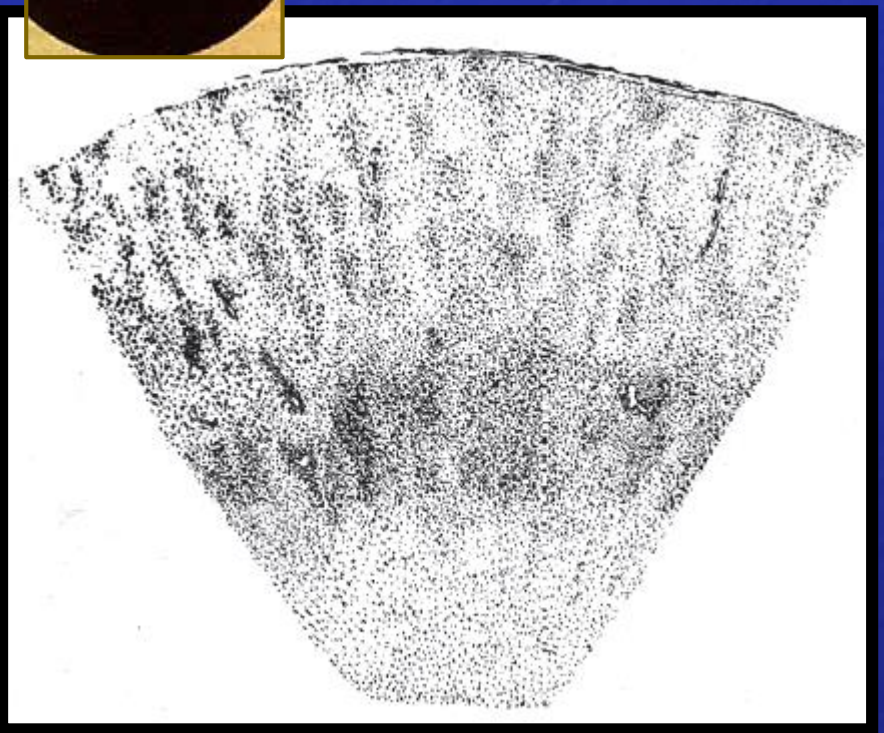
I. INFECTIONS ~ 10-15%

II. DRUGS ~ 65-70%

III. SYSTEMIC DISEASES ~ 10-15%

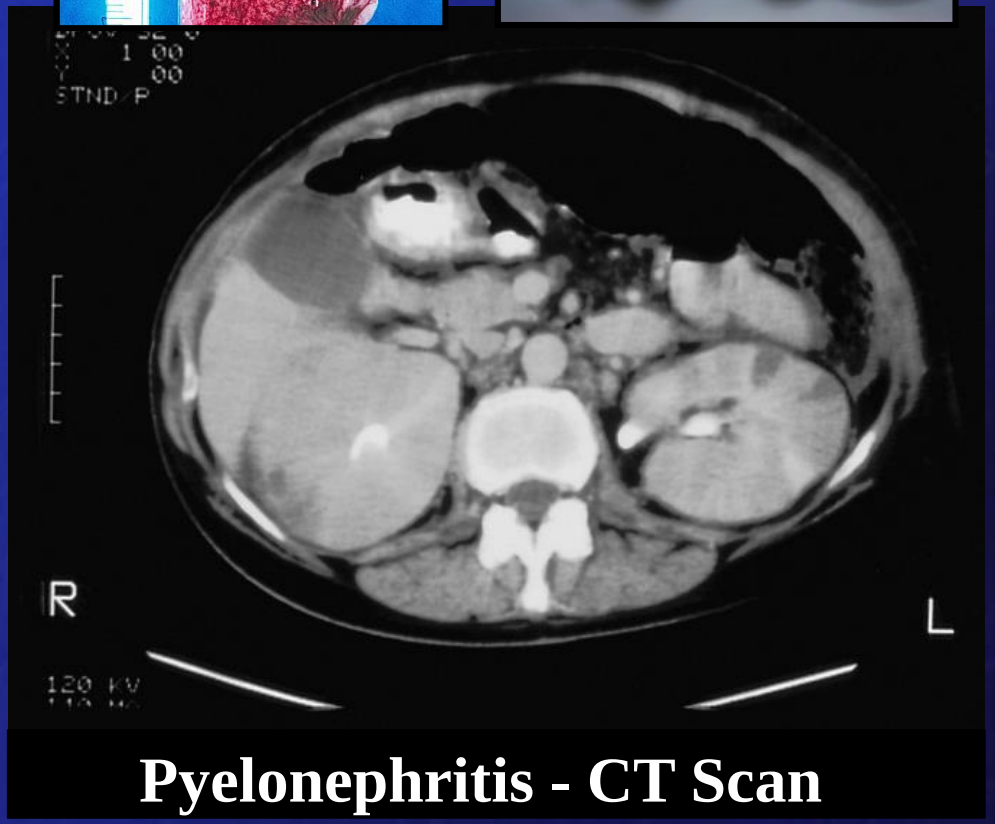
IV. IDIOPATHIC ~ 15% ±

AIN – I. INFECTIONS



Acute Interstitital Nephritis

J Exp Med 1898; 3:393



Pyelonephritis - CT Scan

AIN - I. INFECTIONS

Bacterial : Streptococcus, diphtheria, legionella

- **Viral :** Epstein-Barr, cytomegalovirus, Hanta, HIV, measles, polyoma

Fungal : Candida, herpes simplex

Other : schistosomaiasis, mycoplasma, malaria leptospira

AIN – II. DRUGS

>150+

A. ANTIBIOTICS

1. Penicllins: Methicillin, Ampicillin, Amoxicillin
2. Cephalosporins: Cephalothin
3. Rifampin
4. Fluoroquinalones: Ciprofloxacin

B. SULFONAMIDES

1.Sulfamethaxozole

C. NSAIDs

1. Propionic acid derivatives: Fenoprofen, Ibuprofen, Naproxen
2. Others (Glafenin) , COX 2 - inhibitors, 5-ASA

D. MISCELANEOUS

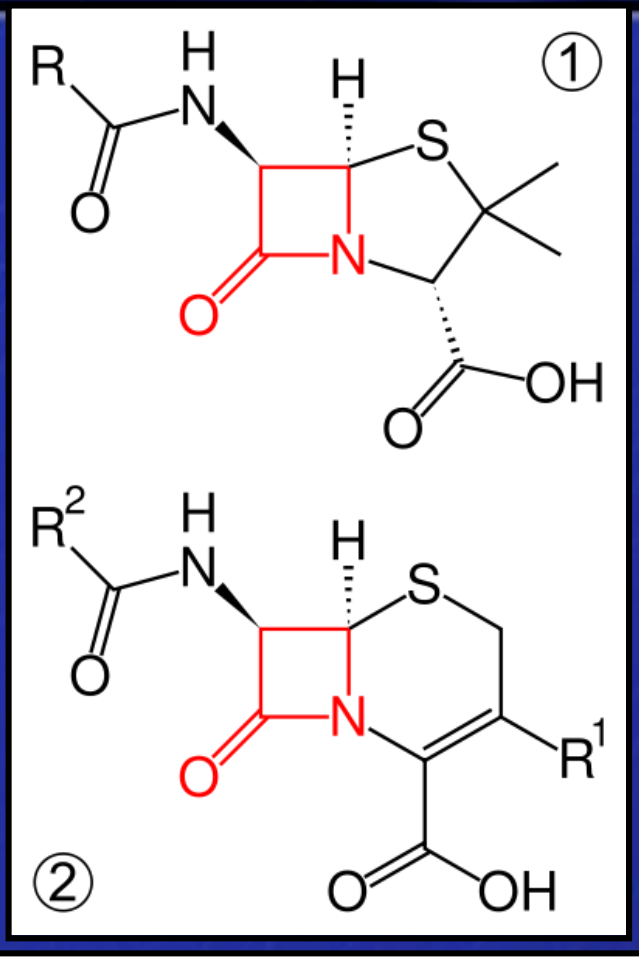
1. Anticoagulants: (Phenindione)
2. Anticonvulsants: Phenytoin
3. Diuretics: Thiazides, Furosemide
4. Others: Cimetidine, Allopurinol, Cyclosporine, Omeprazole

AIN- II. DRUGS

- Unrelated group of agents
- Not dose related
- Small number of those exposed
- Recurs (severe) upon re-exposure
- Systemic manifestations

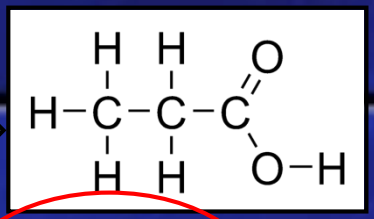
  Fever, Rash, Arthralgias, Flank pain, Eosinophilia

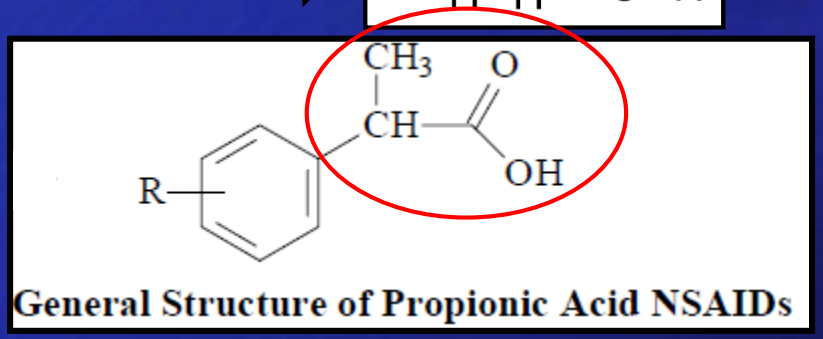
Drug Hypersensitivity - Could there be a structural role?



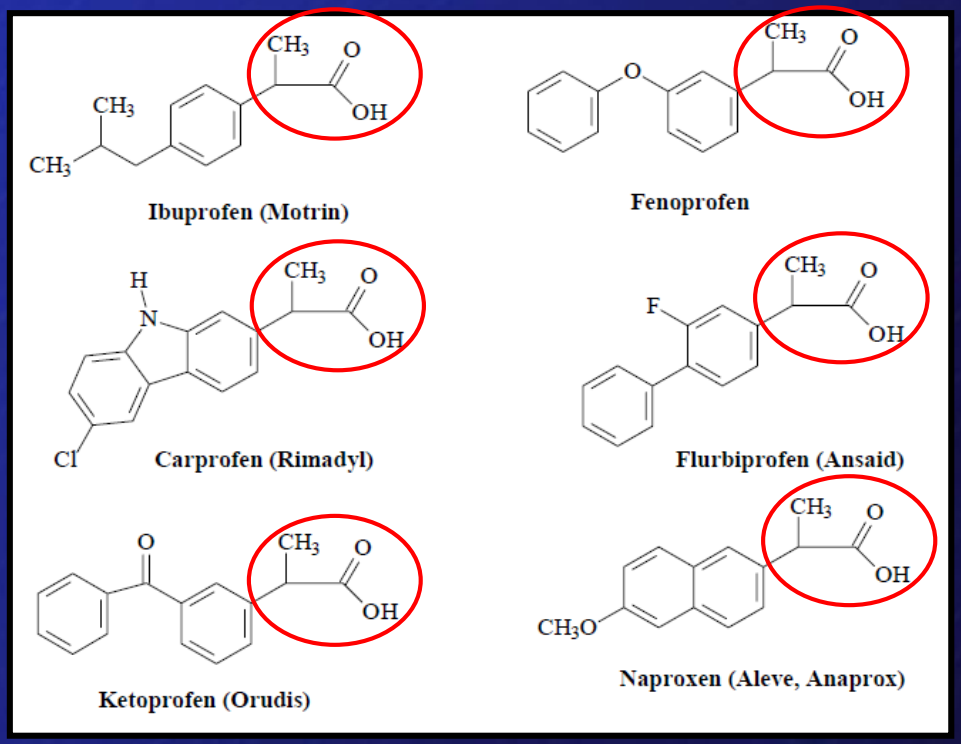
Core structure of penicillins (top) and cephalosporins (bottom). β-lactam ring in red

Propionic Acid

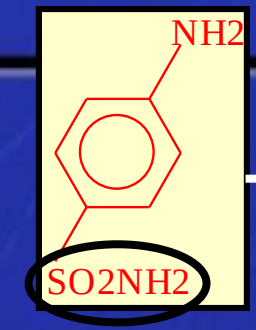




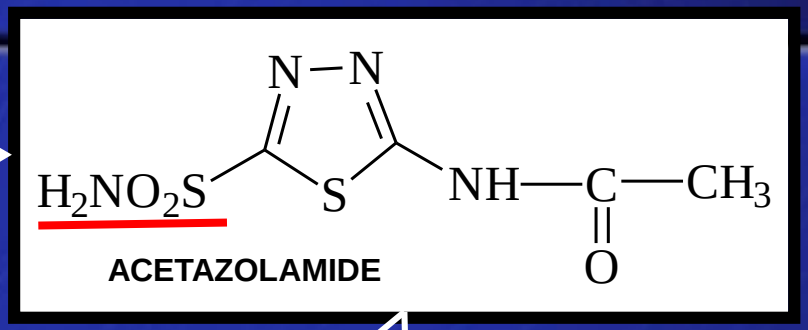
General Structure of Propionic Acid NSAIDs



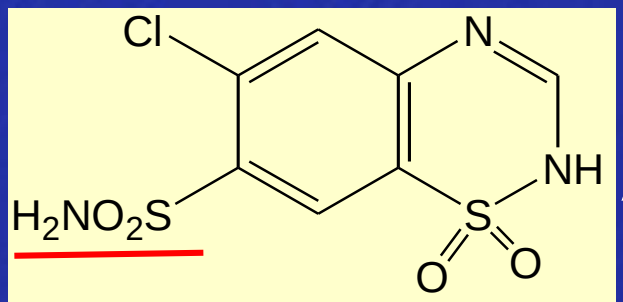
… and of DIURETICS: Sulfamoyl



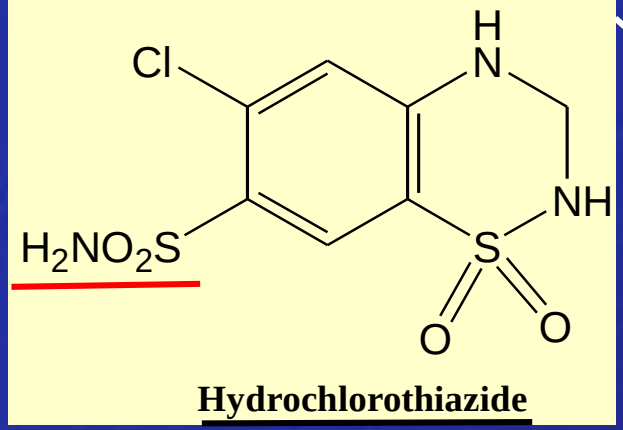
SULFANILAMIDE



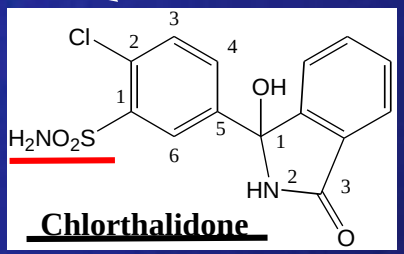
ACETAZOLAMIDE



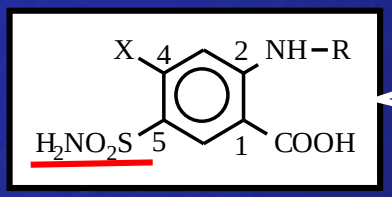
Chlorothiazide

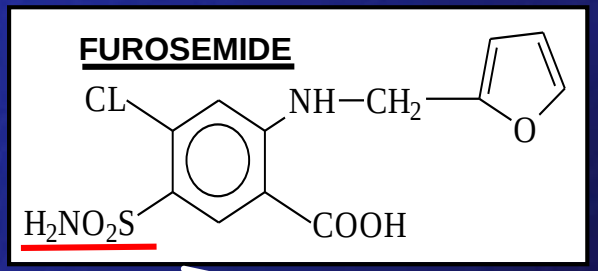


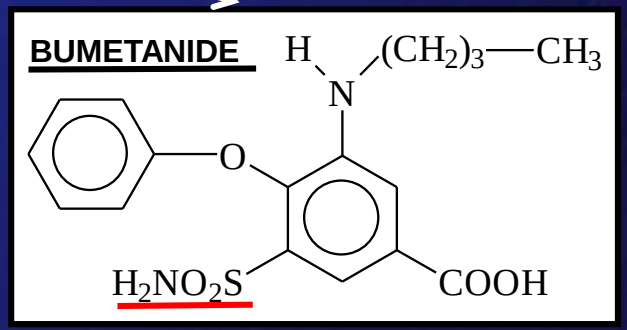
Hydrochlorothiazide



Chlorthalidone







Reported cases of Drug-induced AIN

DRUG	# of Cases	Principal agents
Antibiotics	> 50	Methicillin, Ciprofloxacin, Rifampin
NSAIDs	> 40	Propionic acid derivatives
Proton pump inhib. H_2 Antagonists	> 50	Omeprazole Cimetidine
Cancer drugs	> 20	Ifosfamide
Diuretics	> 10	HCTZ, Furosemide
Others	> 20	Allopurinol, 5-Aminosalicylic acid

Clin Nephrol 2014; 82:149-162

AIN - Etiology

III. SYSTENIC DISEASES

Metabolic : *Urate, gold, lead etc…*

Immune : *SLE, Sjögren's, Sarcoid,* ***IgG4***

Neoplastic : *Plasma cell dyscrasias*

IV. IDIOPATHIC

TINU

Overview of Presentation

- Historical Background
- Pathology
- Kidney Function
- Etiology

Clinical & Laboratory Manifestations

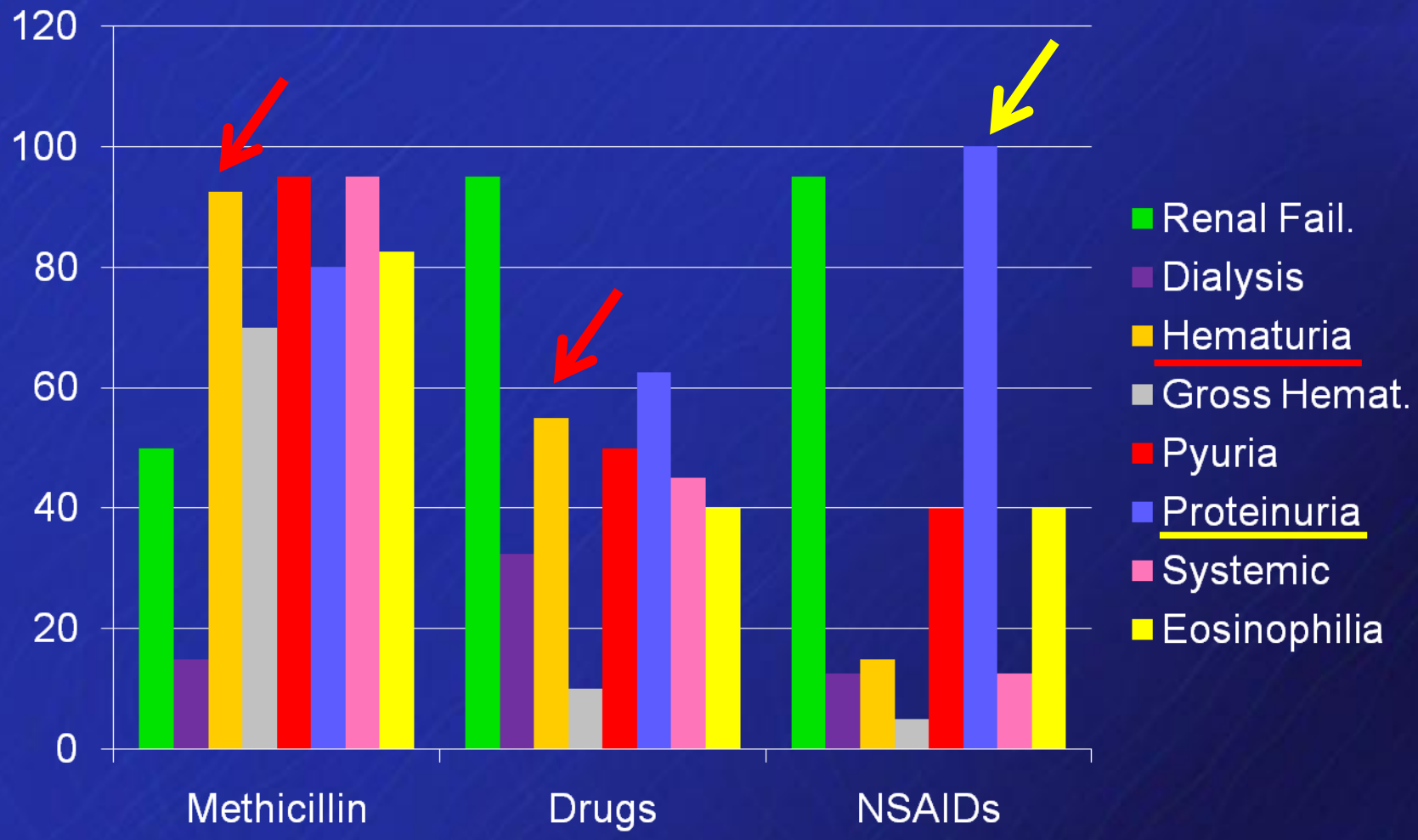
- Diagnosis
- Treatment and Outcomes
- Take Home Messages

AIN – Systemic Manifestations

- Fever 35-70% ?
- Rash 25-40% ?
- Eosinophilia 35-60% ?
- Flank pain 25-40% ?
- Arthralgias 25-40% ?
- Hypertension 10-15% ?

Drug-induced Acute Interstitial Nephritis

Kidney Int 2001; 60:804-817



The changing profile of AIN
3. SYSTEMIC MANIFESTATIONS

	NEJM '68	Nephron '72	AJM '78	QJM '83	Adv. Nephrol '83	NDT '90	NDT ' 04	KI '08
n	**7**	5	**14**	7	19	27	60	61
Etiology	**Pen/Meth**	**Drugs**	**Methiciliin**	**Drugs**	**Drugs**	**Drugs**	**Drugs**	**Drugs**
Eosinophilia	60%	?	100%		25%	50%	30%	30%
Pyuria/Eos.		60%	100%					40%
Hematuria		40%	93%		30%		65%	65%
Fever	100%	20%	100%	60%	55%		30%	30%
Rash	60%	40%	30%	60%	25%		20%	20%
↑ BUN/Cr.	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**
Arthralgia		?	7%		5%		<40%	
Steroids		+	+	+	±		-	+
Triad (FER)		?	20%	?	?	15%	< 10%	13%

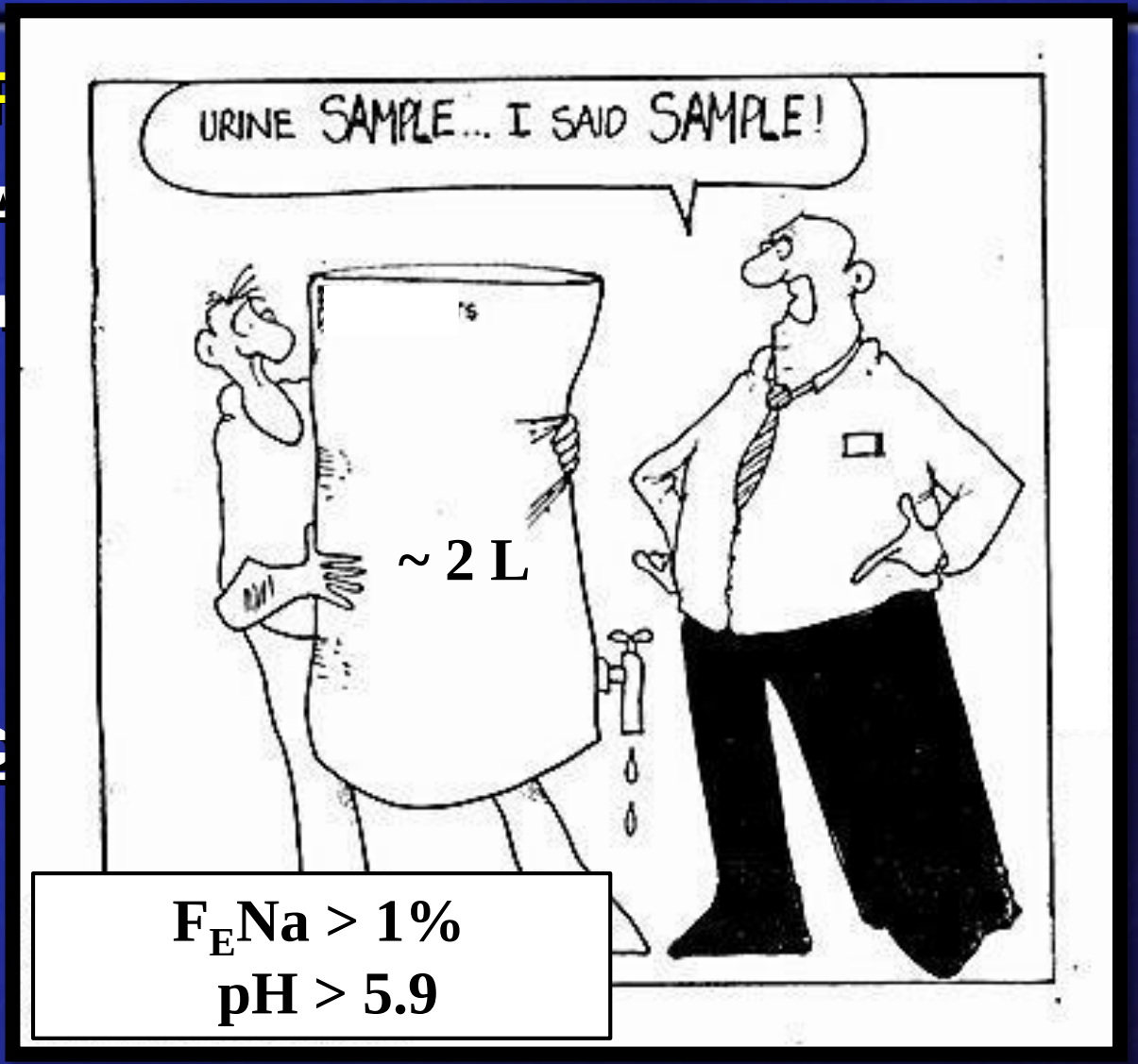
Acute TIN - KIDNEY FUNCTION

A. TUBULAR DYSF

1. Proximal: U.A
   β_2 I
2. Distal: K^+, H^+
3. Medulla:

B. GLOMERULAR

1. Non-Oliguric
2. Oliguric ARF
3. Proteinuria



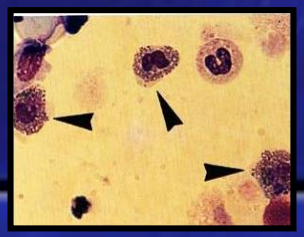
$F_ENa > 1\%$
$pH > 5.9$

AIN - URINALYSIS

Gross hematuria	5 - 20%
Micro-hematuria	70 - 90%
Proteinuria (1-2 Gm/day)	70 - 85%
→ Pyuria	70 - >80%
FENa > 1%	100%
→ Eosinophiluria	? %

(> 1-5% of WBCs)

AIN - Eosinophiluria



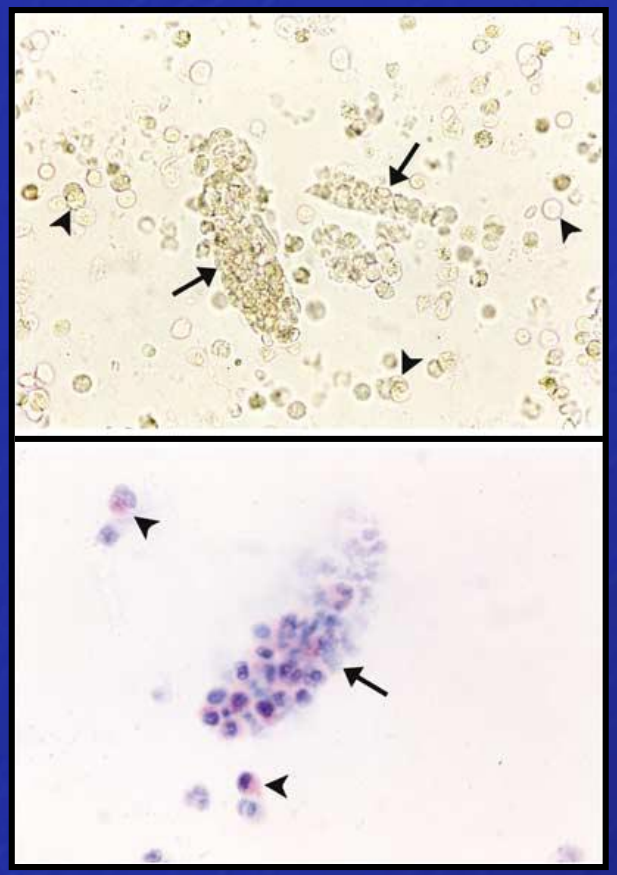
Reference	Arch Int Med 1985 Wright	NEJM 1986 Hansel	Arch Pathol Lab Med 1989 Hansel	Clin Nephrol 1994 Hansel
n	65	92	183	199
PATIENTS with AIN				
Eosinophiluria	8	10	5	6
NO Eosinophiluria	1	1	3	9
PATIENTS without AIN				
Eosinophiluria	27	12	15	16
NO Eosinophiluria	29	69	160	168

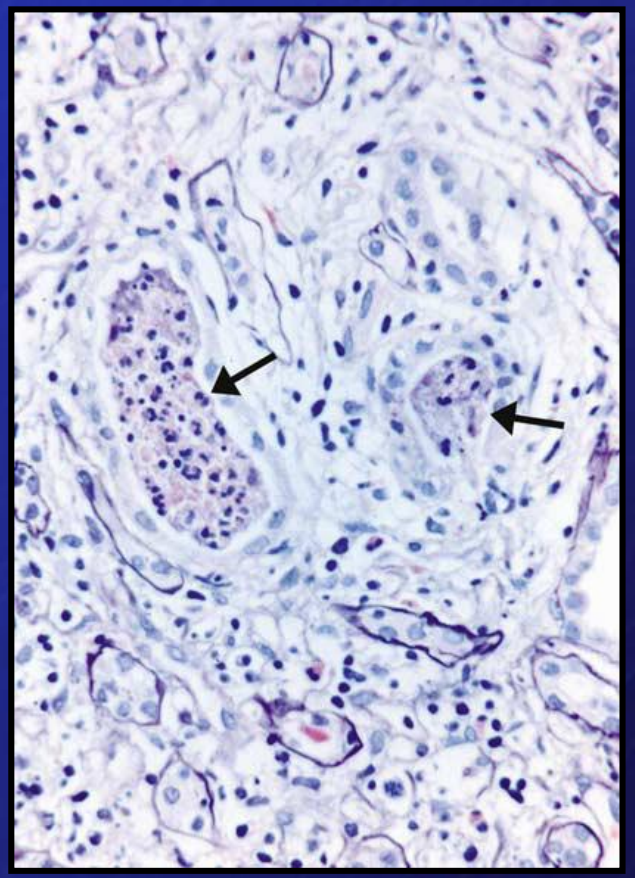
LOW SENSITIVITY ~ 60%

HIGH SPECIFICITY ~ 85%

Acute allergic interstitial nephritis and eosinophiluria

Kidney International 2008; 73: 980





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- Treatment and Outcomes
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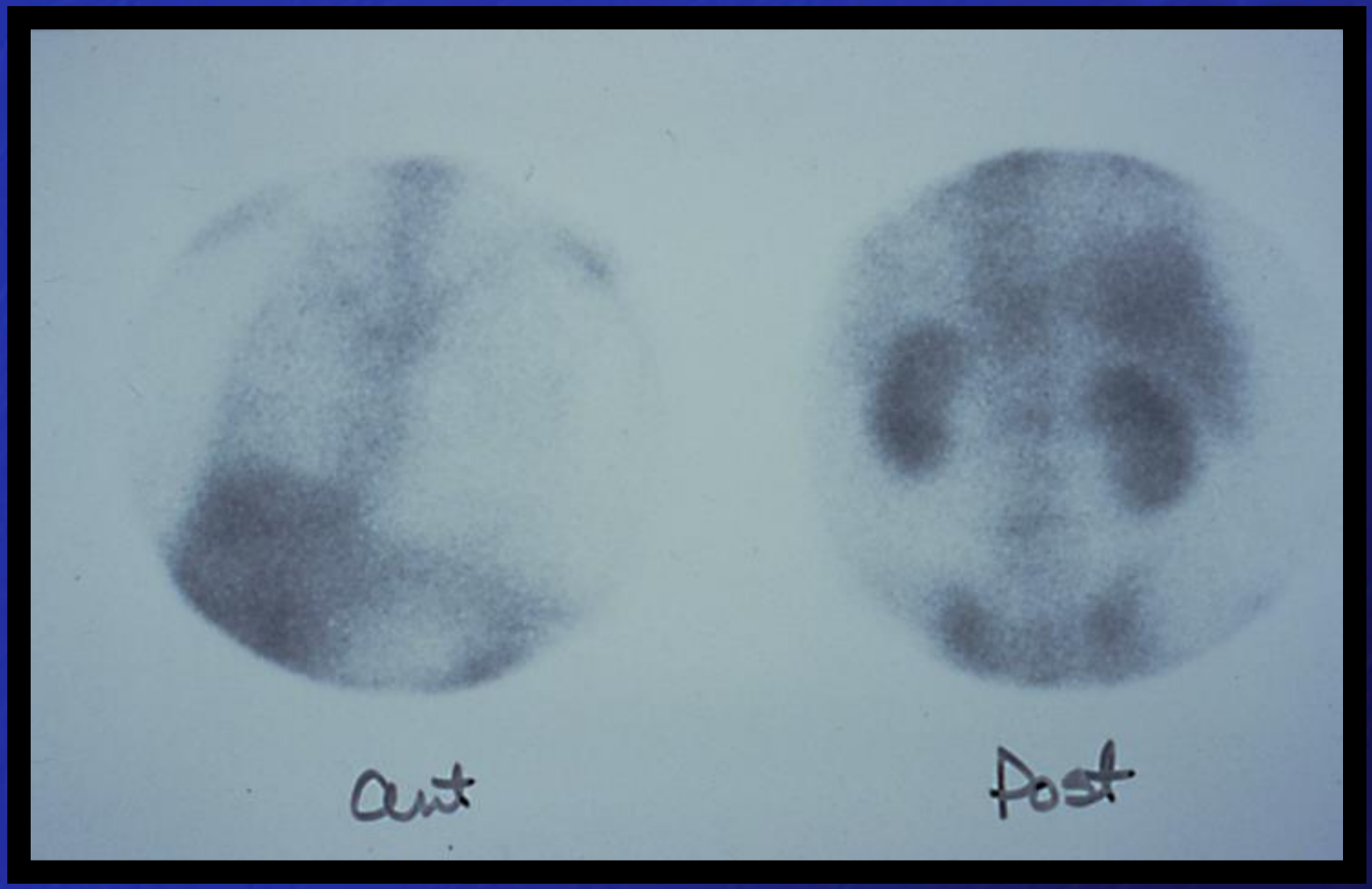
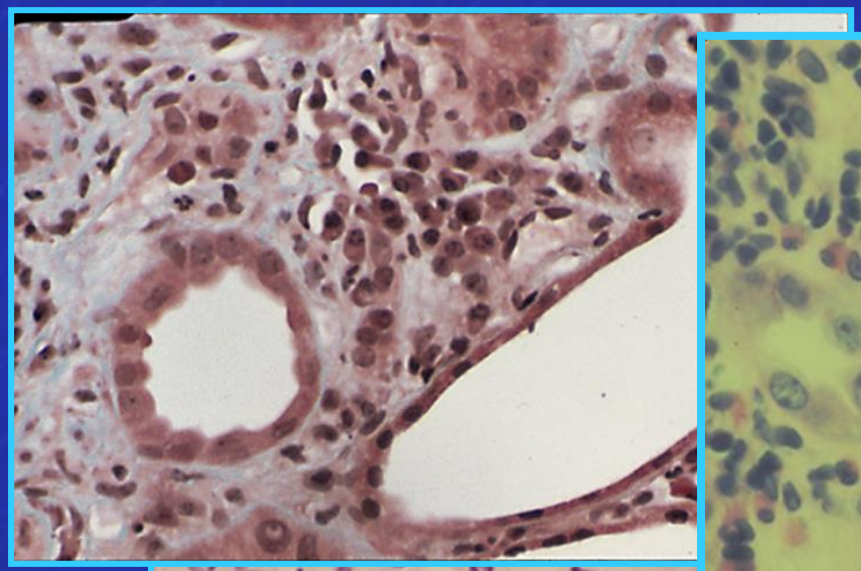
AIN - DIAGNOSIS

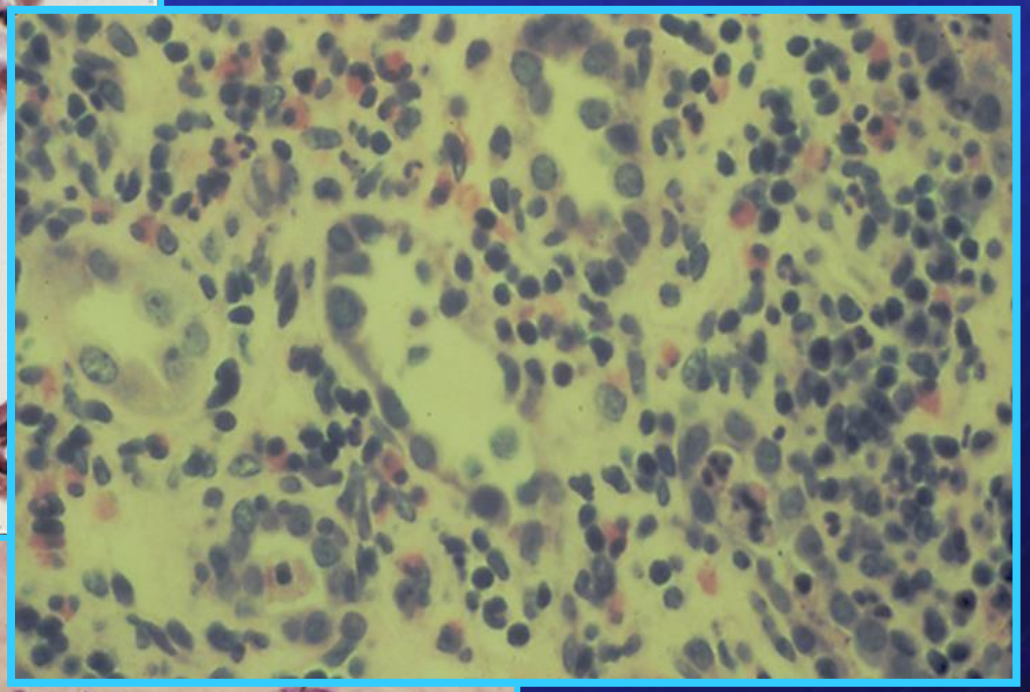
1. Ultrasound
2. Gallium scan
3. Kidney biopsy

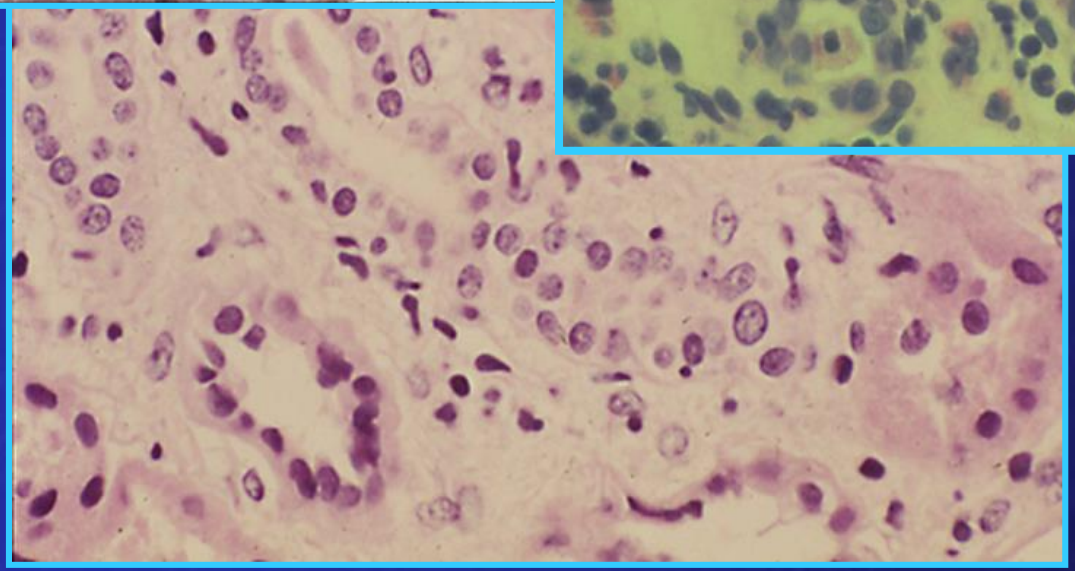
AIN Dx: GALLIUM SCAN



AIN Dx: KIDNEY BIOPSY







Overview of Presentation

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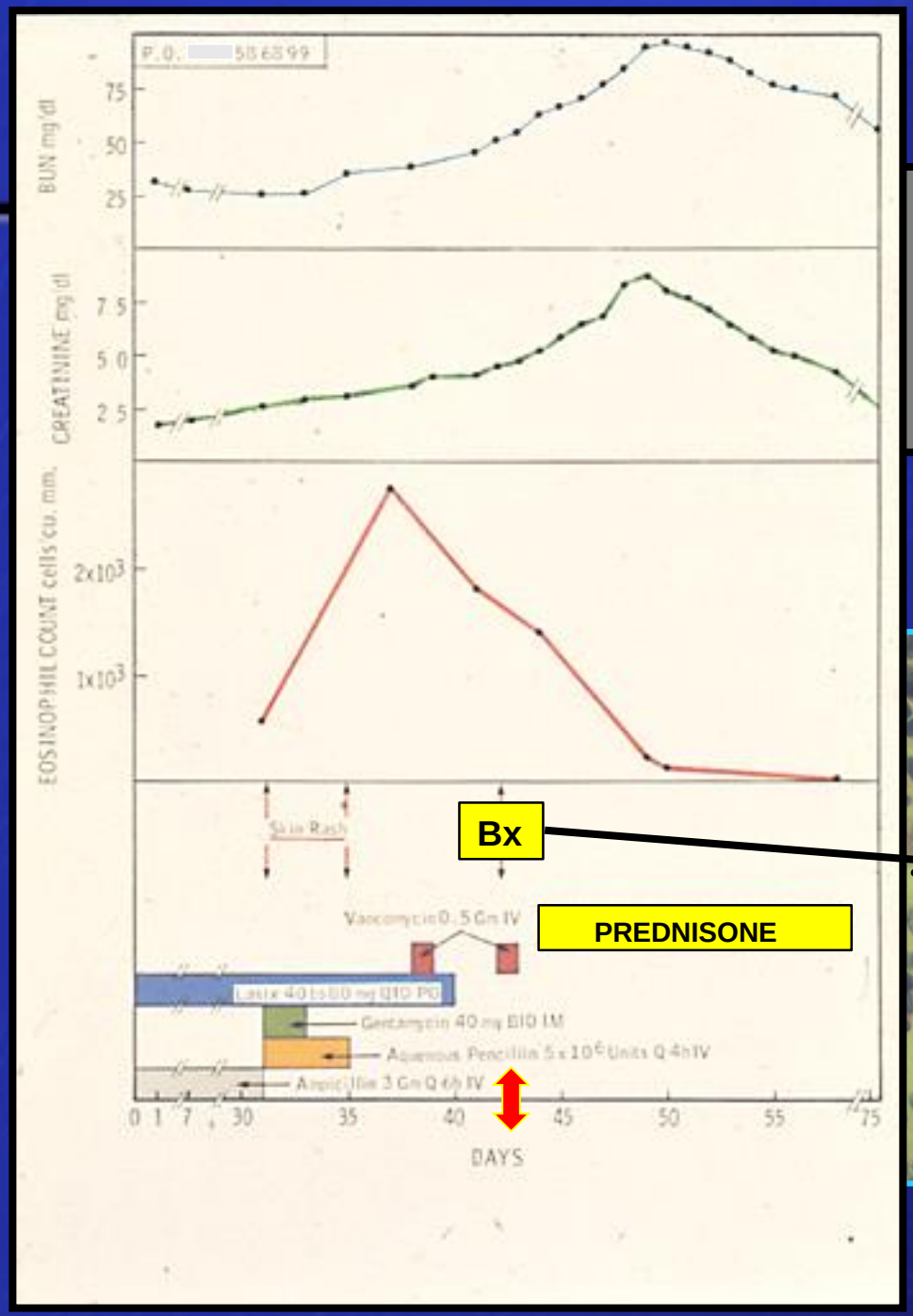
AIN - TREATMENT

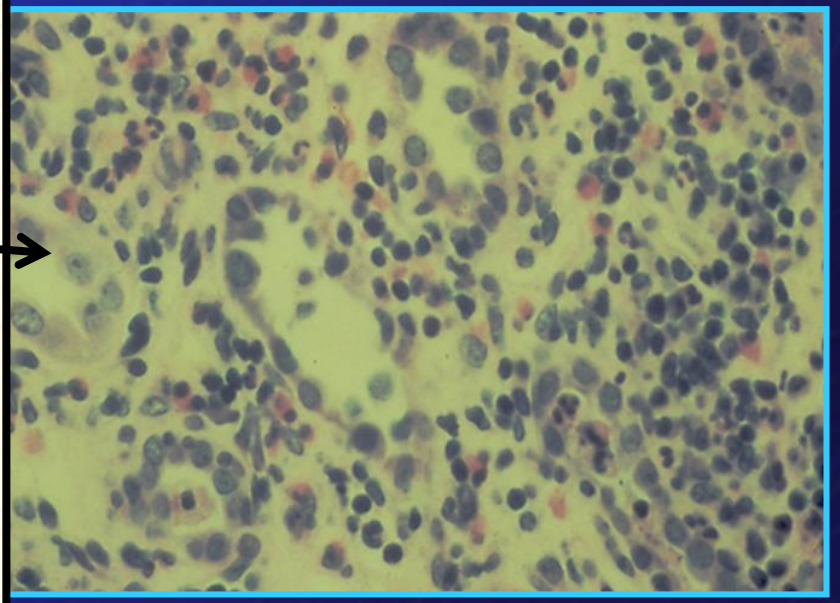
1. Discontinue drug
2. Supportive measures
3. Inform patient
4. Steroids

AIN Treatment

An autobiographical footnote

1970





Early steroid treatment of drug induced acute interstitial nephritis

Kidney Int 2008; 73: 940-946

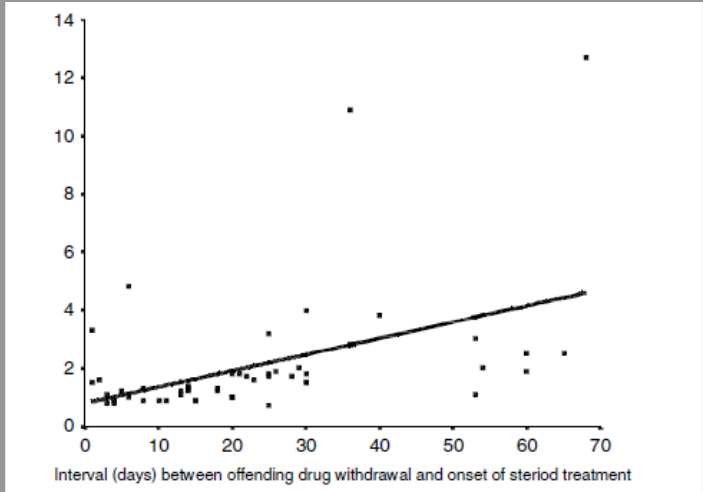


Figure 1 | Correlation between the delay in steroid treatment and final Scr.

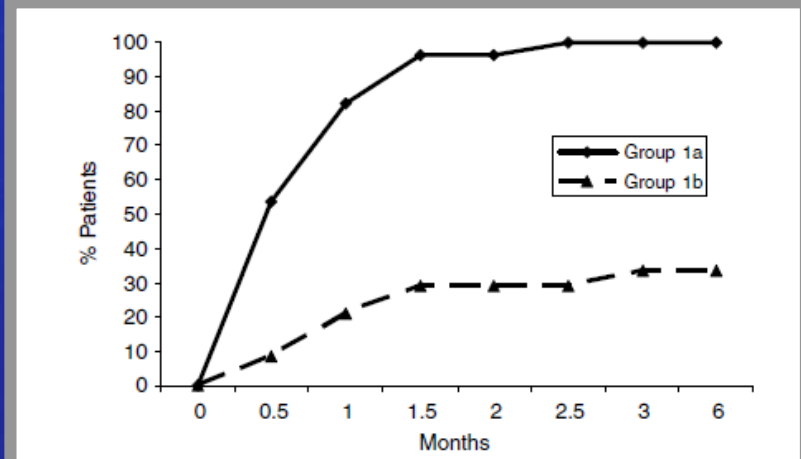


Figure 2 | Rate of renal function recovery, expressed by a > 50% decrease of highest Scr, in Group 1a (final complete recovery of renal function) and Group 1b (incomplete recovery).

Overview of Presentation

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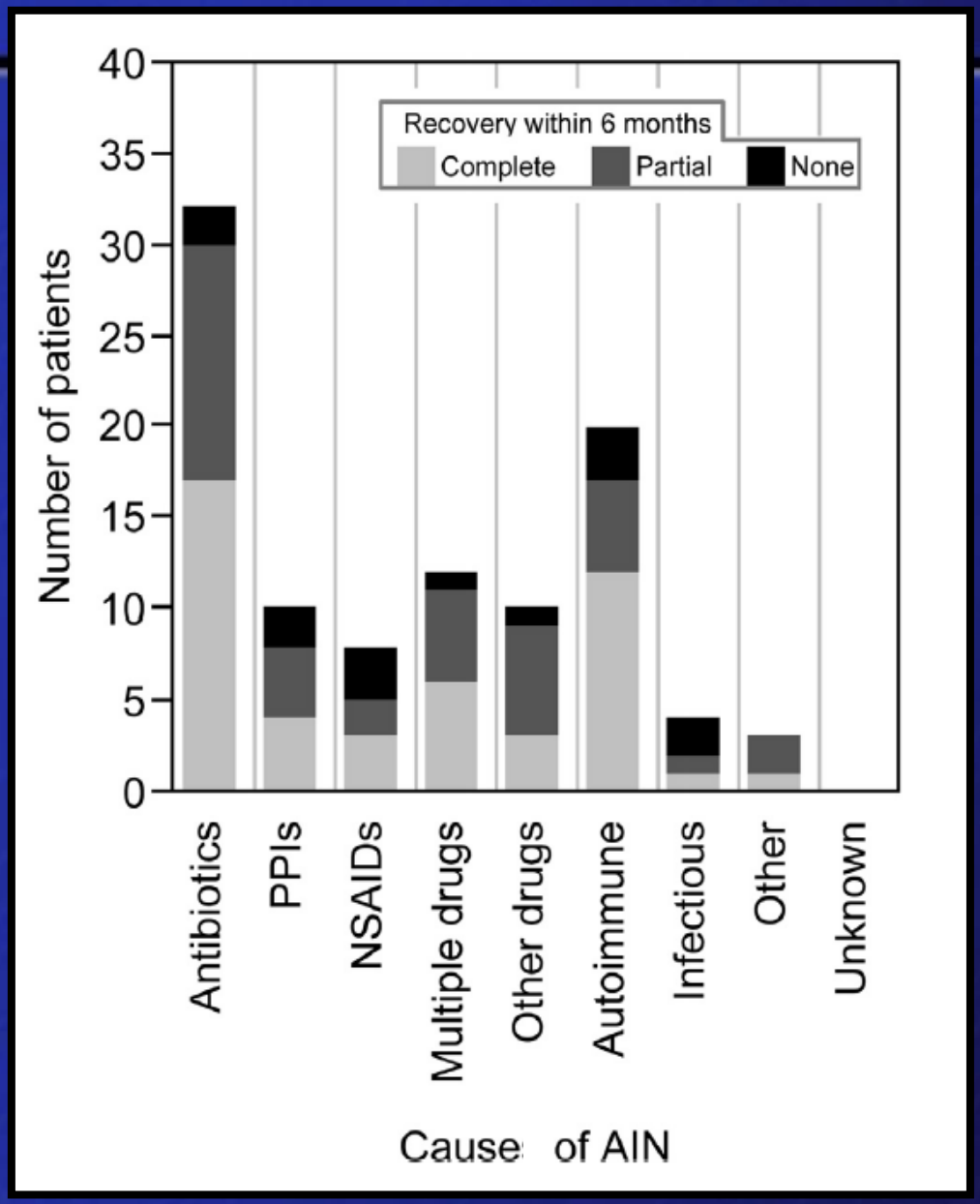
- **Take Home Messages**

Take home messages

- AIN is a disease of tubular dysfunction.
- AIN is NOT rare and is easy to detect: Urine analysis and BMP.
- AIN is a serious disease and a cause of CKD and ESRD.
- Early AIN detection is preventive translational medicine at its best.

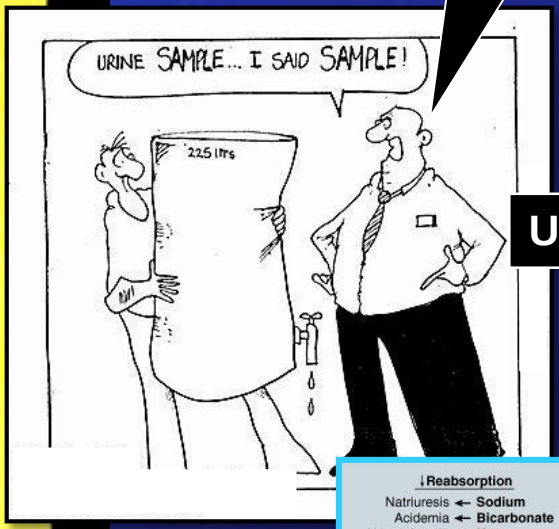
AIN is a serious disease



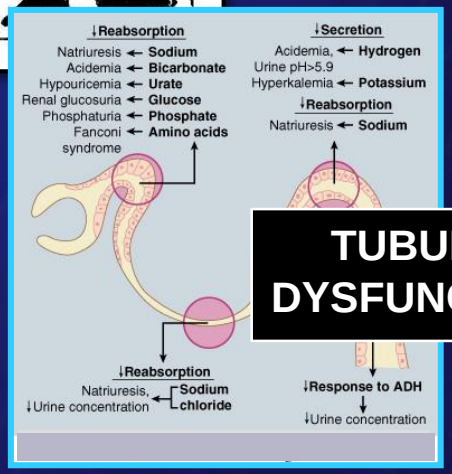
AJKD 2014; 38:736-748

The last word on AIN?

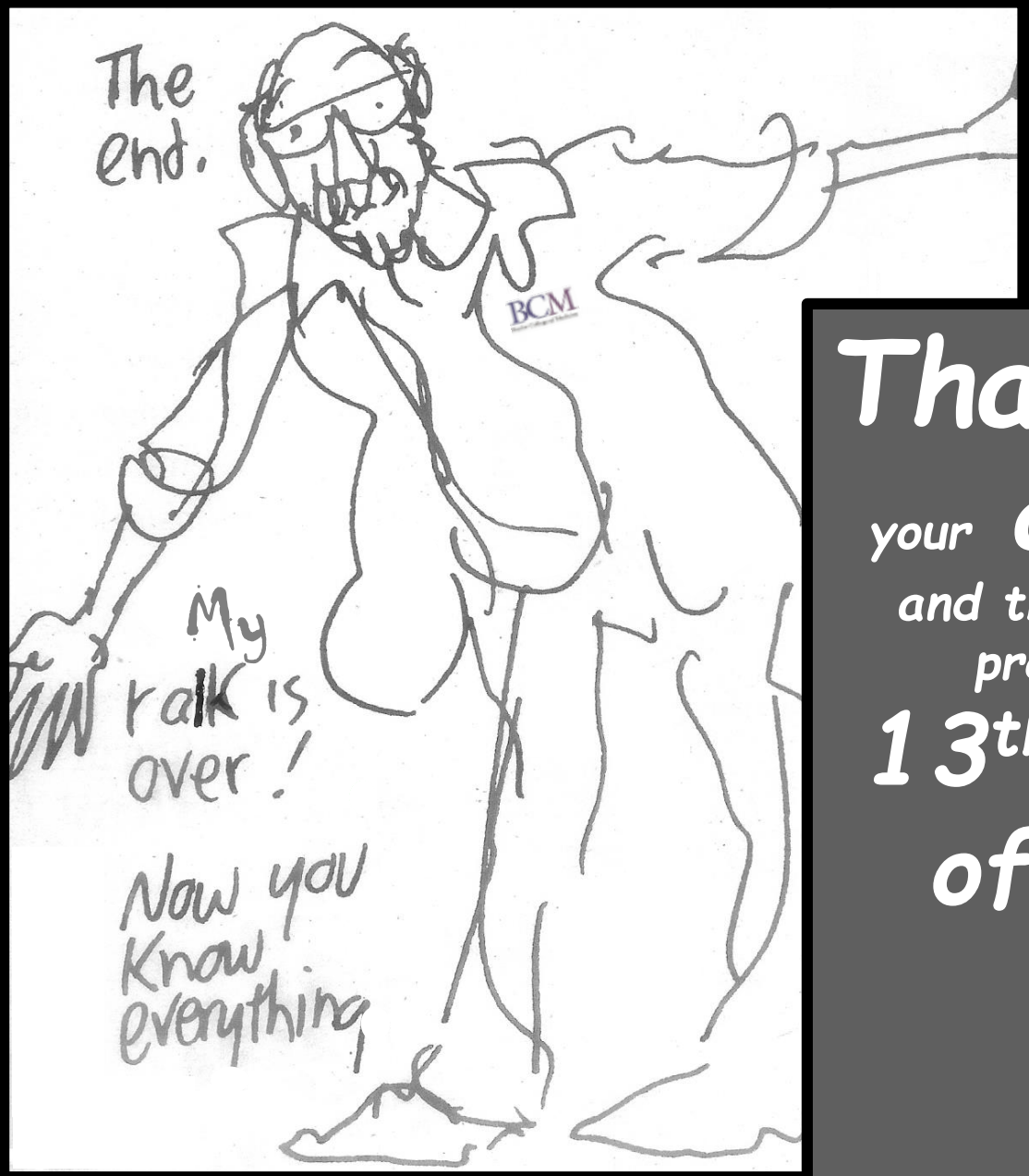
REMEMBER in AKI



URINE VOLUME



TUBULAR DYSFUNCTION



Thank you for your attention

and the opportunity to present at the

13th Congress of BANTAO