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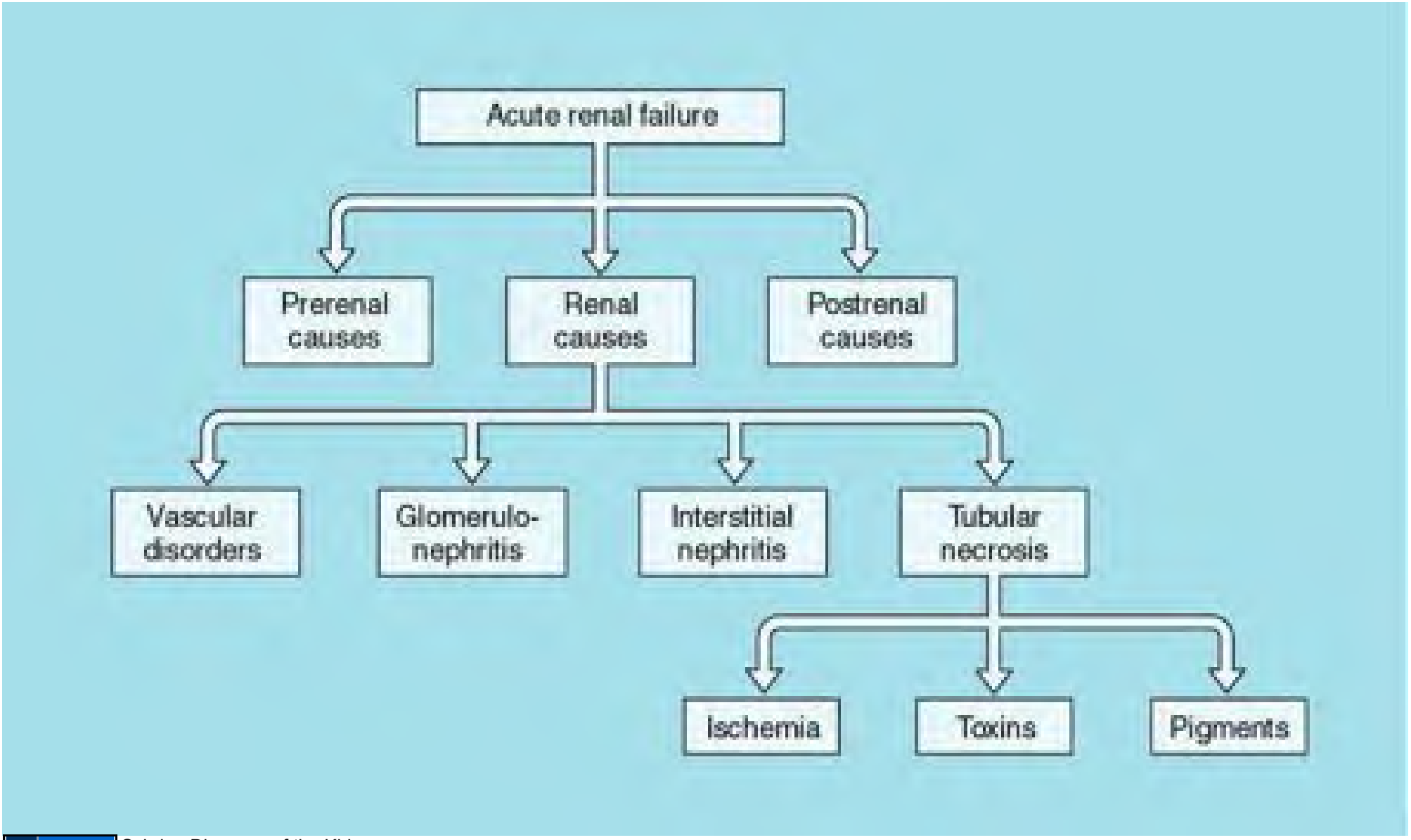
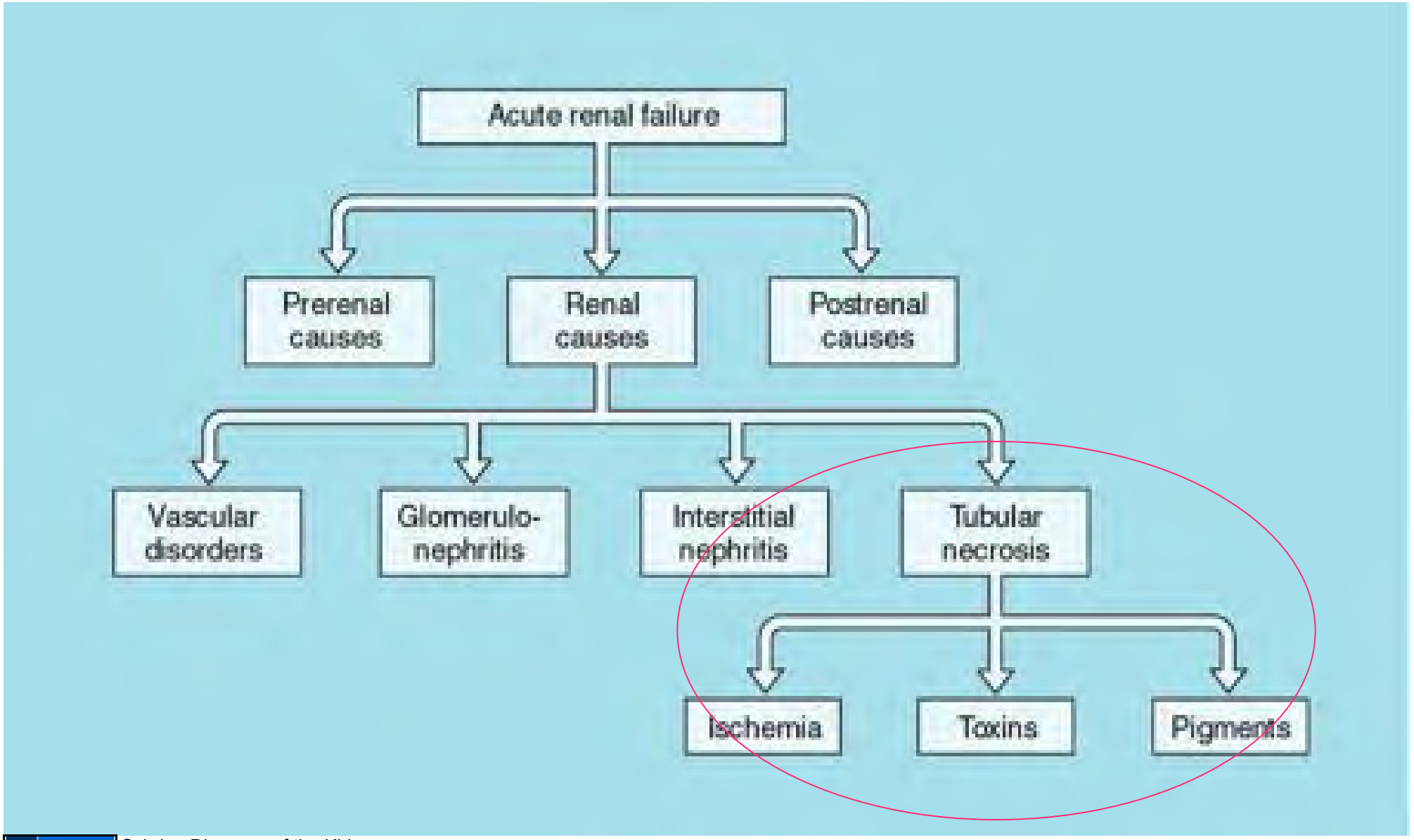
Acute Renal Failure/Acute Kidney Injury

Increase of BUN and/or creatinine of recent, abrupt onset reflecting a sudden loss of net, effective clearance capacity of the kidney.

Urine output can vary. Oliguria refers to < 400 cc./day; many forms are “non-oliguric.”



Schrier, Diseases of the Kidney



Schrier, Diseases of the Kidney

50-75% of inpatient general nephrology activities relate to the diagnosis and management of acute renal failure secondary to renal ischemia, drugs and diagnostic tests, and other toxins.

Incidence of ARF (any ARF)

- 1-2% of all hospital admissions
- 20-30% of Post-operative cases
- 10-25% of ICU admissions
- 20-30% of Acute sepsis
- Up to 40% in Hematologic malignancy
- The kidney fails when other organs fail . . .

Lanore, Crit Care Med 1991; Nolan, J Am Soc Neph 1998; Shusterman, Am J Med 1987; others

Impact of ARF

- ARF (any) increases hospital mortality x 5

  Levy et al, JAMA 1996

- ARF needing RRT carries 45-65% mortality

  somewhat better survival over last 5-10 yr

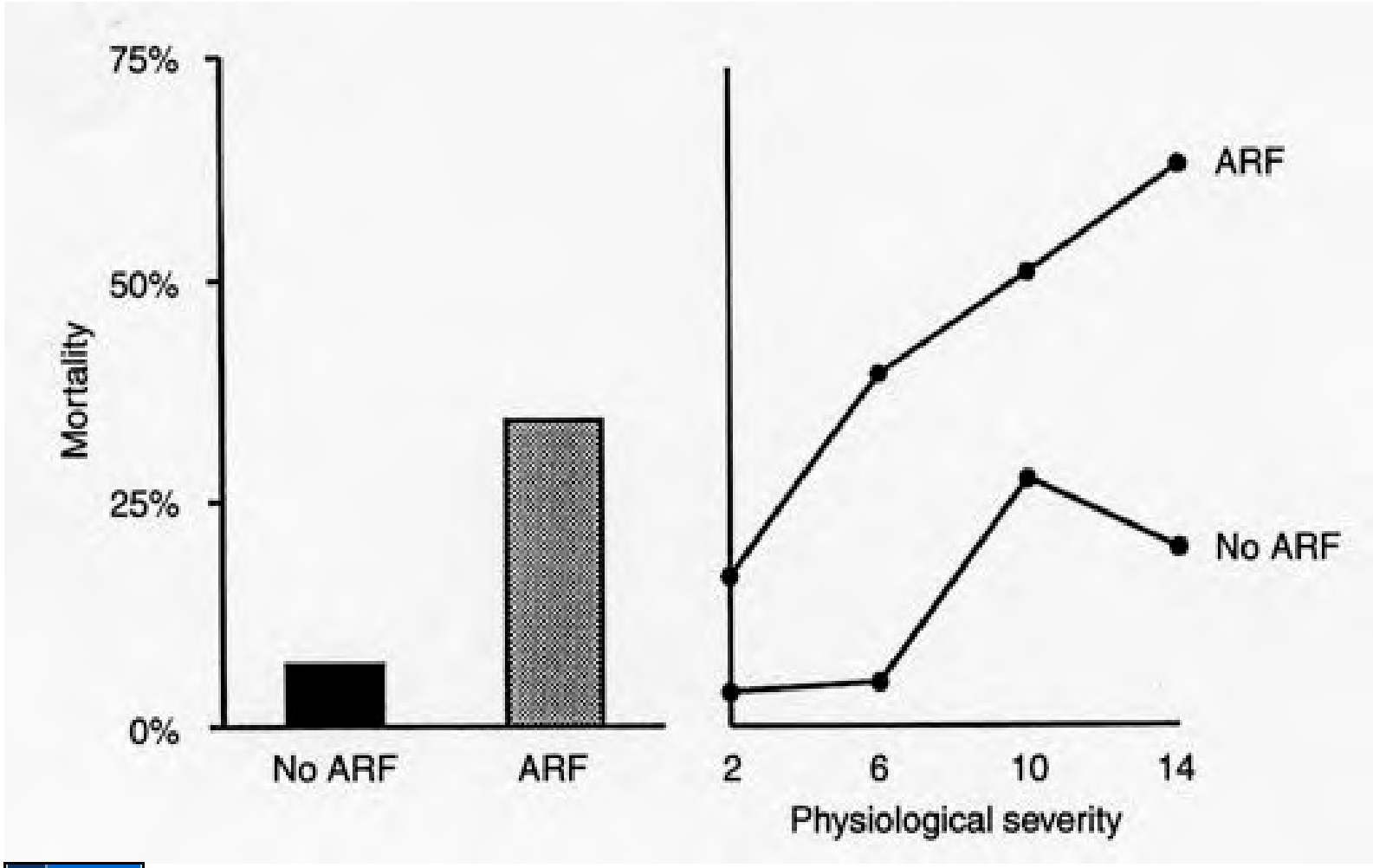
  Nolan et al, J Am Soc Neph 1998

- ARF in "critically ill" - 27% 6 mo survival

  Adj-life-yr cost: $274K/yr in worst cases

  $ 62K/yr in best cases

  Hamel et al, Ann Int Med 1996



PD-1NEL Levy et al. JAMA 275: 1489, 1996

16,000 patients undergoing contrast procedure.
183 developed ARF
34% mortality compared to 7% without ARF matched for age, baseline creatinine, and contrast procedure.
After comorbidity adjustment, odds ratio of dying after ARF was 5.5.

Mechanisms of Acute Renal Failure and Approach to the Patient

Illustrative Case

A 73 year old man develops severe abdominal pain radiating to the back and collapses at home. In the emergency room a blood pressure of 80 and an acute abdomen are present. At laparotomy, a ruptured, infrarenal abdominal aortic aneurysm is found and repaired during an 8 hour procedure in which 40 units of red blood cells and fresh frozen plasma are used. Postoperatively, the patient is putting out less than 200 cc urine/day and creatinine increases between 1 and 1.5 units daily until dialysis is started. Three weeks later, progressive increases in urine volume are noted along with smaller increases of creatinine between dialysis treatments. During the next week, sufficient renal function returns to discontinue dialysis and the patient ultimately leaves the hospital with a serum creatinine of 1.8 (as compared to 1.2 before this illness).

Mechanisms of Acute Renal Failure
Objectives

1. Appreciate why the kidney is susceptible to diverse insults resulting in acute renal failure.

2. Understand the contributions of the major relevant cell types in the vascular and tubular compartments.

3. Understand how the vascular and tubular events combine to produce whole organ dysfunction.

4. Be aware of the processes required for recovery and the time frame over which they occur.

Why are cells in the kidney particularly susceptible to diverse insults?

- High rates of oxidative metabolism

- Marginal oxygenation relative to work demands and complex microcirculation highly susceptible to inflammatory factors

- Reabsorptive functions and resulting urinary concentration expose both exterior and interior of cells to high levels of solutes.

- Metabolic transformation leading to toxic activation

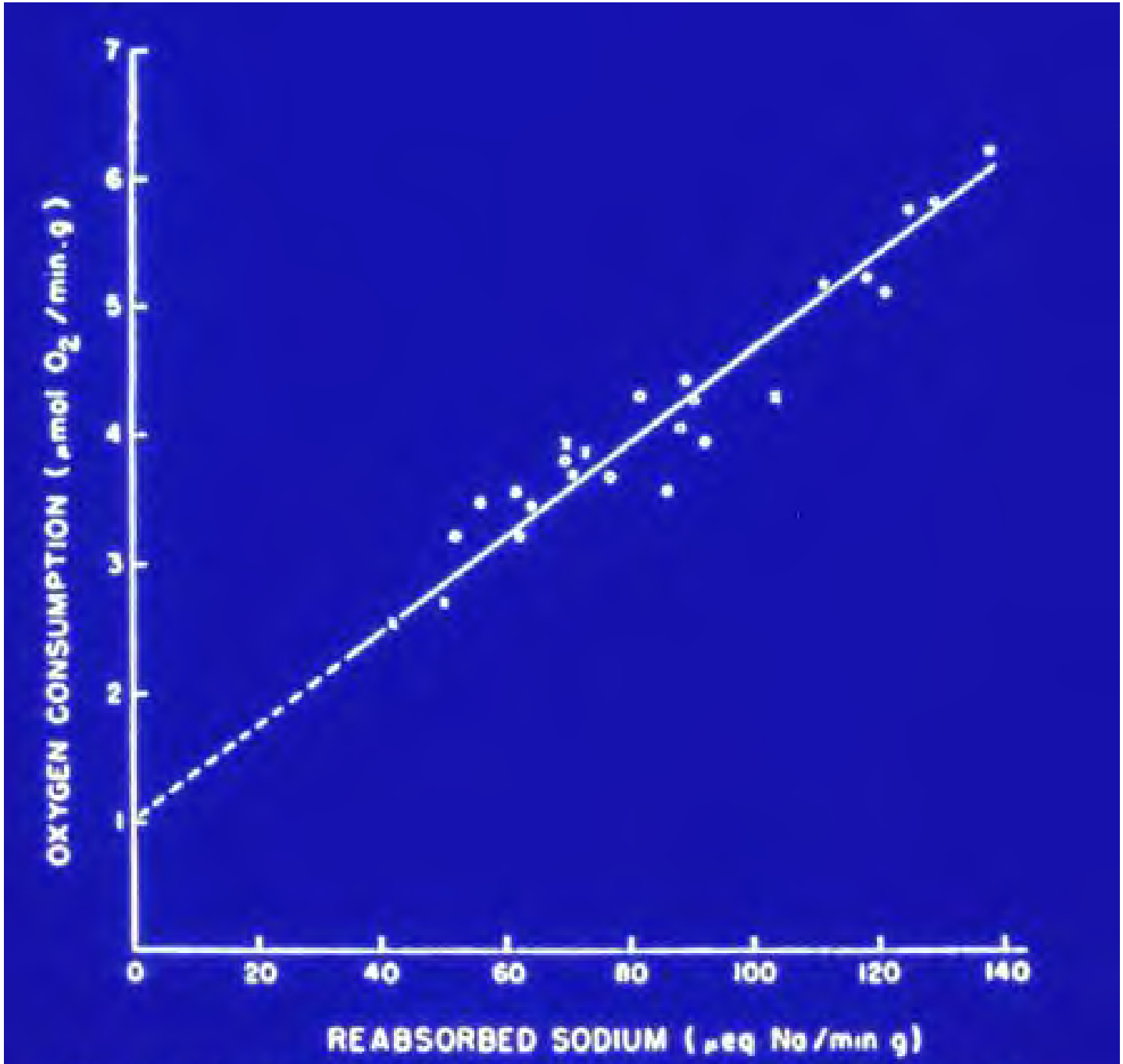


Figure 2–8. The relation between renal oxygen consumption and sodium reabsorption in the dog kidney. Redrawn from Thurau,[206] as shown in reference 31.

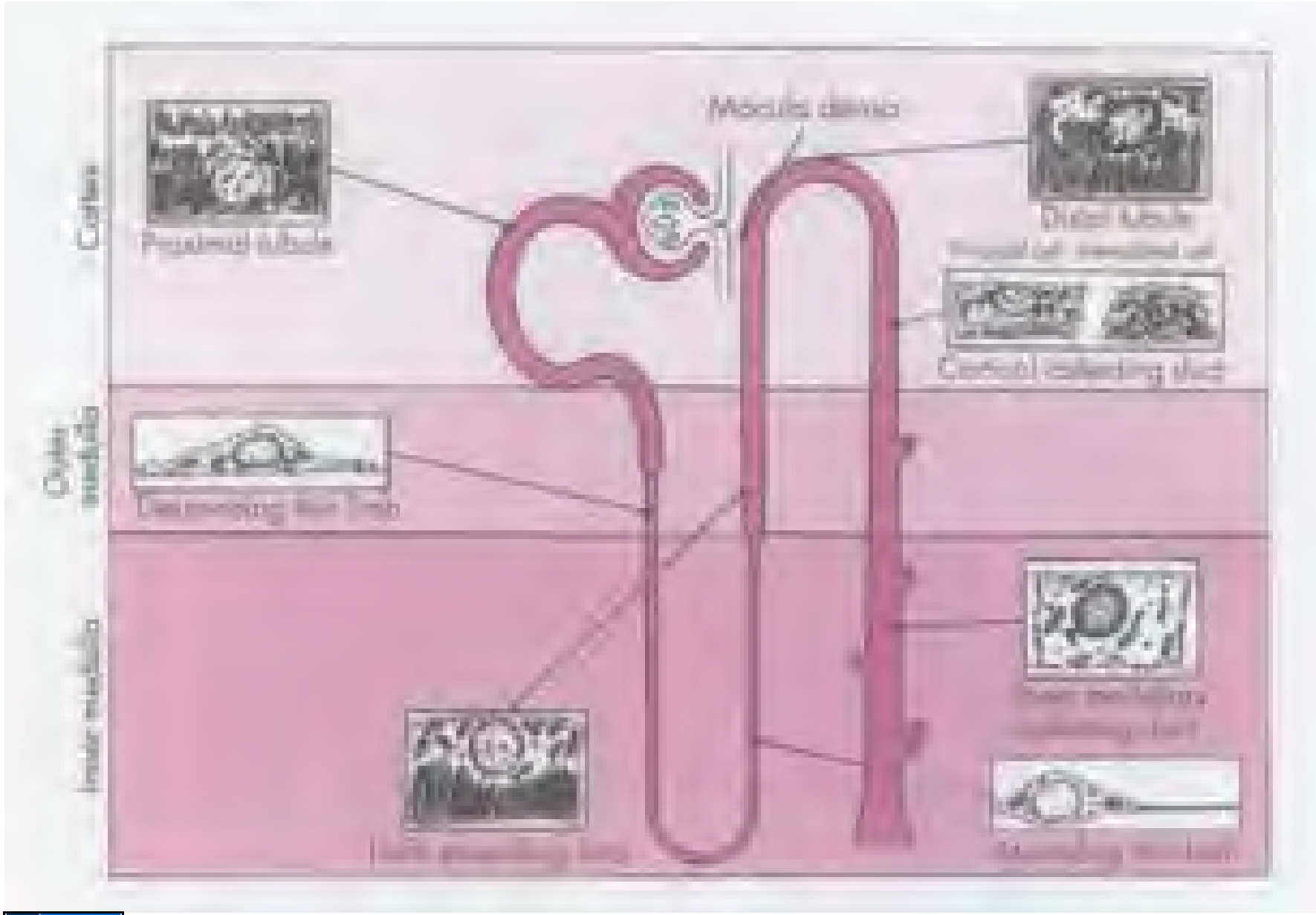


Fig 2-3

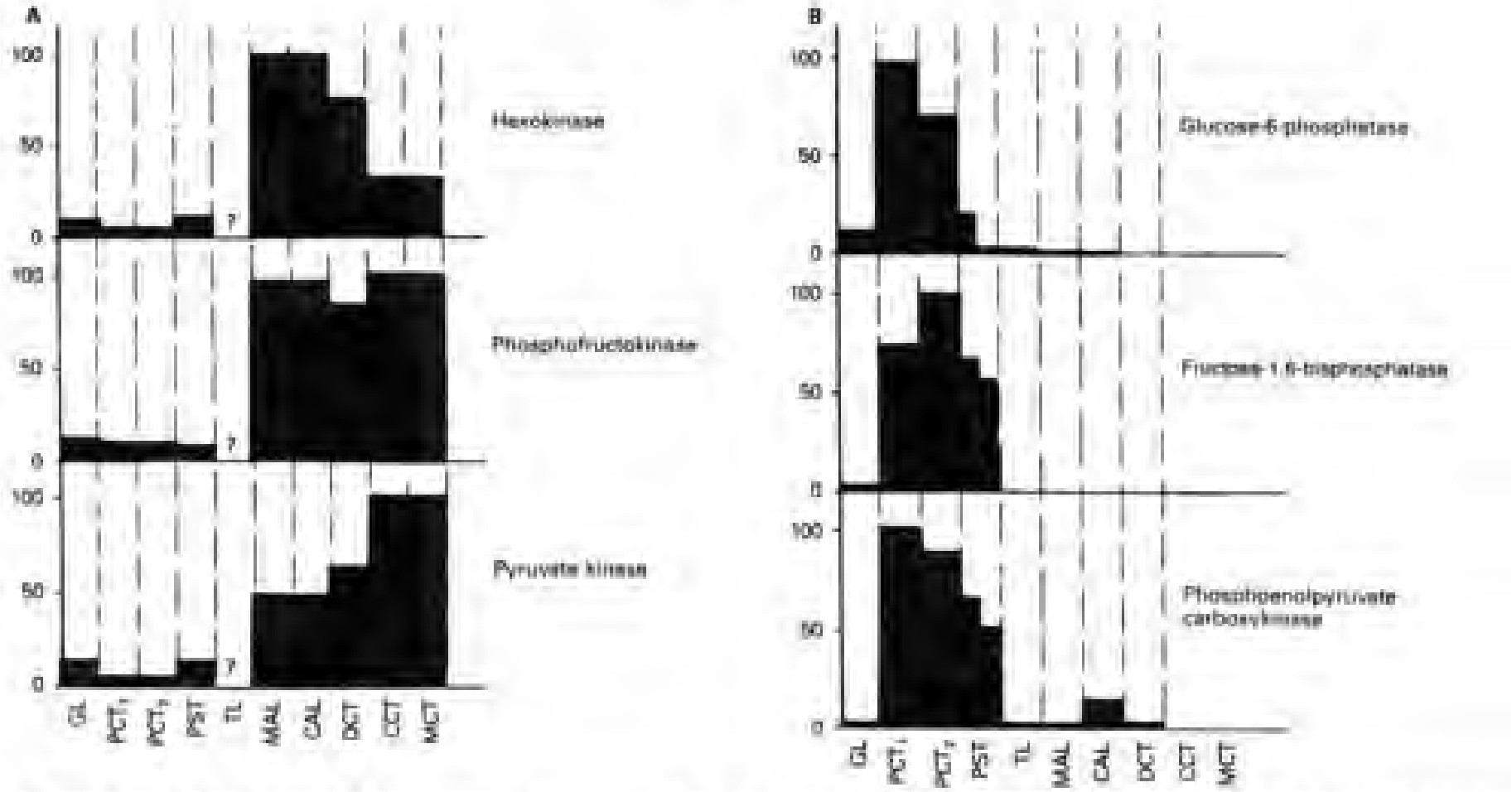


Fig. 1. *Distribution of glycolytic and gluconeogenic enzymes along the rat nephron.* Nephron segments were dissected from fed (A) and starved (B) rats, respectively. The activity of hexokinase (E.C. 2.7.1.1.) [7], phosphofructokinase (E.C. 2.7.1.11.) [8], pyruvate kinase (E.C. 2.7.1.40.) [8], glucose-6-phosphatase (E.C. 3.1.3.9.) [15], fructose-1,6-bisphosphatase (E.C. 3.1.3.11.) [15, 16], and phosphoenolpyruvate carboxykinase (E.C. 4.1.1.32.) [15, 17] were determined in individual segments. Enzyme activities are expressed as percent of the maximal value observed, based on the original activity per gram of dry weight. For methodological details and absolute activities the reader is referred to the references cited. The abbreviations of nephron segments used are: GL, glomerulus; PCT_1, early proximal convoluted tubule; PCT_2, late proximal convoluted tubule; PST, proximal straight tubule; TL, loop of Henle, thin limbs; MAL, medullary thick ascending limb; CAL, cortical ascending limb; DCT, distal convoluted tubule; CCT, cortical collecting tubule; MCT, medullary collecting tubule.

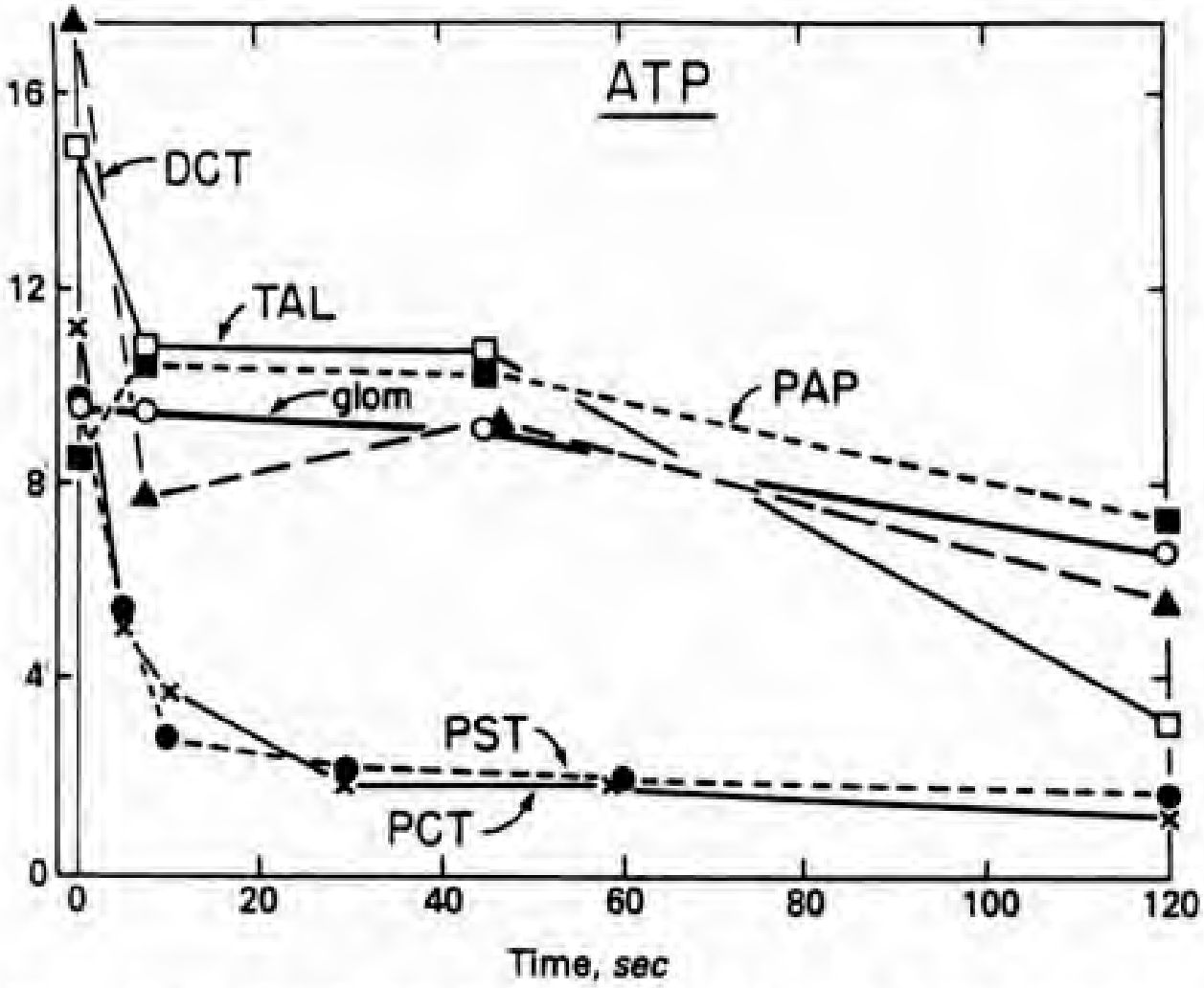
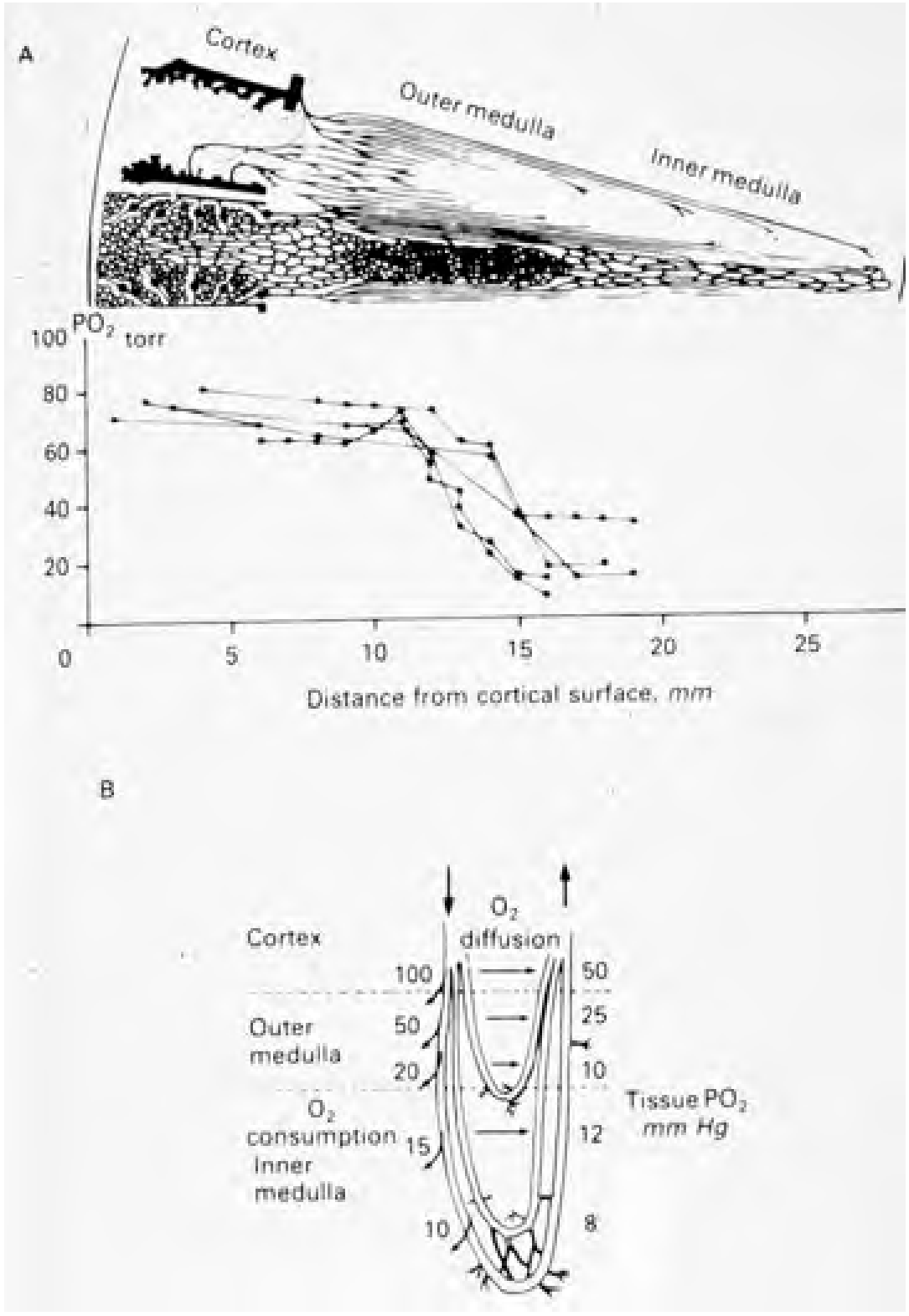
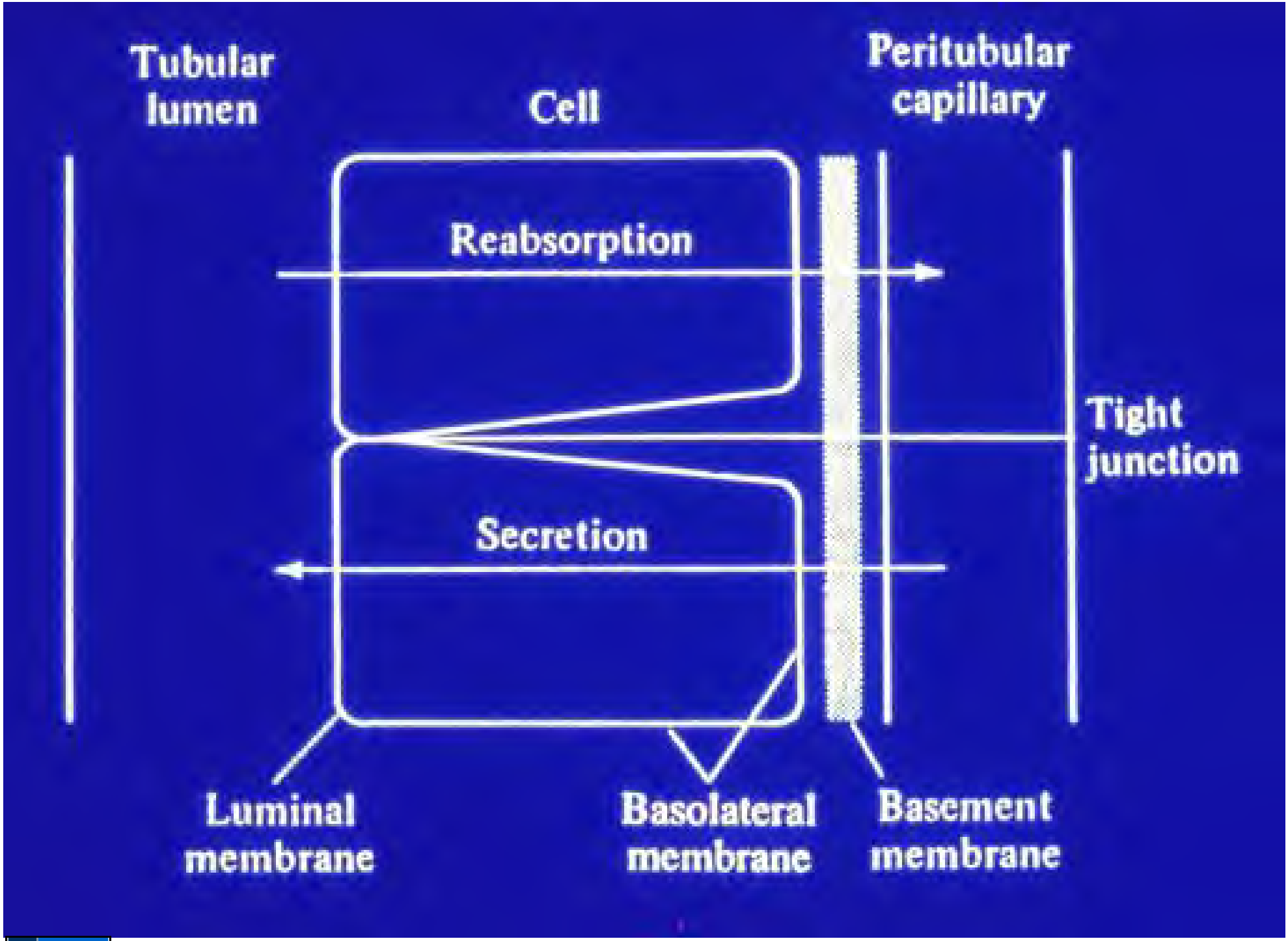
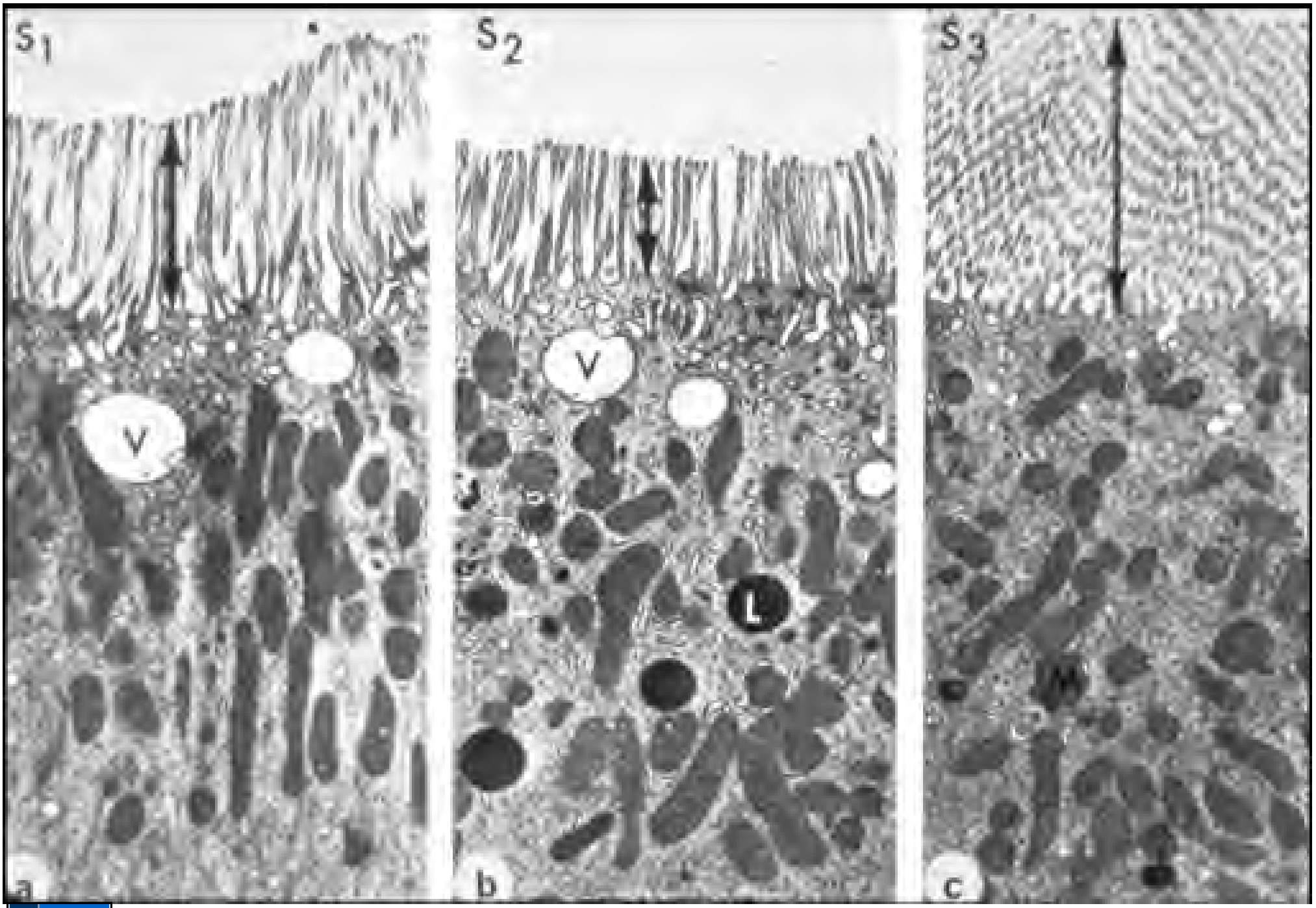


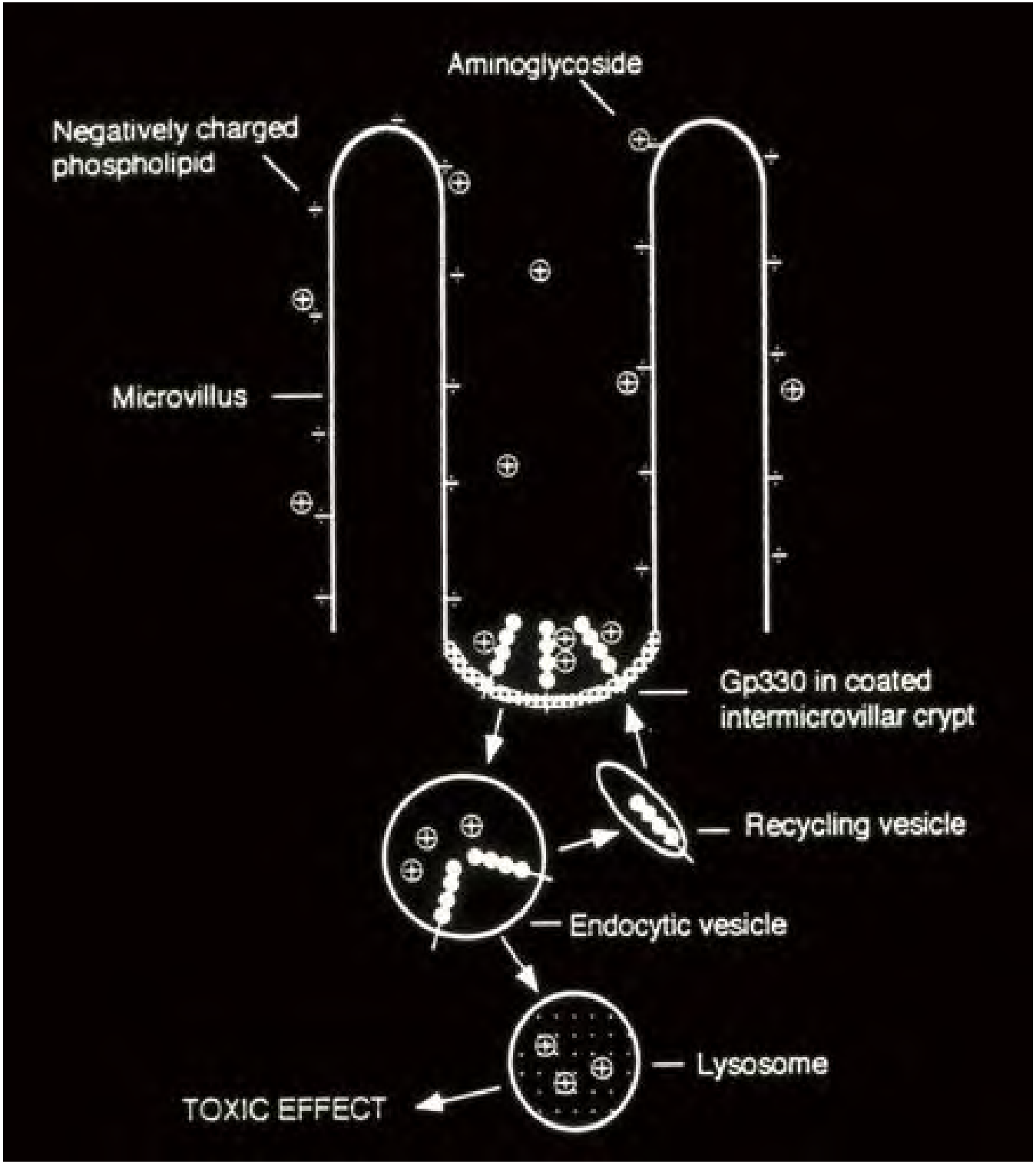
Fig. 2. *Effect of ischemia on ATP levels in 6 parts of the nephron and in the papilla.* Concentrations are mmol · kg^{-1} (dry wt). Except as indicated, each value is the average for 3 to 8 kidneys. The 7.5 and 45 sec values are the averages of data for 5 and 10 sec, and 30 and 60 sec periods of ischemia respectively. Symbols are: (▲) DCT, (□) TAL, (■) PAP, (○) glom, (●) PST, and (×) PCT.

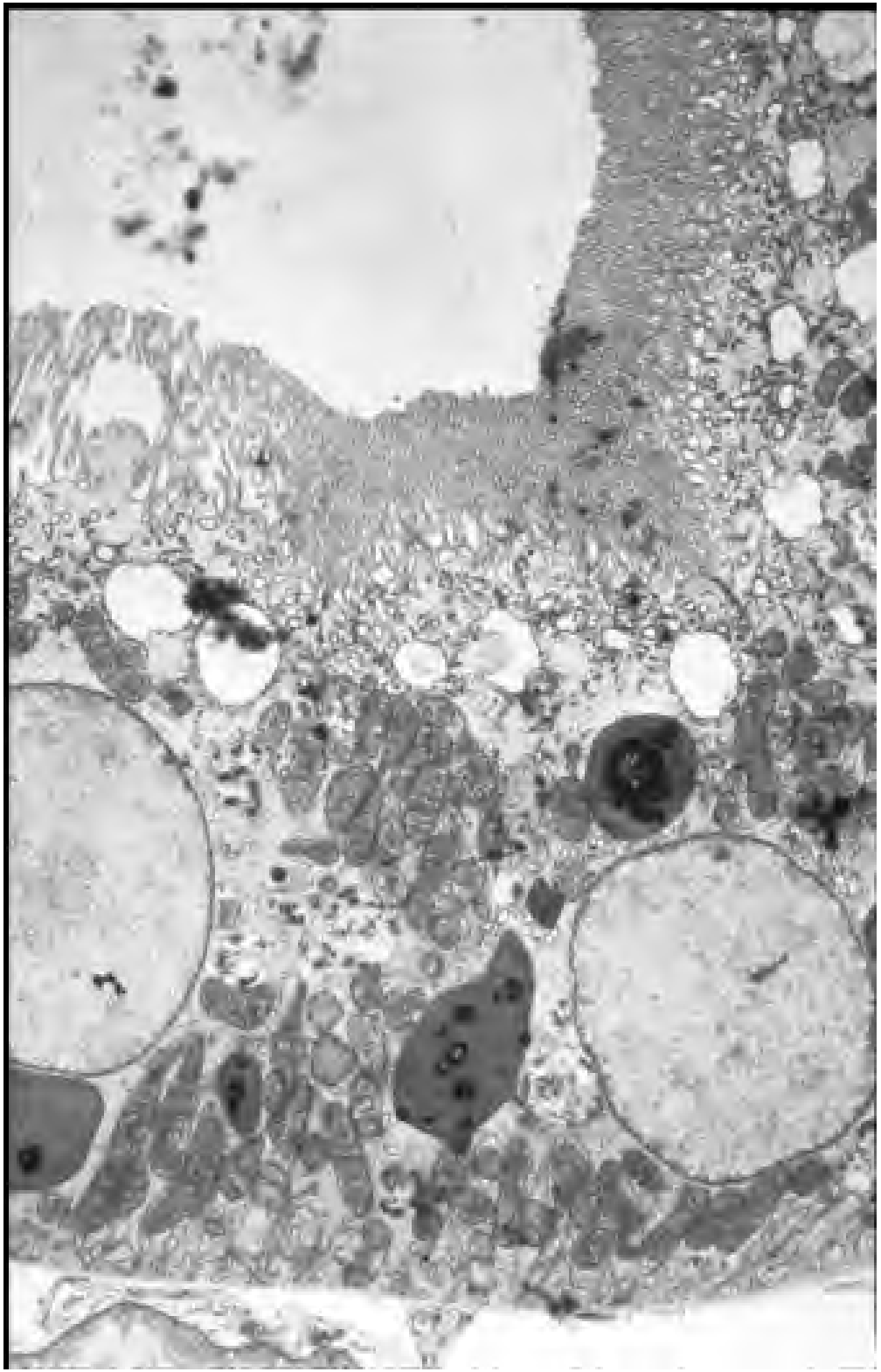
Bastin, J. et al. Kidney Int. 31:1239,1987

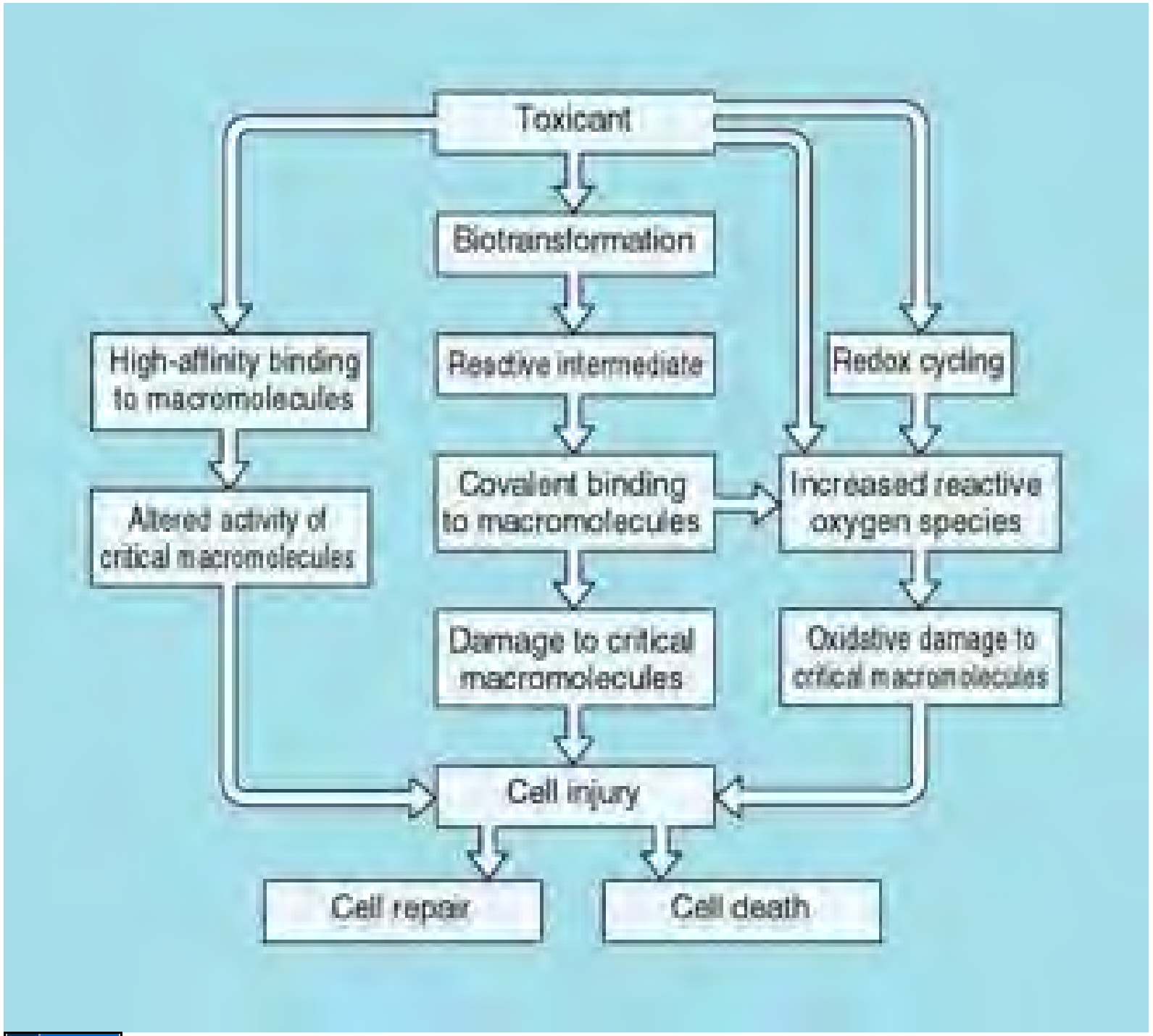




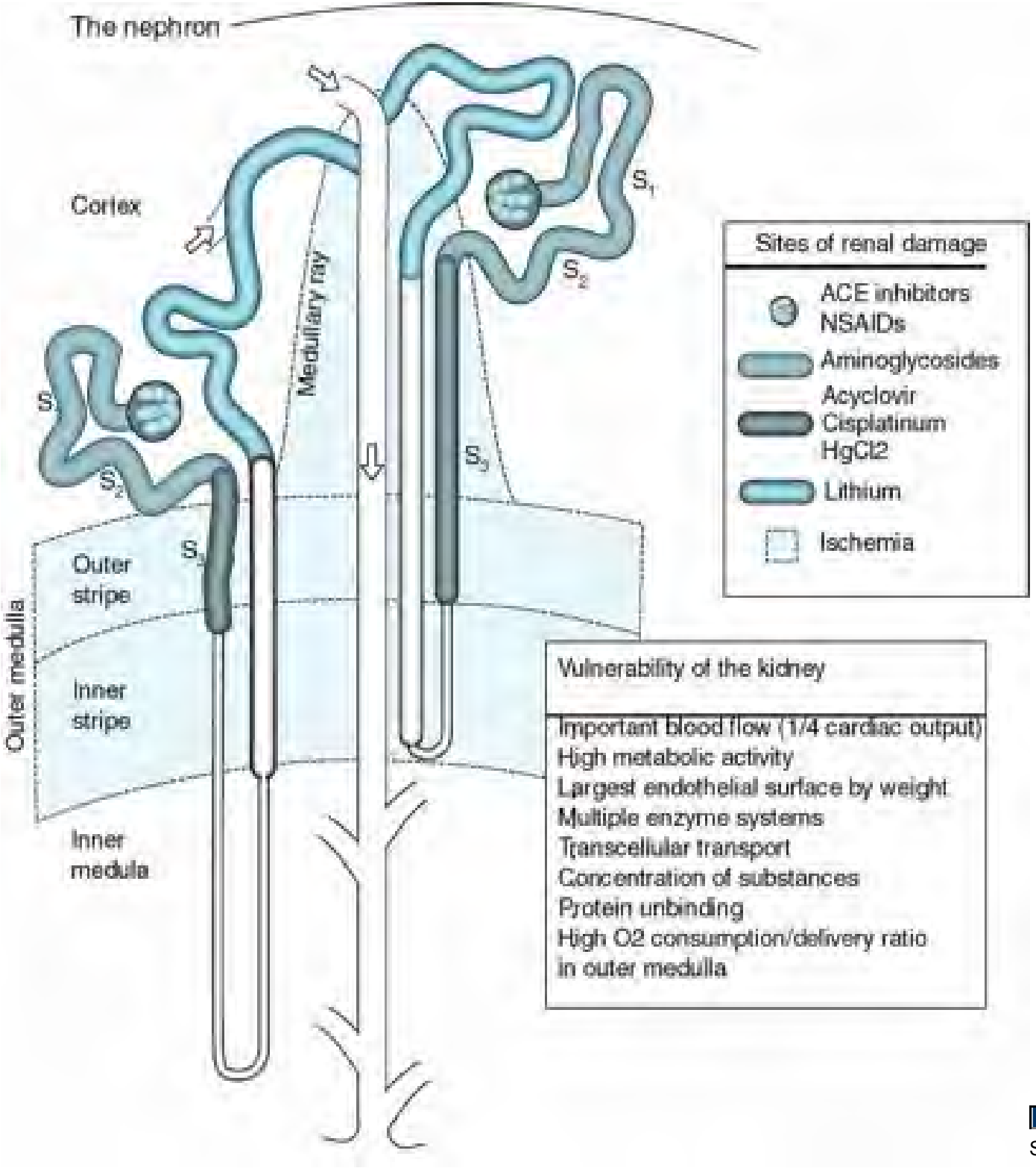




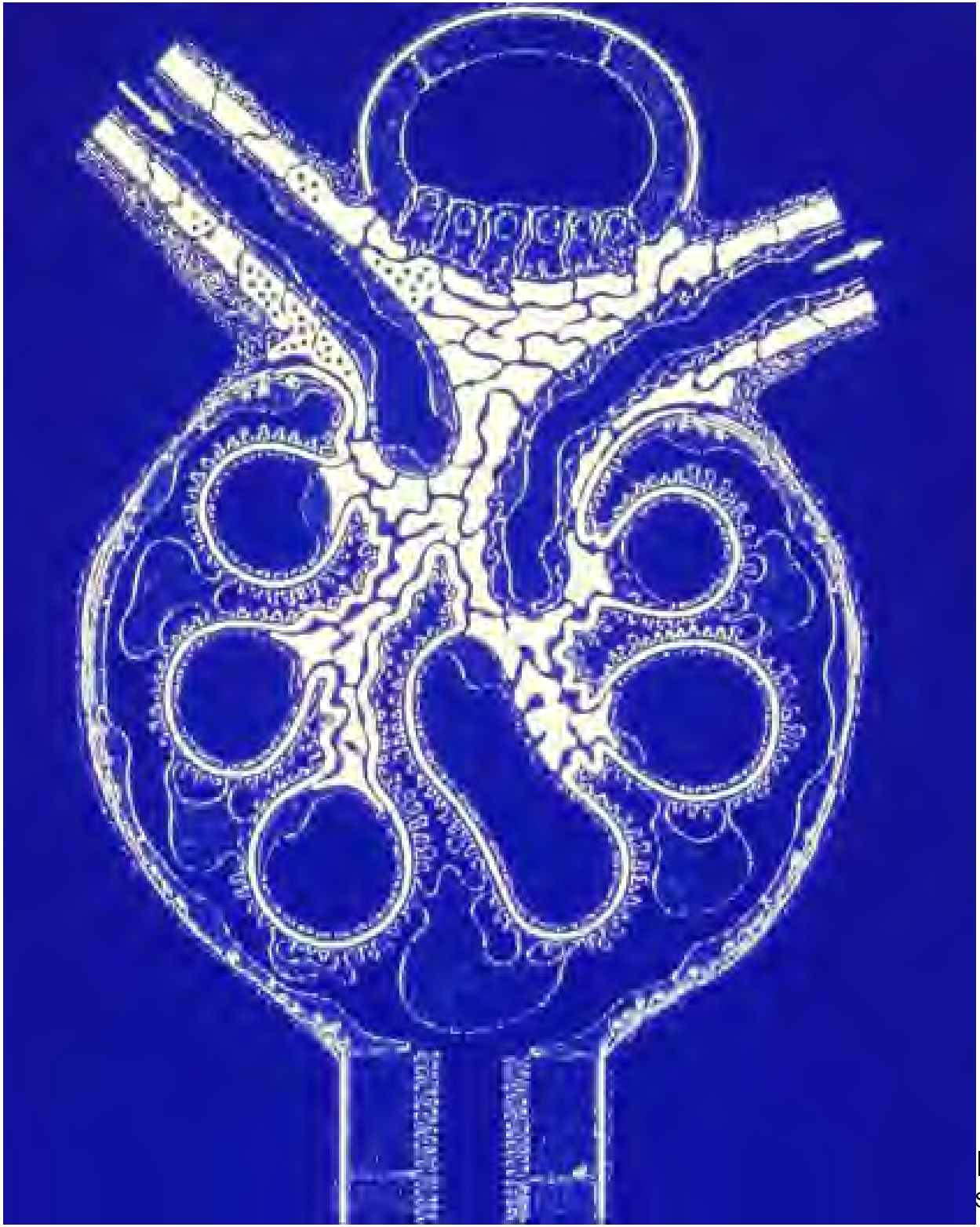


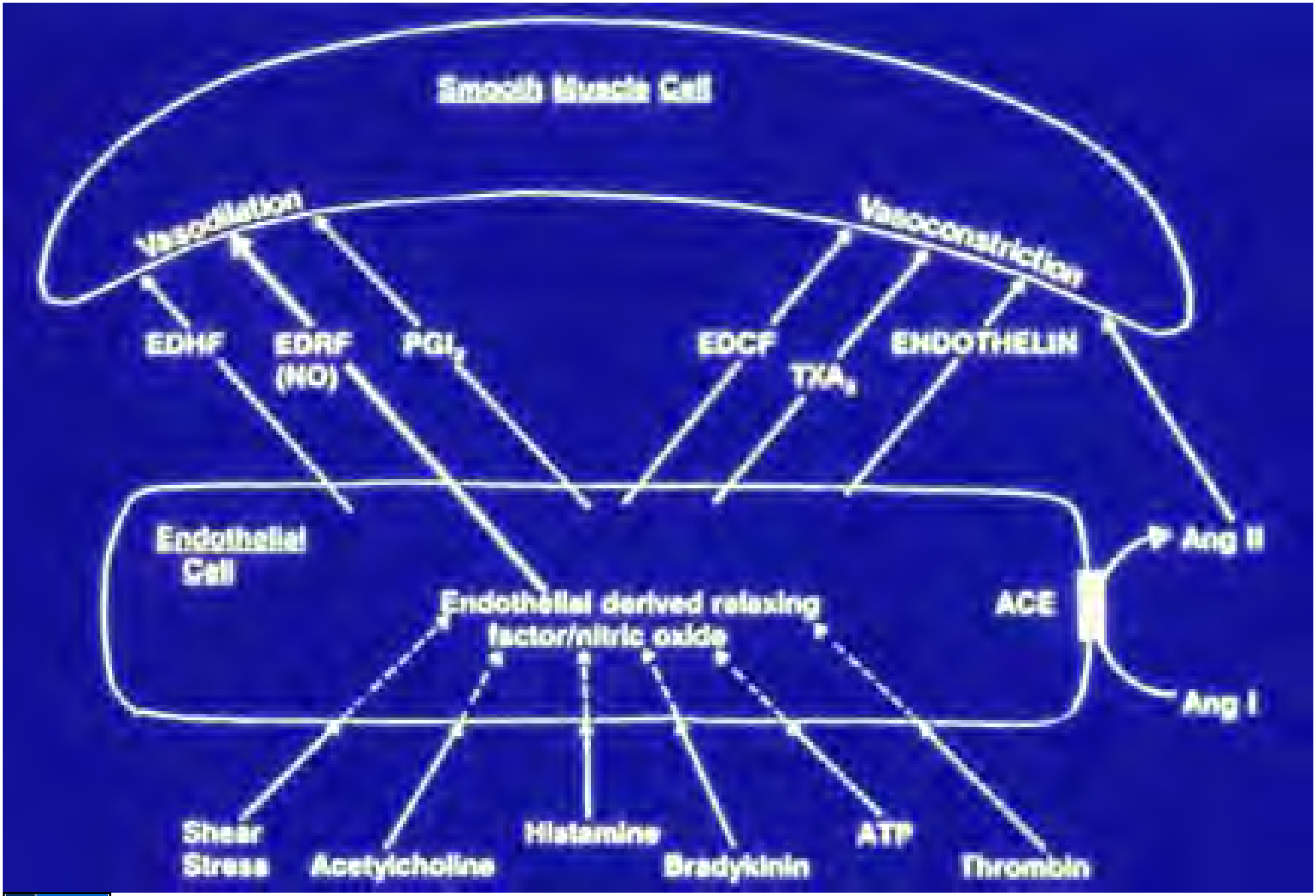


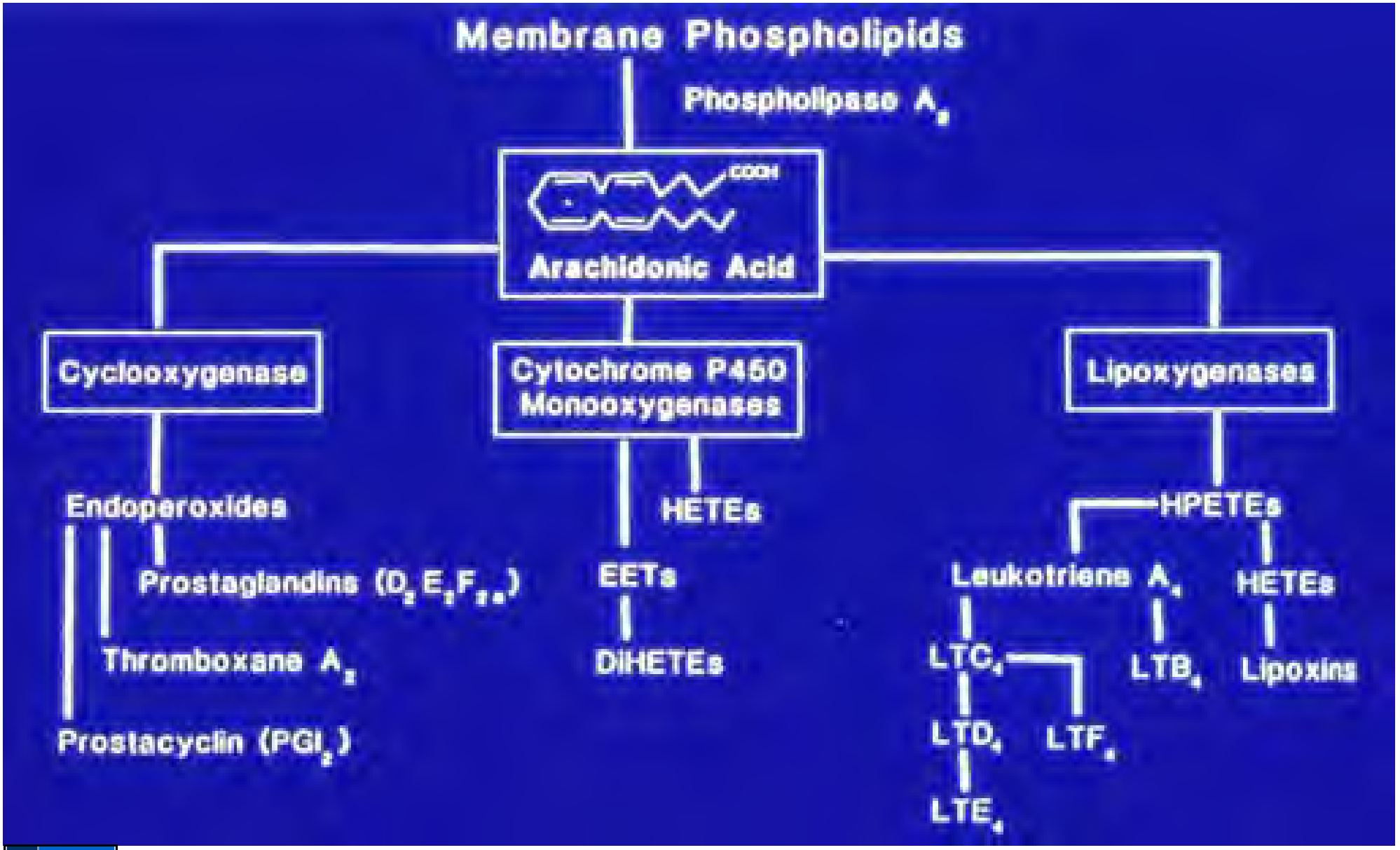
PD-INEL Schrier, Diseases of the Kidney



Schrier, Diseases of the Kidney







Predominant Actions of Regulators of Renal Hemodynamics With Potential Effects During Acute Renal Failure

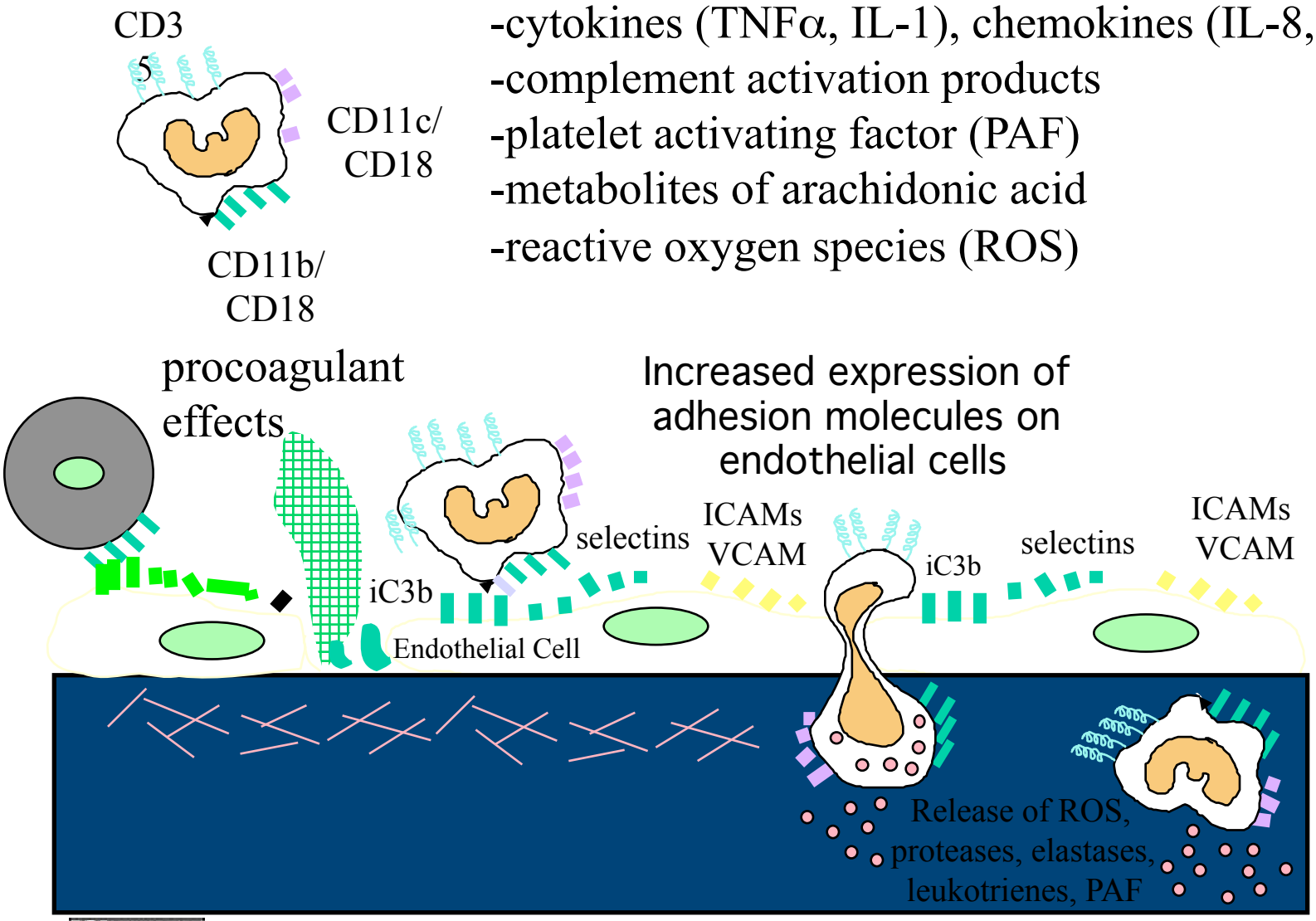
Vasoconstricting	Vasodilating
Macula densa-mediated tubuloglomerular feedback	Prostaglandins PGI_2 PGE_2
Angiotensin II	Nitric oxide
Arachidonic Acid Products Thromboxane Leukotrienes P450 metabolites	Atrial Natriuretic Peptides
Endothelins	Dopamine
Adenosine	Kinins
Platelet activating factor	Histamine
Adrenergic nerves	Acetylcholine

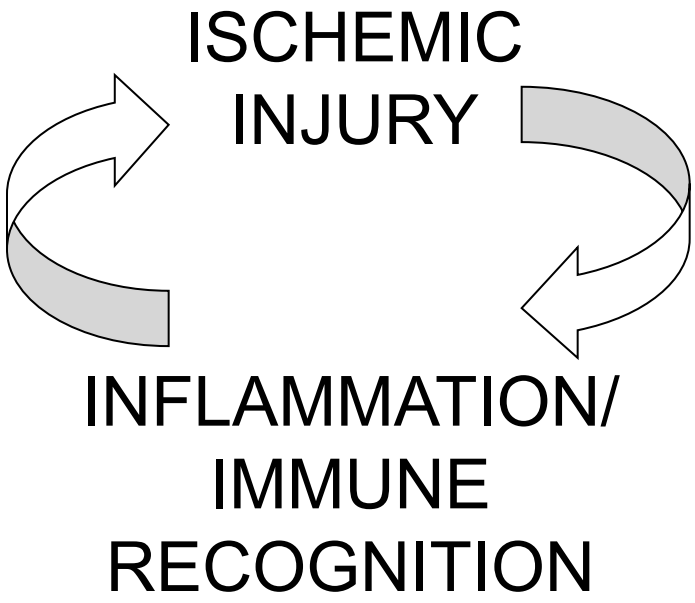
Leukocyte Activation in Ischemic ARF

Ischemic Kidney

Activated Leukocytes

Local production of inflammatory mediators
-cytokines (TNFα, IL-1), chemokines (IL-8, MCP-1)
-complement activation products
-platelet activating factor (PAF)
-metabolites of arachidonic acid
-reactive oxygen species (ROS)




ISCHEMIC
INJURY
INFLAMMATION/
IMMUNE
RECOGNITION

Amelioration of experimental acute renal failure by inhibition of leukocyte infiltration:

anti-neutrophil serum
anti-ICAM-1 mAb
ICAM-1 antisense oligonucleotides
ICAM-1 knockout
anti-CD11 mAb
P-selectin glycoprotein ligand-1
blockade of the CD28-B7 costimulatory pathway
Adenosine A2A receptor antagonists

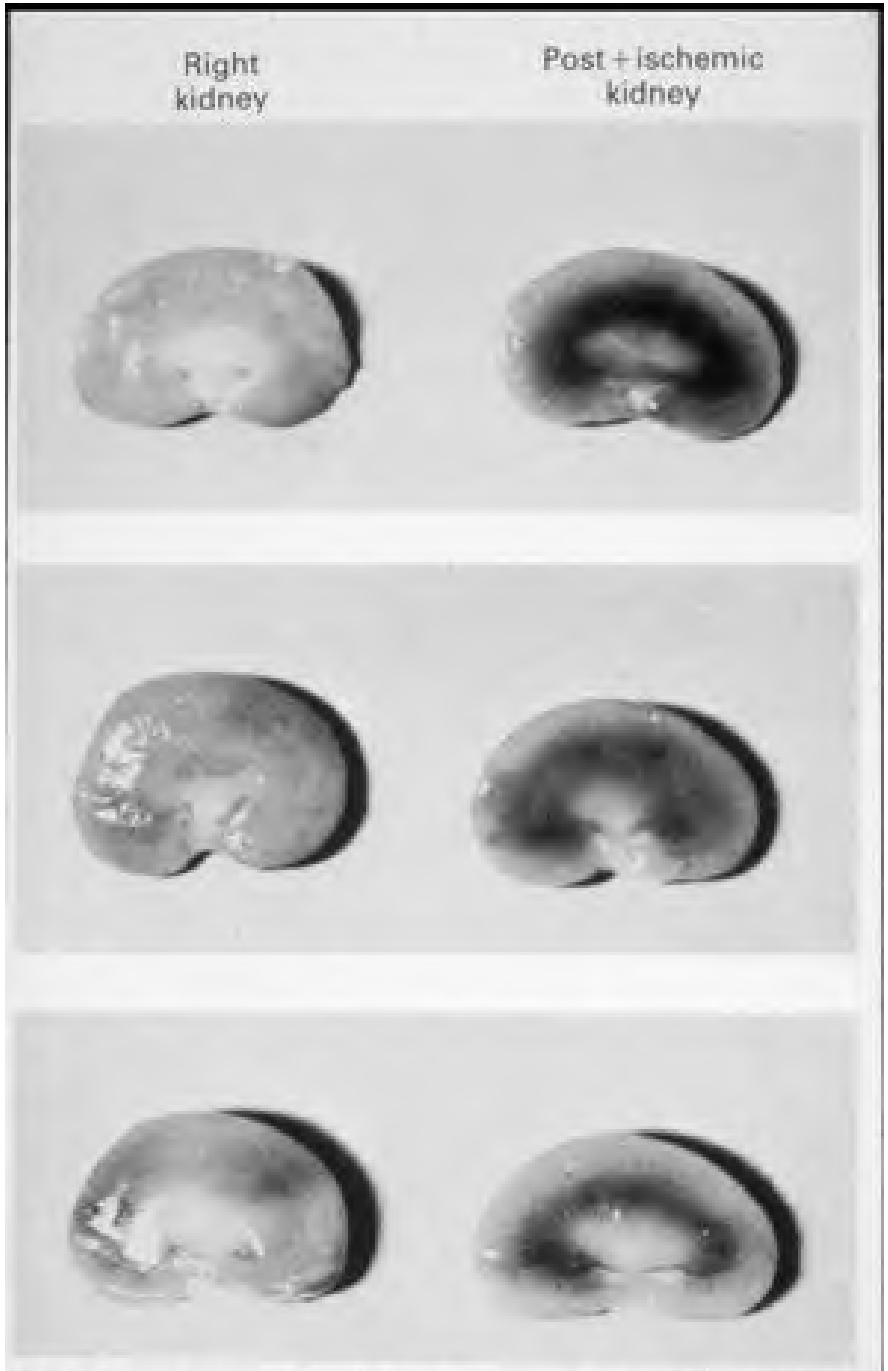


Fig. 1. *Three degrees of medullary hyperemia distinguished within 3 hr of ischemia.* Each ischemic, left kidney, is shown beside the contralateral, right kidney of the same animal. The ischemic kidney at the *bottom right* is one from the mildly affected group. The *middle right* ischemic kidney is typical for the moderately affected group. The *top right* ischemic kidney is one from the severely affected group.

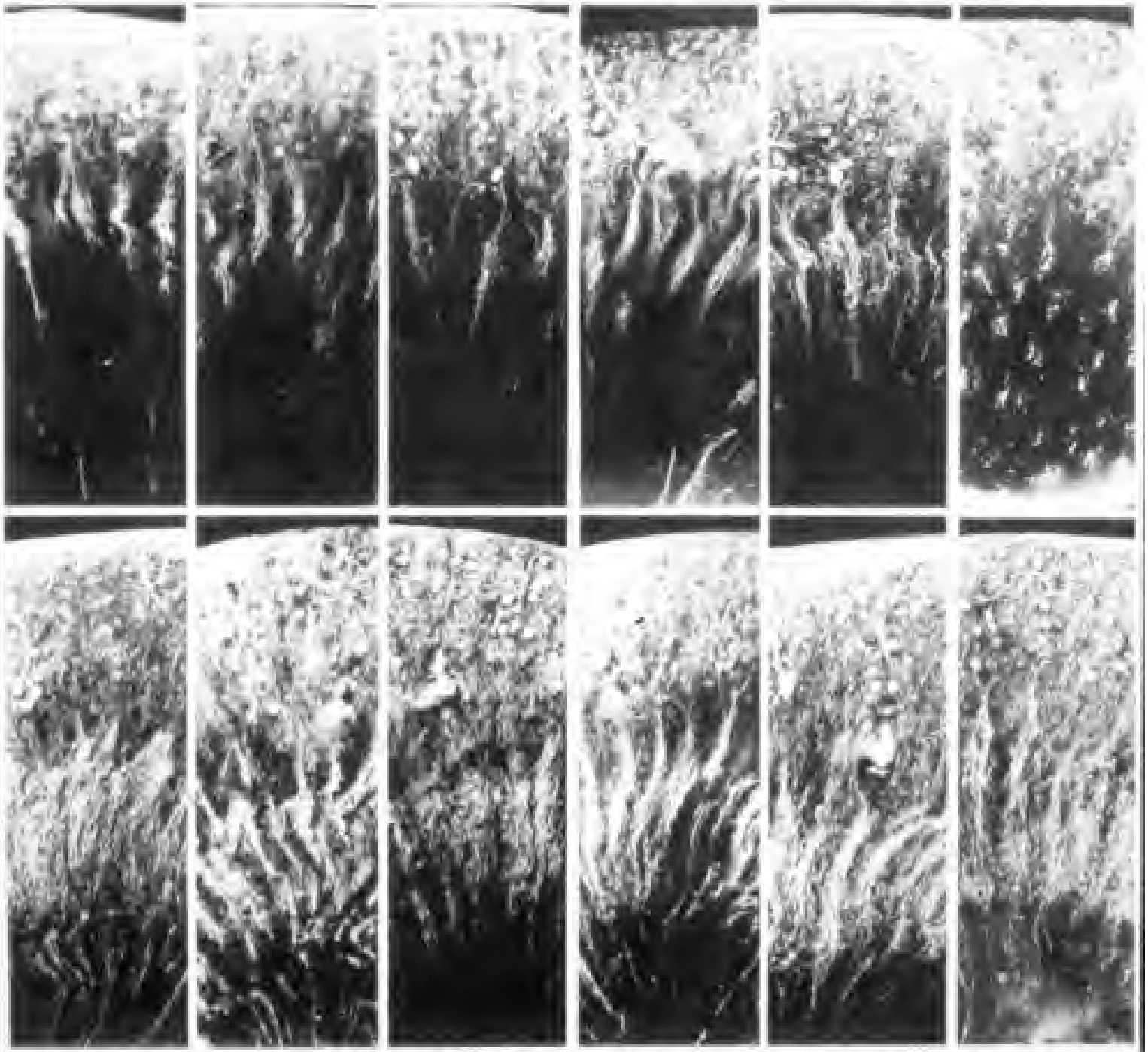
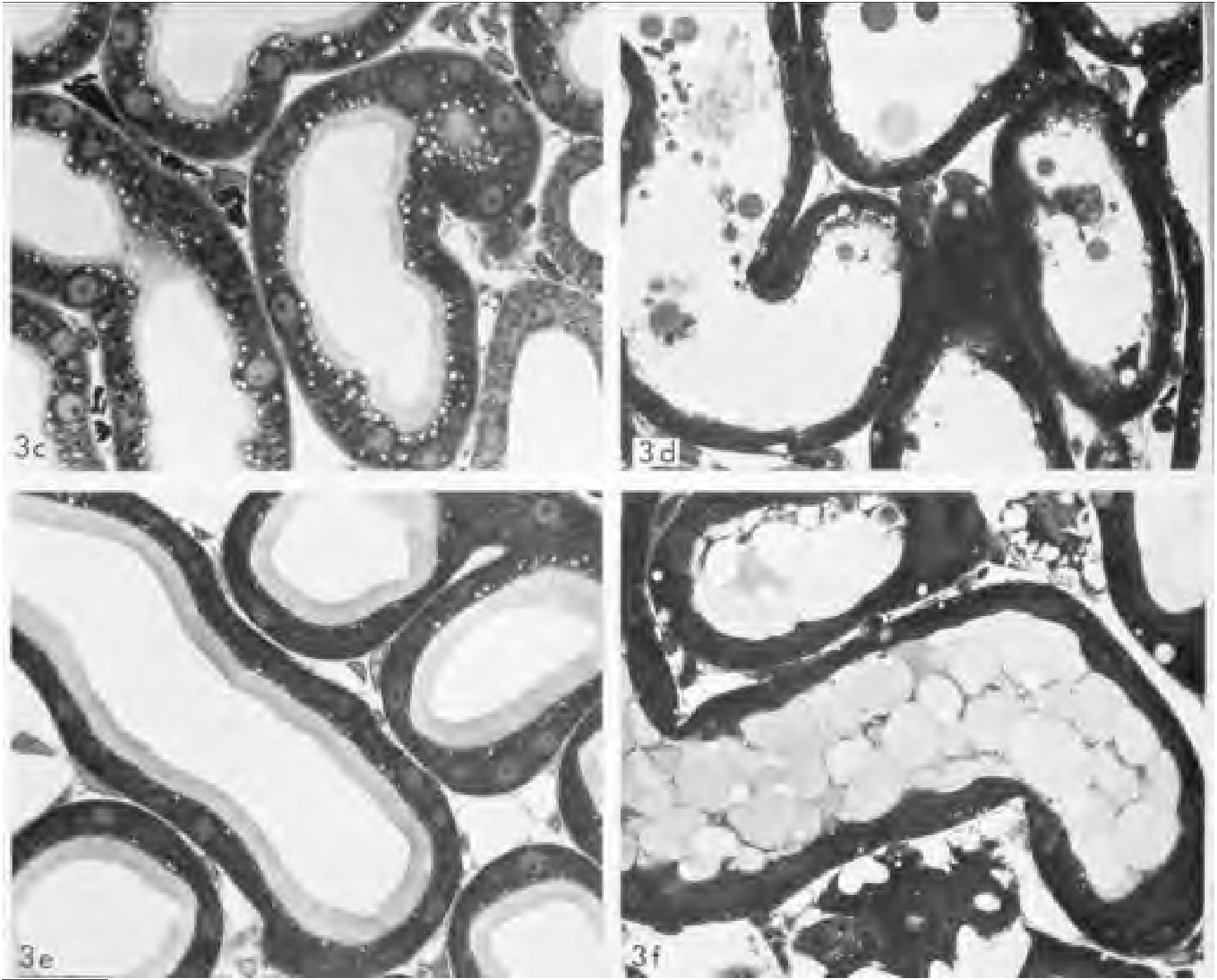
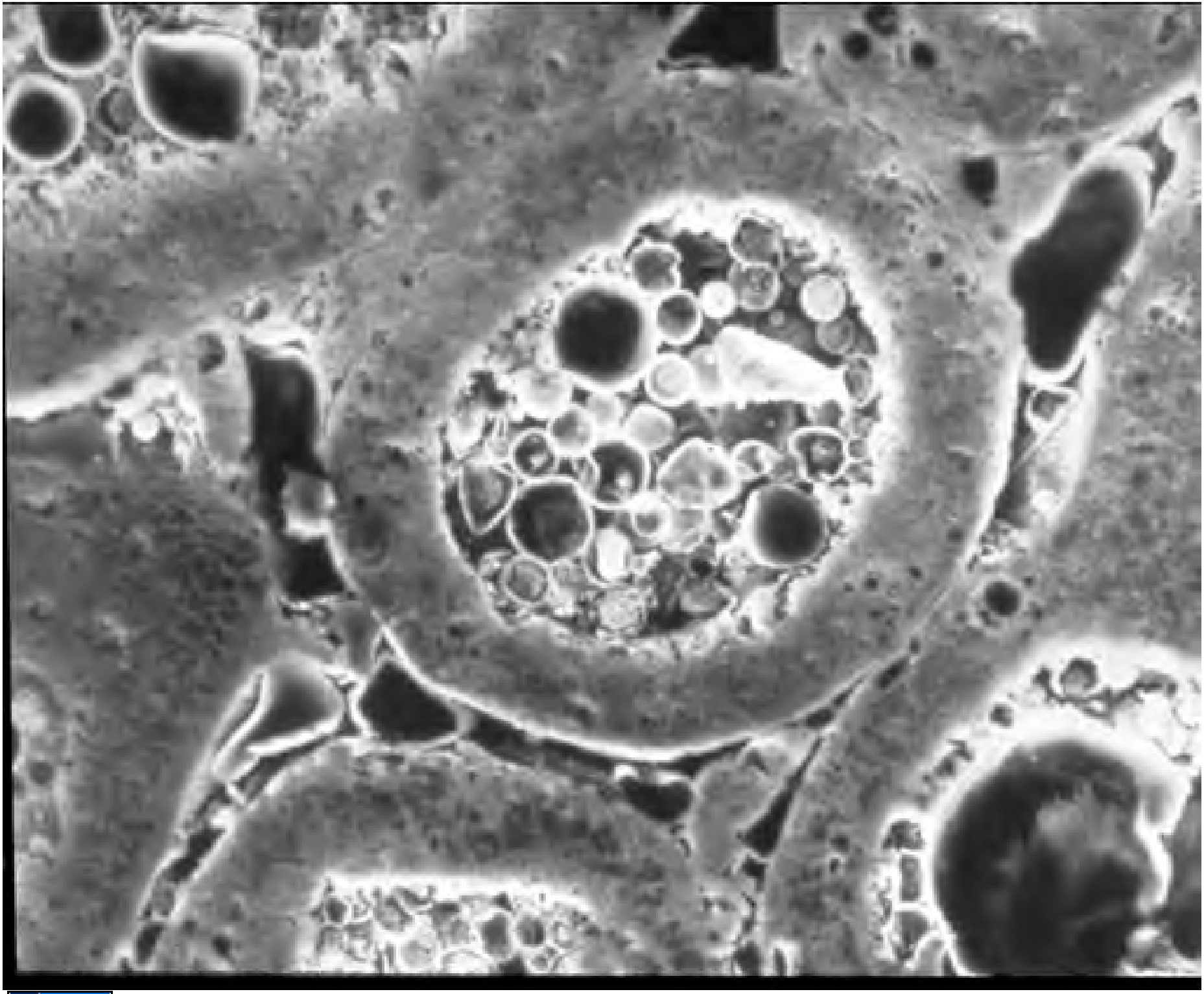
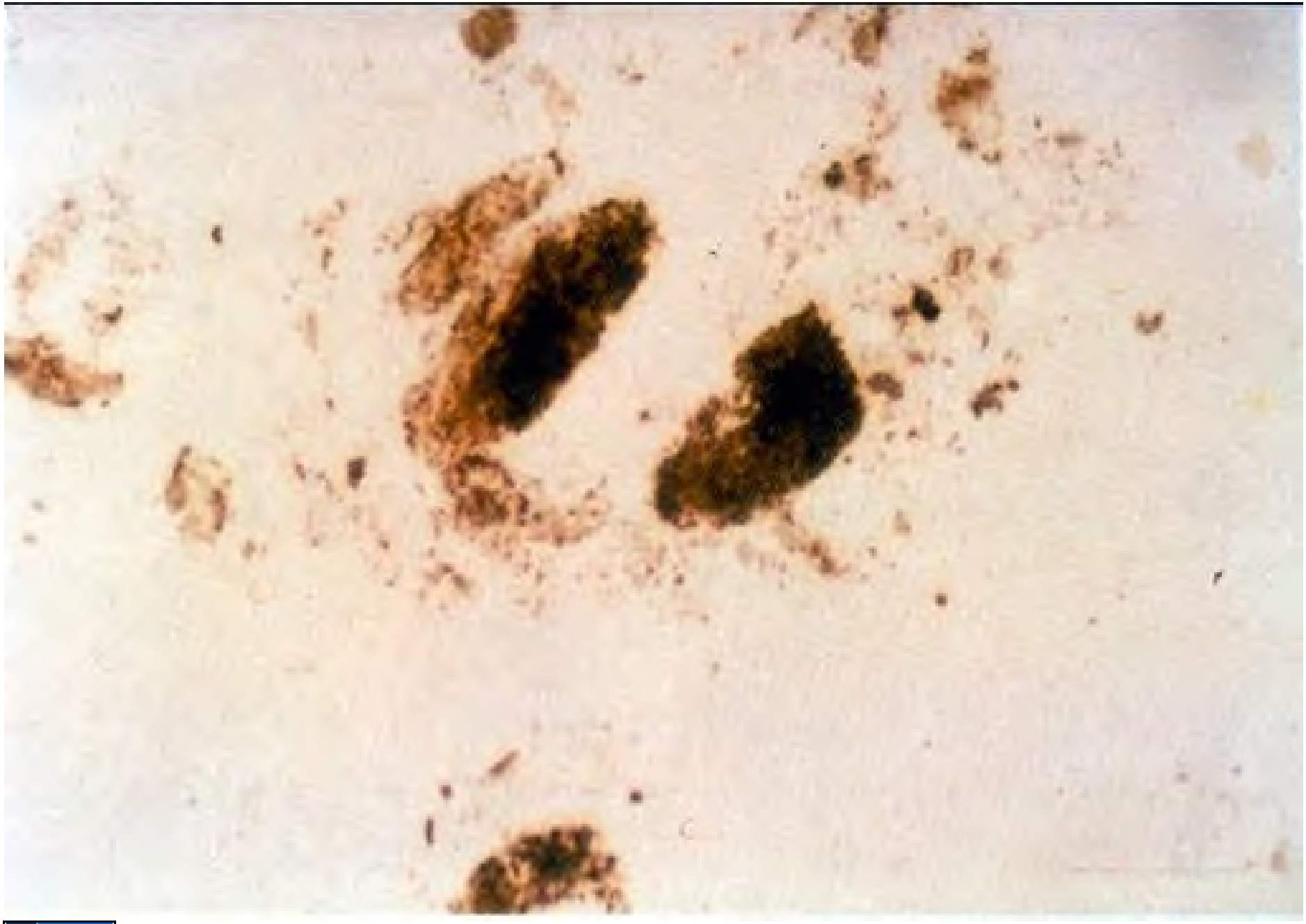


Fig. 1. *The degree to which the renal vasculature can be filled with silicone rubber in the ischemic kidney above and in the contralateral control kidney from the same animal immediately below.* The cortical vasculature is equally well-filled in each kidney pair, but in the ischemic kidney, there is no filling of the inner stripe vessels, except for the descending vasa recta, and the capillary plexus cannot be demonstrated.







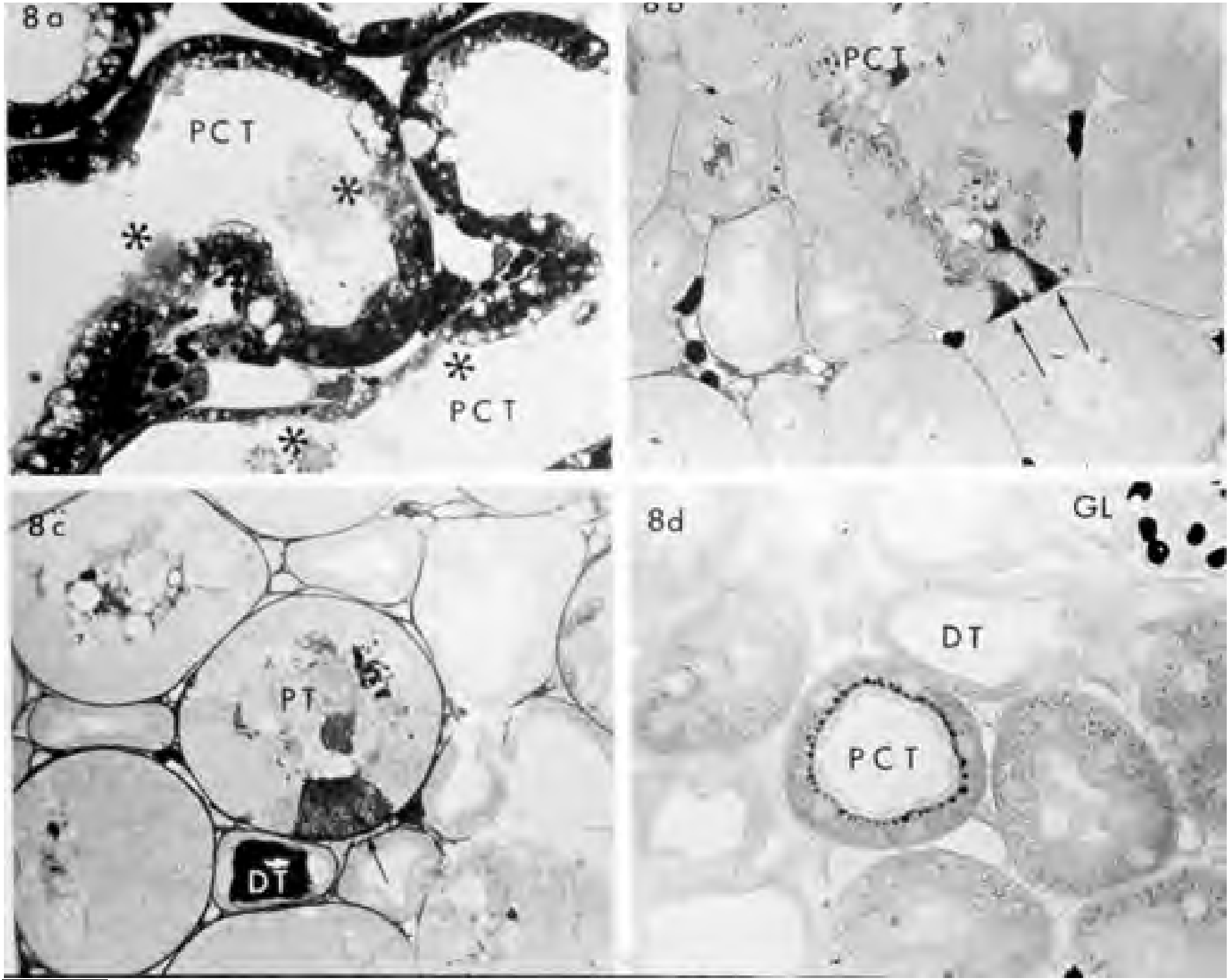
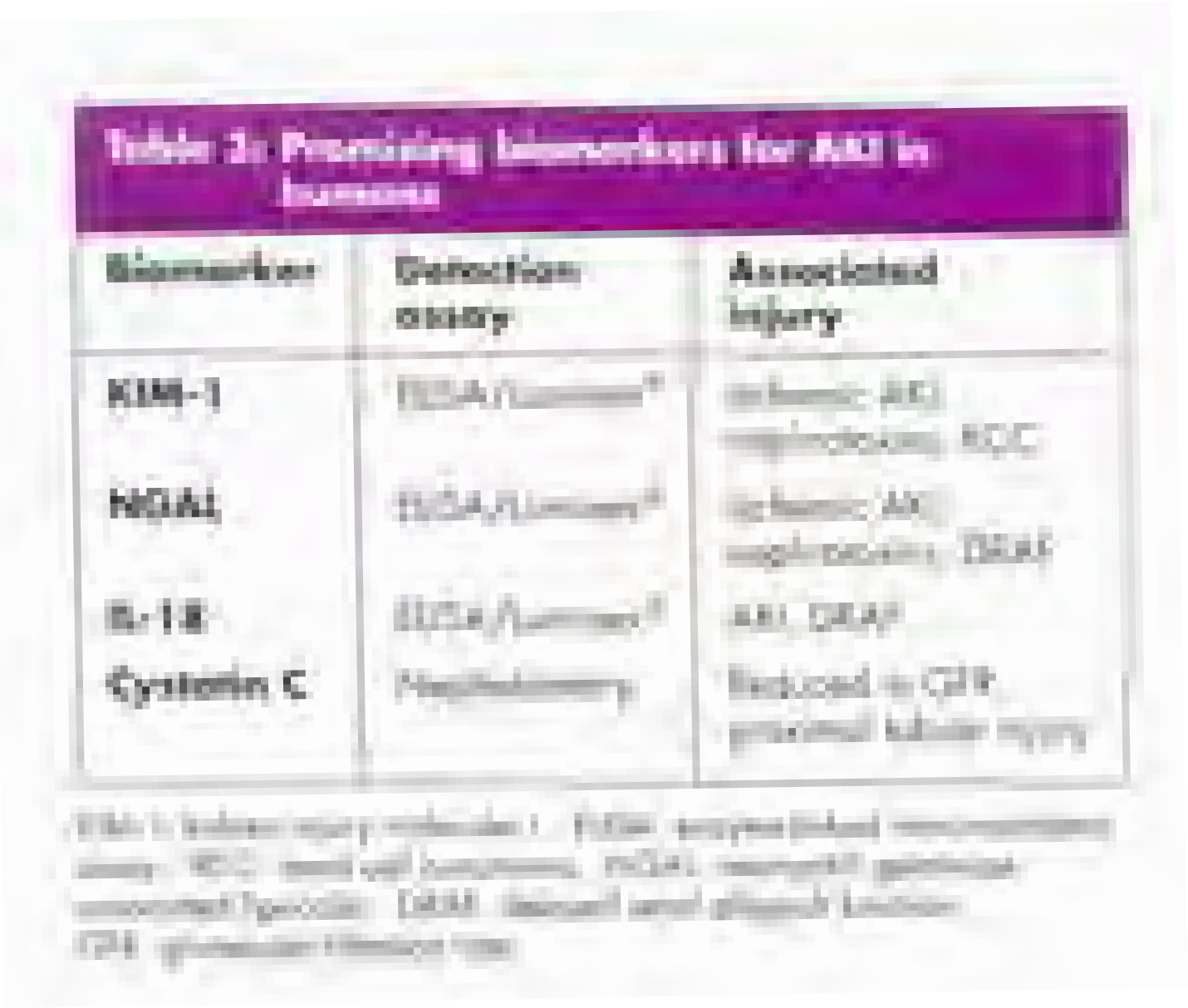


Table 2: Urinary biomarkers for kidney injury in humans

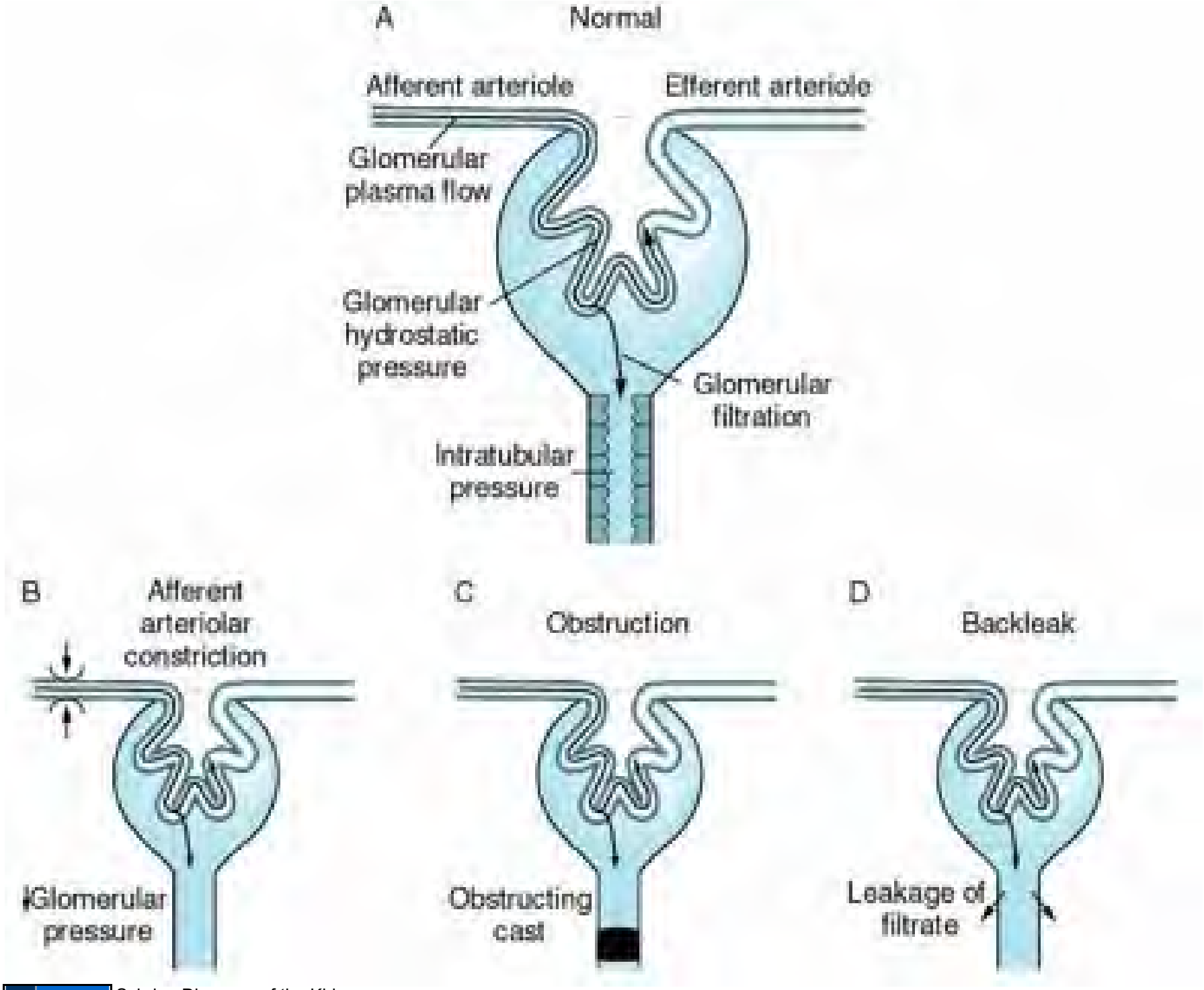
Biomarker	Site of renal injury
Low-molecular-weight proteins	
α1-microglobulin	Proximal tubule
β2-microglobulin	Proximal tubule
Retinol binding protein	Proximal tubule
High-molecular-weight proteins	
Albumin	Glomerular
Immunoglobulin	Glomerular
Transferrin	Glomerular
Brush border antigens	
Adenosine deaminase binding protein	Proximal tubule
Cadherin-17/Intestinal	Proximal tubule
Other tubule antigen	Proximal tubule
Urinary enzymes	
N-acetyl-β-D-glucosaminidase	Proximal tubule
Alanine aminopeptidase	Proximal tubule
Alkaline phosphatase	Proximal tubule > distal tubule
Cathepsin B	Proximal tubule
Sglucosidase	Proximal tubule > distal tubule
γglutamyltranspeptidase	Proximal tubule
γglutamyl-Sdicysteinase	Proximal tubule
Lactate dehydrogenase	Distal tubule > proximal tubule
Others	
Cystatin C/γ-trace	Proximal tubule
Cytokines (IL-1, IL-6, IL-8, TNF-α)	Proximal tubule
Kidney injury molecule-1	Proximal tubule
Hepatocyte growth factor	Proximal tubule
Sodium/hydrogen exchanger isoform	Proximal tubule
Tamm-Horsfall glycoprotein	Distal tubule

IL = interleukin; TNF = tumor necrosis factor

PD-I-NEL Han, 2008



Biomarker	Detection assay	Associated injury
KIM-1	[illegible]	[illegible]
NGAL	[illegible]	[illegible]
IL-18	[illegible]	[illegible]
Cystatin C	[illegible]	[illegible]



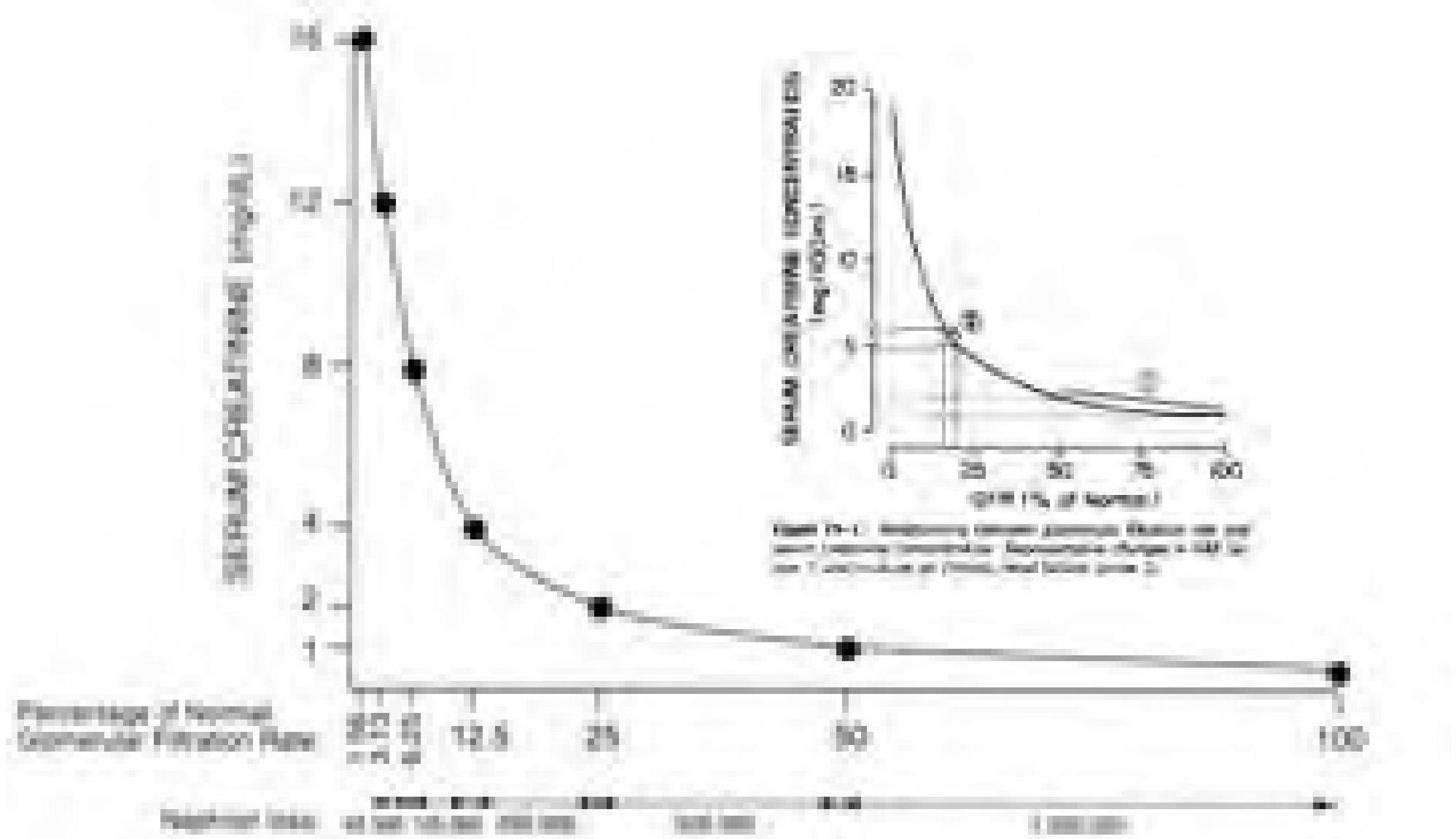
 Schrier, Diseases of the Kidney

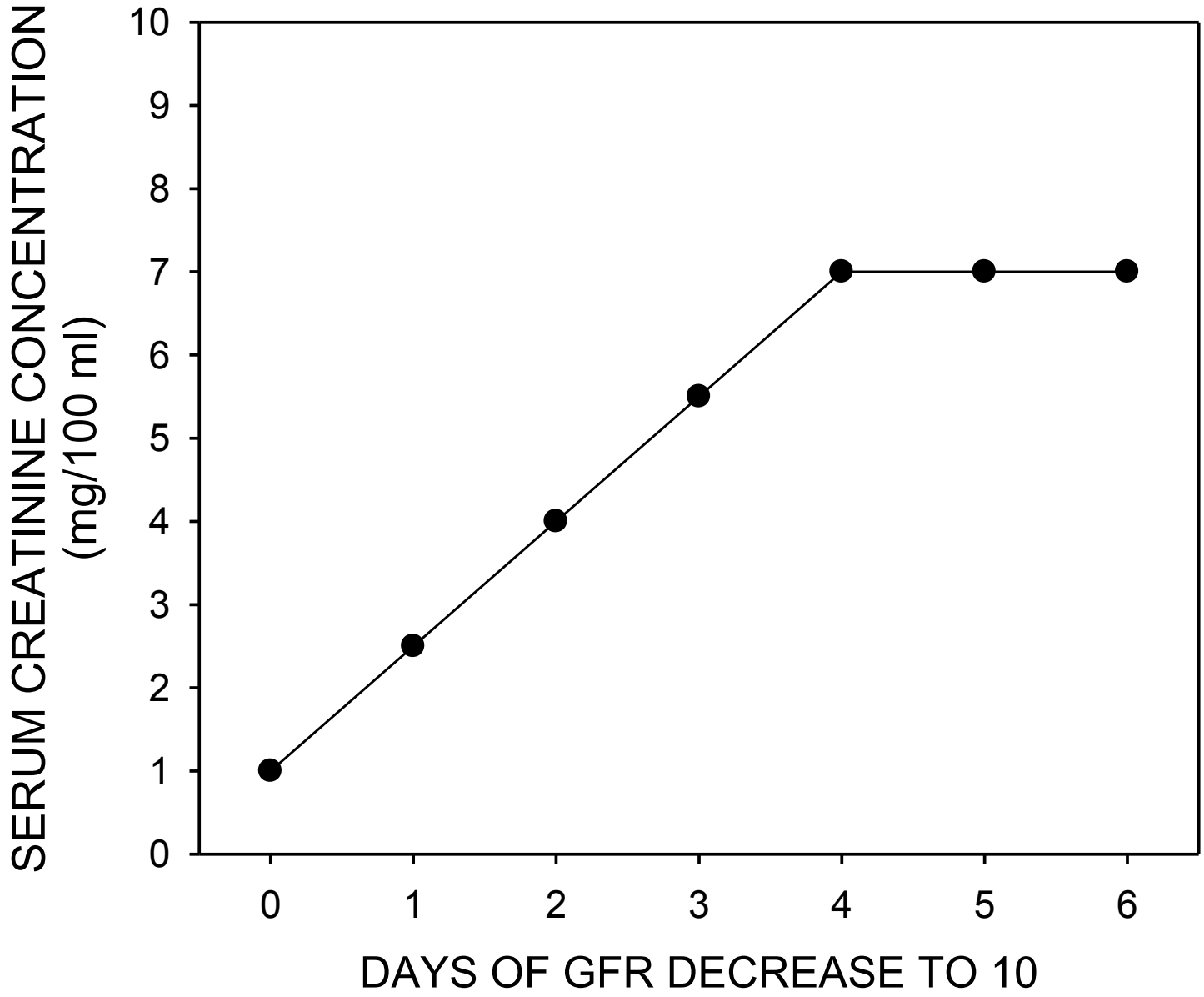
Measuring Glomerular Filtration Rate

$$\text{Clearance} = \frac{\text{Total Amount Excreted in Urine}}{\text{Serum Concentration}}$$

Clearance of a compound is equal to the glomerular filtration rate (GFR) when that agent is delivered to blood at a constant rate, is freely filtered in the glomerulus, and is neither secreted nor reabsorbed by the tubules.

Under normal conditions, creatinine is produced at a constant rate in muscle, is freely filtered, is not reabsorbed, and is only minimally secreted, which allows creatinine clearance to be used as a measure of GFR.


12.5
25
50
100



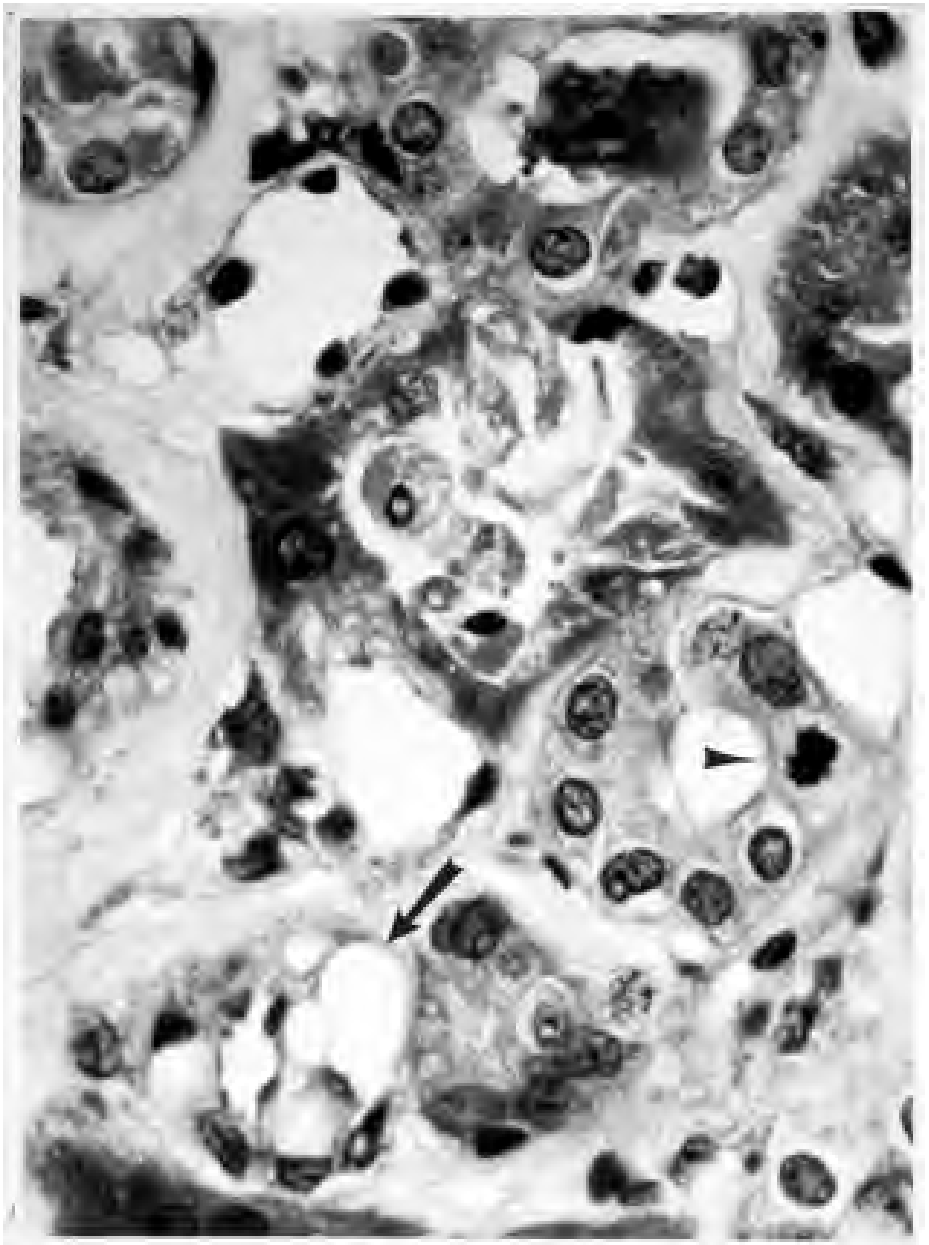


Fig. 6. Biopsy of renal cortex from a patient with 'acute tubular necrosis', showing focal coagulative necrosis of tubular cells (center tubule). Other features include tubular cells and cell debris in tubular lumina, regenerative changes and a tubular cell mitosis (arrowhead), interstitial edema, and vacuolization of vascular smooth muscle cells (arrows). ×650.

The Recovery Process

a) In the absence of cell loss - simple reprocessing and resynthesis of structural macromolecules and transporters with recovery of polarity and tight junctions.

b) After cell loss -

- Spreading and simplification of adjacent cells to 'seal' the epithelium.
- Proliferation under the control of autocrine and both local and distant paracrine growth factors.
- Redifferentiation with recovery of polarity and tight junctions.

c) The time required for this recovery process after cell loss helps explain why recovery of function in ischemic acute renal failure often begins only after a delay of 1-2 weeks.

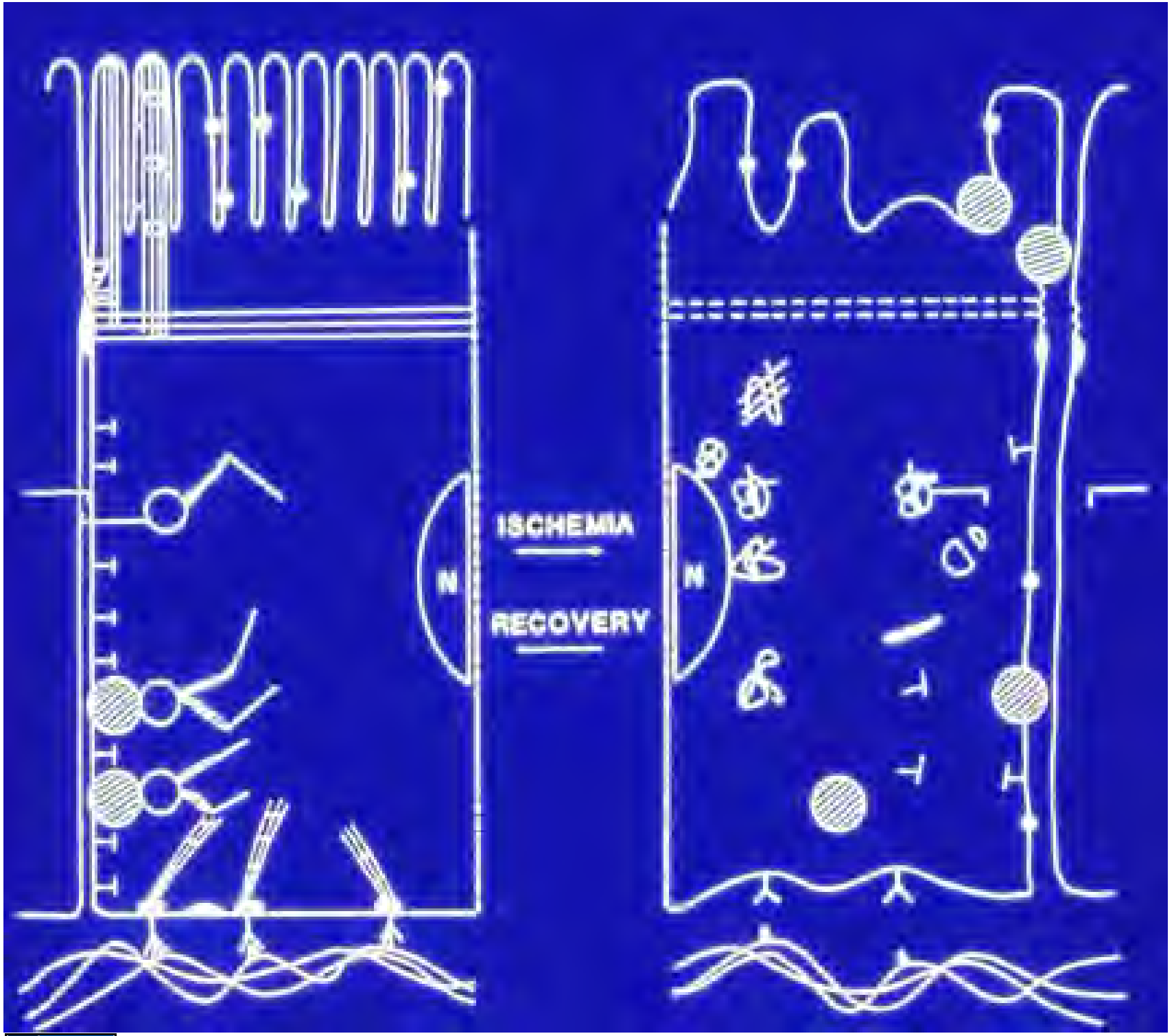


Fig. 6. *Growth regulation in regenerating renal epithelial cells.* Cells at the edge of an injured segment of the nephron are shown during early renal regeneration following acute tubular necrosis. Pictured are non-necrotic cells, a dividing cell, and a migrating squamoid cell. Proliferation may be mediated in part by synthesis of growth-stimulatory factors, followed by cellular processing and release of the active molecules. Symbols for growth factors, precursors, and receptors are as in Figure 3.

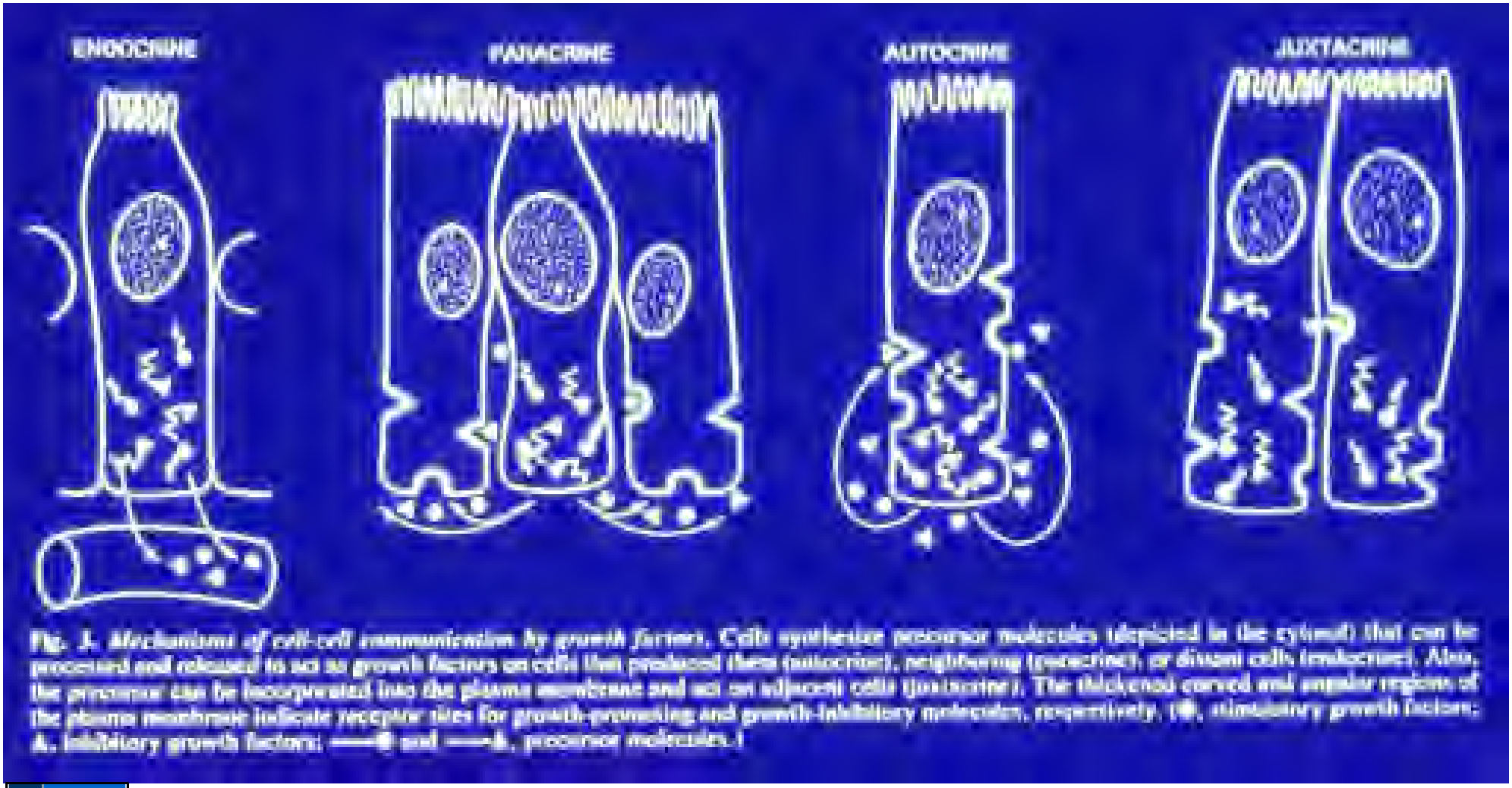


Fig. 1. *Mechanisms of cell-cell communication by growth factors.* Cells synthesize precursor molecules (depicted in the cytosol) that can be processed and released to act as growth factors on cells that produced them (autocrine), neighboring (paracrine), or distant cells (endocrine). Also, the precursor can be incorporated into the plasma membrane and act on adjacent cells (juxtacrine). The thickened curved and angular regions of the plasma membrane indicate receptor sites for growth-promoting and growth-inhibitory molecules, respectively. (●, stimulatory growth factors; ▲, inhibitory growth factors; ——● and ——▲, precursor molecules.)

Pathophysiology of Ischemic and Toxic Acute Renal Failure

MICROVASCULAR

Glomerular

Medullary

- ↑ Vasoconstriction
  - endothelin, adenosine, angiotensin II, thromboxane A2, leukotrienes, sympathetic nerve activity
- ↓ Vasodilation
  - nitric oxide, PGE2, acetylcholine bradykinin
- ↑ Endothelial and vascular smooth muscle cell structural damage
- ↑ Leukocyte-Endothelial adhesion
  - vascular obstruction, leukocyte activation, and inflammation

O_2/TOXINS

Inflammatory and vasoactive mediators

TUBULAR

- Cytoskeletal breakdown
- Loss of polarity
- Apoptosis and Necrosis
- Desquamation of viable and necrotic cells
- Tubular obstruction
- Backleak

Approach to the Patient with Acute Renal Failure

Objectives

1. Understand the three element etiological approach to acute renal failure and be aware of the major disease entities in each category.

2. Be able to calculate fractional sodium excretions and use them in the evaluation of acute renal failure.

3. Know the urinary sediment abnormalities that provide clues to the etiology of acute renal failure.

4. Understand the use and interpretation of ultrasound examination of the kidneys in the diagnosis of ARF.

5. Know the general indications for dialysis.

6. Be aware of specific considerations in approaching some common causes of ARF, i.e. NSAIDs, angiotensin blockade, contrast nephropathy, aminoglycosides.

Acute Renal Failure/Acute Kidney Injury

Increase of BUN and/or creatinine of recent, abrupt onset reflecting a sudden loss of net, effective clearance capacity of the kidney.

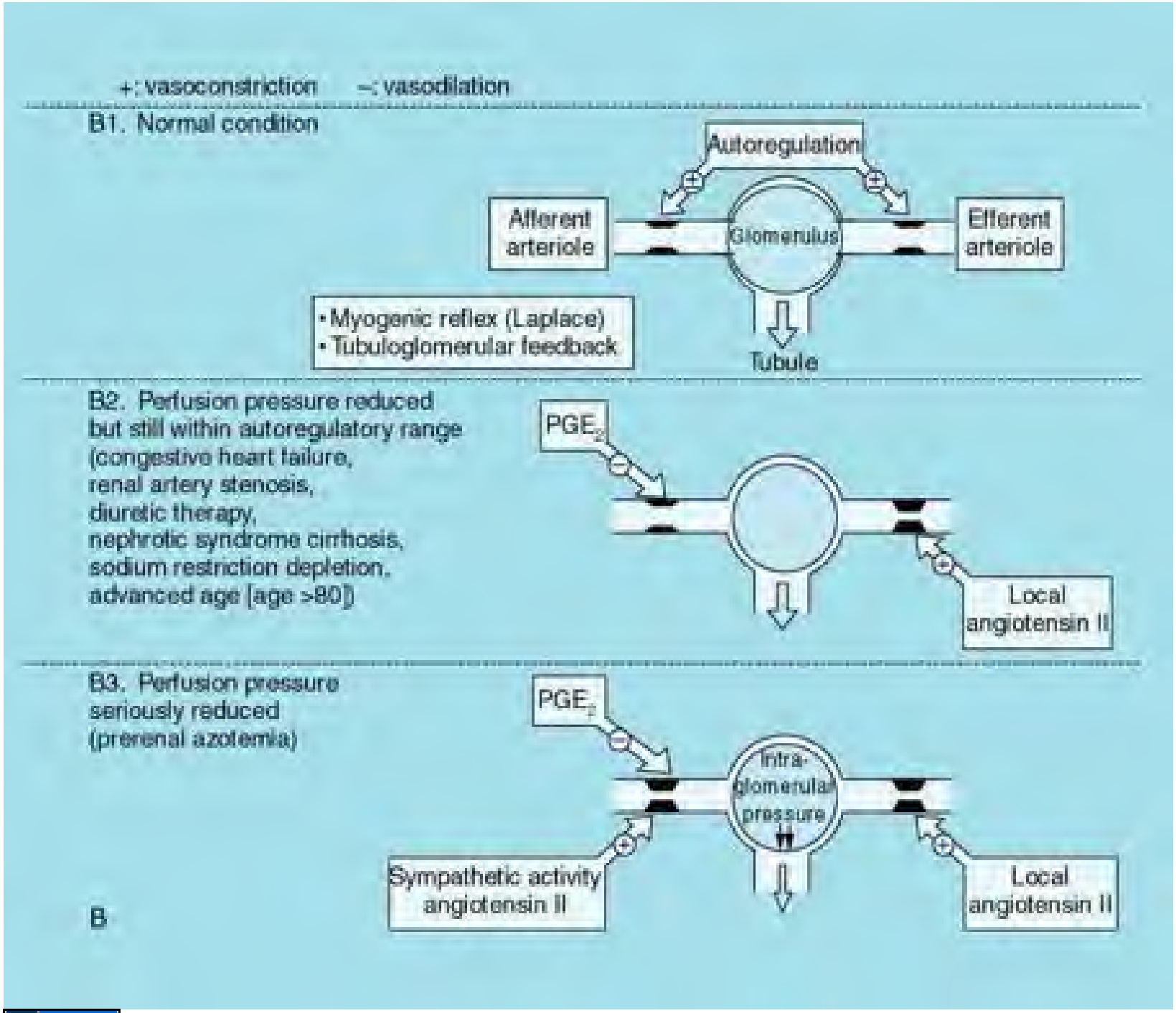
Urine output can vary. Oliguria refers to < 400 cc./day; many forms are “non-oliguric.”

APPROACH TO ACUTE RENAL FAILURE

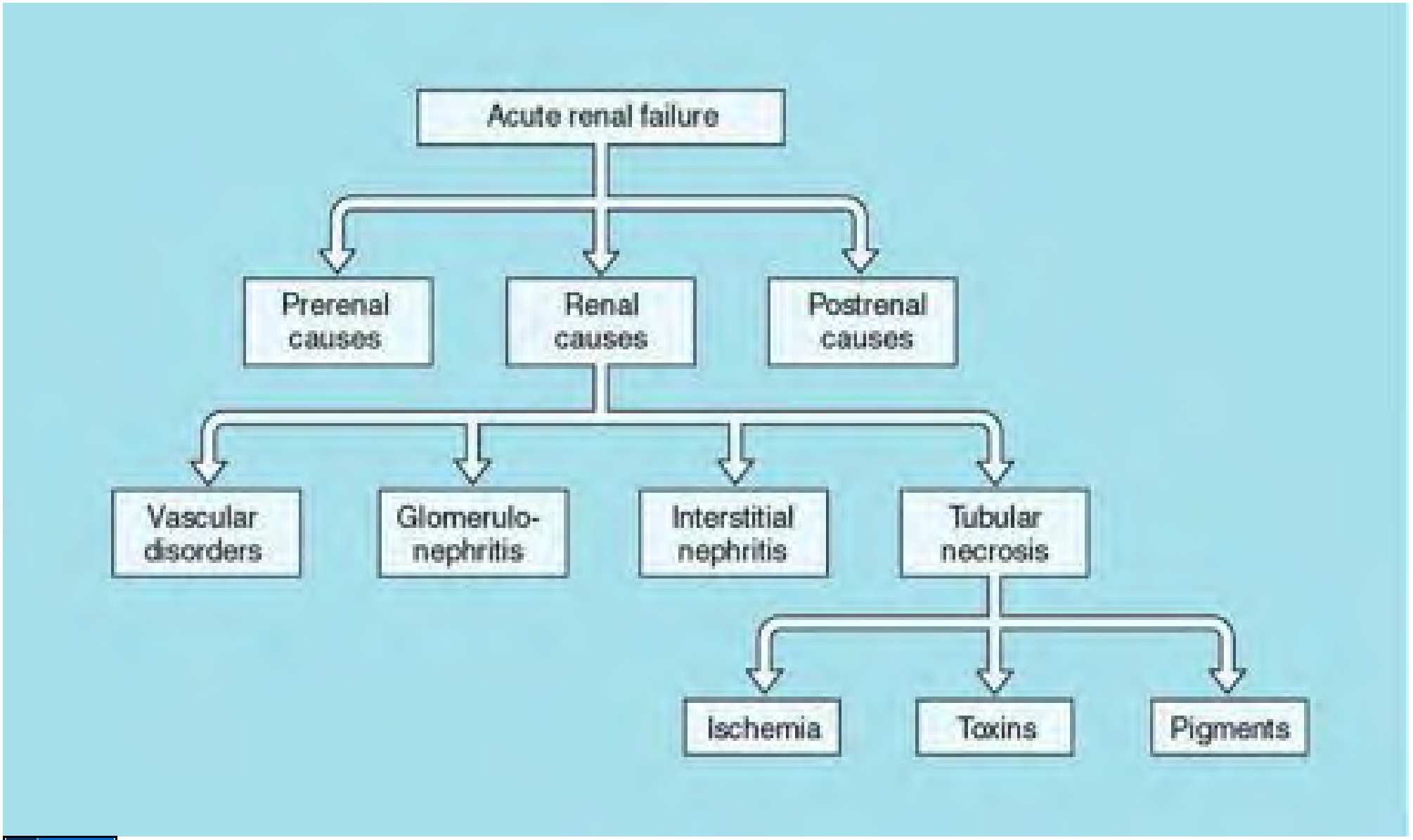
PRERENAL
RENAL
POSTRENAL

PRERENAL ETIOLOGIES

- Hypovolemia
    - Gastrointestinal, renal, or skin fluid and electrolyte losses
    - Hemorrhage
    - Third spacing - burns, pancreatitis, peritonitis, anaphylaxis, sepsis, portal hypertension
- Cardiac failure
    - Infarction
    - Cardiomyopathy
    - Valvular disease
- Hepatorenal syndrome
- Nonsteroidal anti-inflammatory drugs
- Angiotensin blockade - ACEI, ARB



 Schrier, Diseases of the Kidney



 Schrier, Diseases of the Kidney

POST RENAL ETIOLOGIES

Extrarenal obstruction

- Urethral stricture
- Bladder, pelvic, prostatic or retroperitoneal neoplasms
- Prostatic hypertrophy
- Surgical complications
- Stones
- Hematoma
- Anticholinergics
- Neurogenic bladder

Bladder rupture

MAJOR INITIAL ELEMENTS OF THE WORKUP

- Medication issues
  - Nonsteroidals
  - ACE inhibitors
  - Contrast studies
  - Antibiotics
    - Direct nephrotoxicity
    - Hypersensitivity reactions
- Volume status
- Urinalysis
- Urine chemistry
- Bladder emptying capacity and renal ultrasound

Assessment of Volume Status During Acute Renal Failure

- Physical examination
  - Blood pressure with orthostatic changes
  - Jugular venous pressure
  - Temperature of the extremities
  - Skin color and turgor

- BUN/Cre ratio
  - >20 - prerenal
  - ~10 - renal

- Pulmonary artery catheter
  - RA and wedge pressure
  - Cardiac output and peripheral resistance

Use of the Urinary Sediment in the Differential Diagnosis of Intrinsic Acute Renal Failure

Red Blood Cells

- Favor glomerular rather than tubulointerstitial processes
- Even more strongly suggestive of glomerular disease if dysmorphic and/or present as red cell casts
- Red colored, strongly heme positive urine without substantial numbers of RBCs suggests pigment nephropathy.

Tubule epithelial cells and granular casts

- Present in ischemic and toxic ATN, but may also be seen during 'prerenal' azotemia, interstitial nephritis, and acute glomerulonephritis.
- Highly colored in pigment nephropathy

Pyuria and WBC casts

- Pyelonephritis
- Identify eosinophils by Wright's or Hansel's stains
- Need to discriminate WBCs from tubule epithelial cells - Sternheimer-Malben stain

Crystals

- Uric acid during uric acid nephropathy
- Oxalate after polyethylene glycol intoxication

Urinary Chemical Indices in the Diagnosis of Oliguria

	Prerenal Azotemia	Acute Tubular Necrosis
U_{Na} (mEq/L)	<20	>40
U_{Cl} (mEq/L)	<20	>40
U_{osm} (mosm/kg/H_2O)	>500	<350
U/P osmolality	>1.3	<1.1
U/P creatinine ratio (mg/dL)	40	<20
RFI $\frac{U_{Na}}{U/P_{cr}}$	<1	>1
Fe_{Na} $\frac{(U/P)_{Na}}{(U/P)_{cr}}$	<0.01	>0.01

CAUSES OF ARF ASSOCIATED WITH LOW FRACTIONAL SODIUM EXCRETION

- PRERENAL
  - Intravascular volume depletion due to hemorrhage, GI losses, third spacing
  - Low cardiac output secondary to myocardial dysfunction
  - NSAIDs
  - Hepatorenal syndrome

- RENAL
  - Acute GN
  - Contrast
  - Early pigment nephropathy

- POSTRENAL
  - Early obstruction

COMPLICATING FACTORS IN THE USE OF LOW FRACTIONAL SODIUM EXCRETION IN THE DIAGNOSIS OF ARF

- Recent use of drugs with diuretic effects including loop diuretics, mannitol, dopamine
- Heavy glycosuria or mannitol treatment
- Continuing excretion of contrast agent
- Recent aggressive fluid replacement
- Alkalemia with increased bicarbonate excretion
- Patient not oliguric

RADIOLOGICAL ASSESSMENT DURING ACUTE RENAL FAILURE

Plain abdominal film
IVP
Retrograde pyelogram
Computed tomography
Angiography
Ultrasound
Radioisotope studies

Factors that determine usefulness - Sensitivity for providing the necessary information, invasiveness, need for IV contrast.

ROLE OF ULTRASOUND IN THE DIAGNOSIS OF ARF

Non-invasive, no IV contrast or other toxicity

Relatively cheap and widely available

ROLE OF ULTRASOUND IN THE DIAGNOSIS OF ARF

Determination of renal size

'Quality' of renal parenchyma

Rule out obstruction
- 98% sensitive
- 74% specific
- 15% false positive

False negatives due to:
- Early (1-3d) obstruction
- Infiltrative (tumor, fibrosis) processes

CLUES TO TYPES OF UNDERLYING KIDNEY DISEASE FROM MEASUREMENTS OF KIDNEY SIZE

- Equal, normal sized kidneys in a patient with renal insufficiency strongly favor a process of recent onset.

- Bilaterally small kidneys favor a chronic process that has affected both kidneys similarly and led to substantial parenchymal loss, e.g. chronic glomerulonephritis, nephrosclerosis secondary to hypertension.

- Assymetrical kidneys suggest large vessel renovascular disease.

- Large kidneys with nephrotic syndrome accompanied by renal insufficiency suggest diabetes or amyloidosis.

'Quality' of renal parenchyma

Rule out obstruction

98% sensitive
74% specific
15% false positive

False negatives due to:

Early (1-3d) obstruction
Infiltrative (tumor, fibrosis) processes

ROLE OF ULTRASOUND IN THE DIAGNOSIS OF ARF

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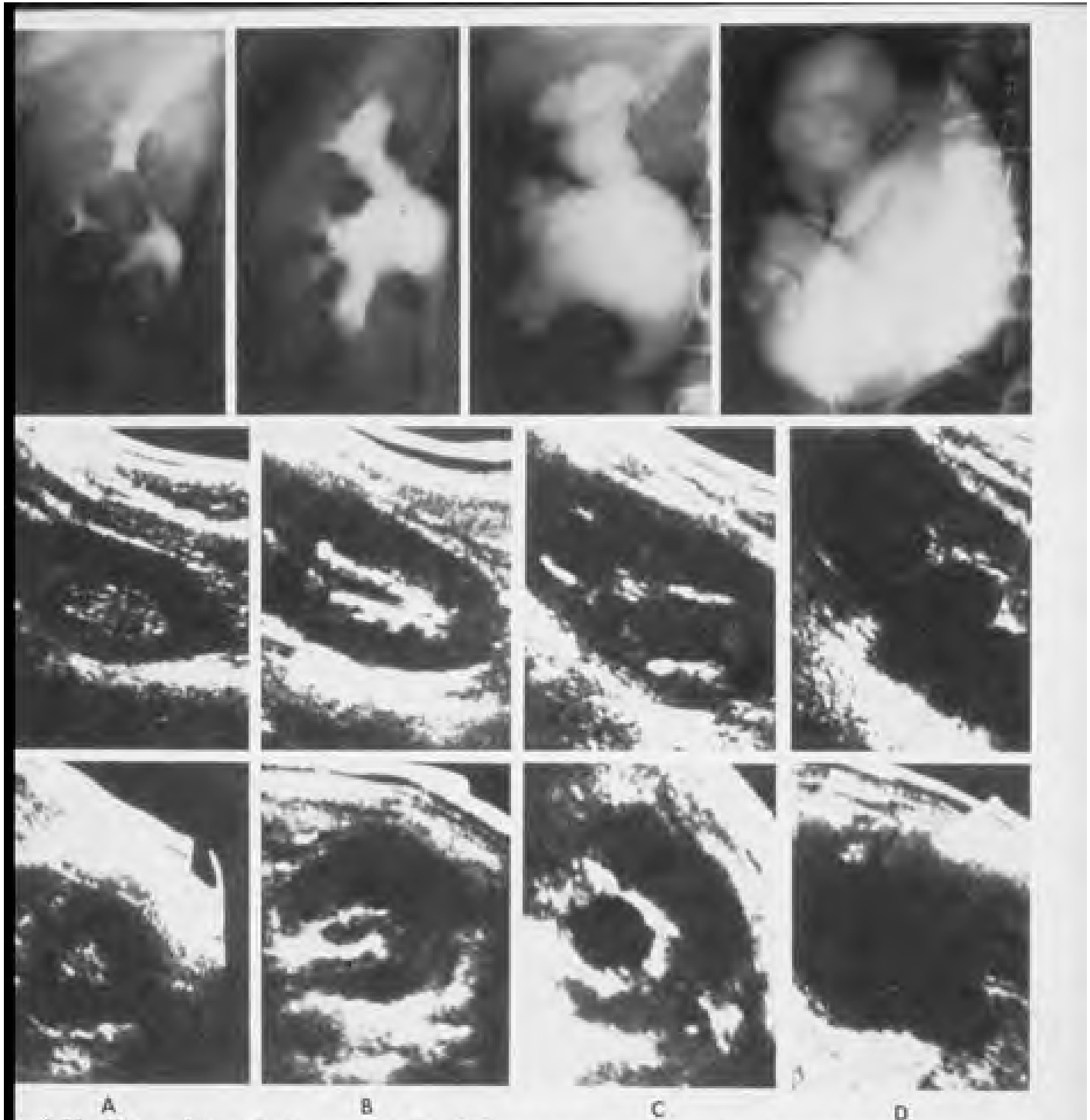


g. 6-11. Urographic and ultrasonographic (US) appearance of normal (column A) and progressively dronephrotic kidneys (columns B–D). Middle horizontal row illustrates longitudinal US scans, and ttom horizontal row depicts transverse scans. (From Ellenbogen et al.,[420] with permission.)

MANAGEMENT

Withdraw offending drugs

Correct hypotension or fluid deficits

Monitor I/O, weight, BUN, Creatinine, lytes, PO_4 daily

Dose adjust renally excreted medications

If oliguric:

??? Diuretics

INDICATIONS FOR DIALYSIS

Unmanageable fluid overload

Hyperkalemia

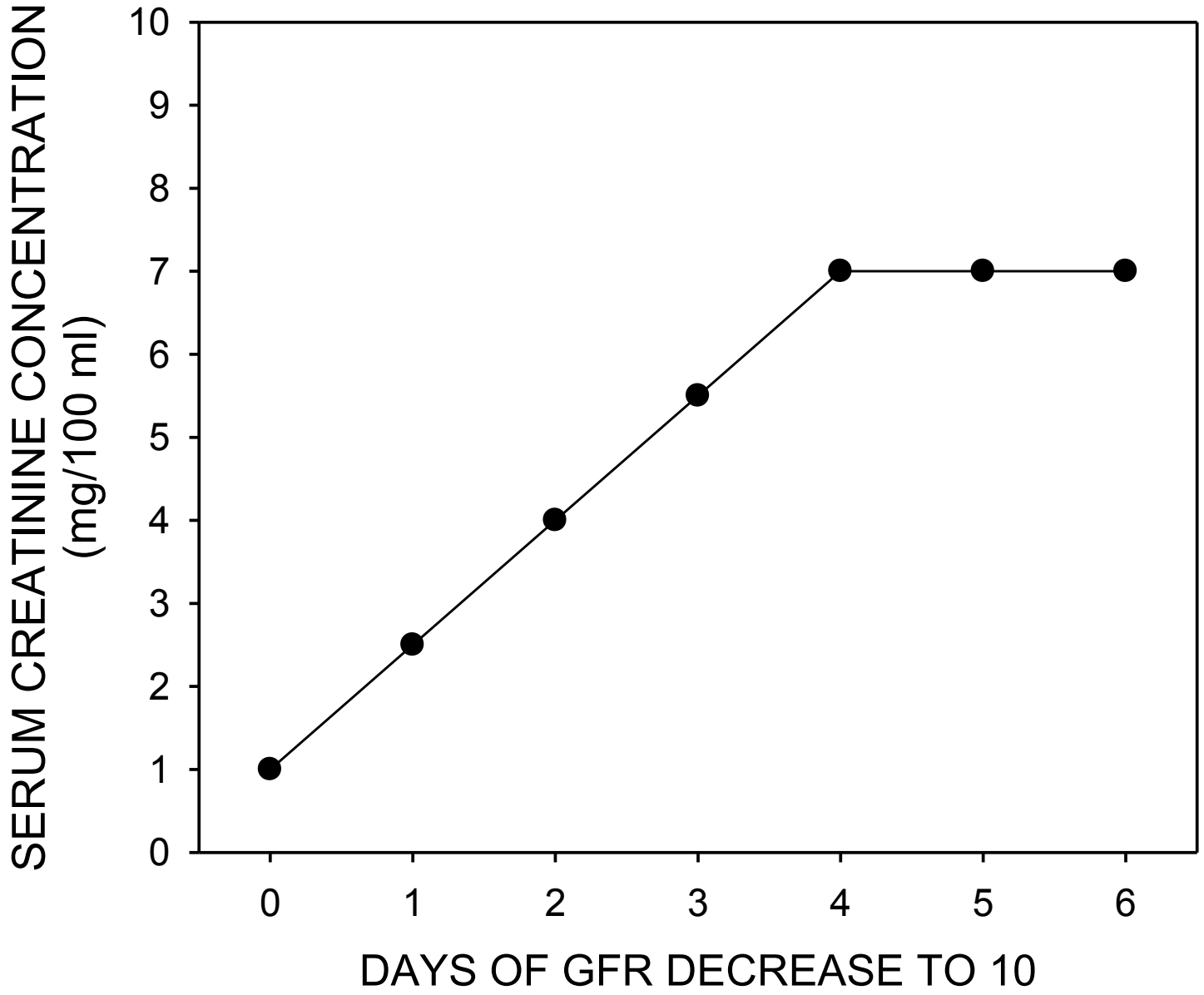
Acidosis

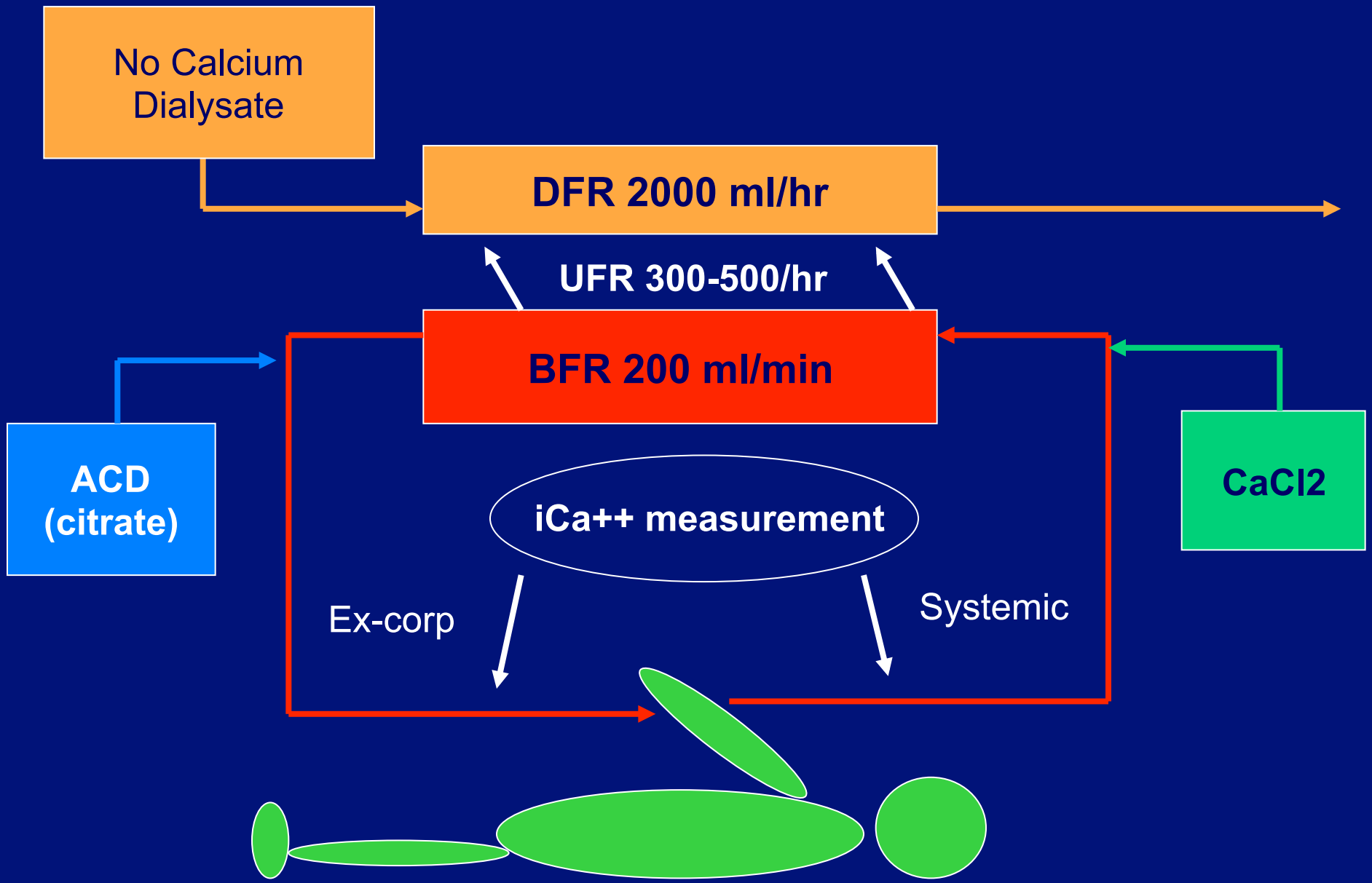
Uremia, BUN > 80-100

Uremic complications - bleeding, mental status

Timing of initiation depends on:

- Severity of labs and clinical findings
- Trajectory



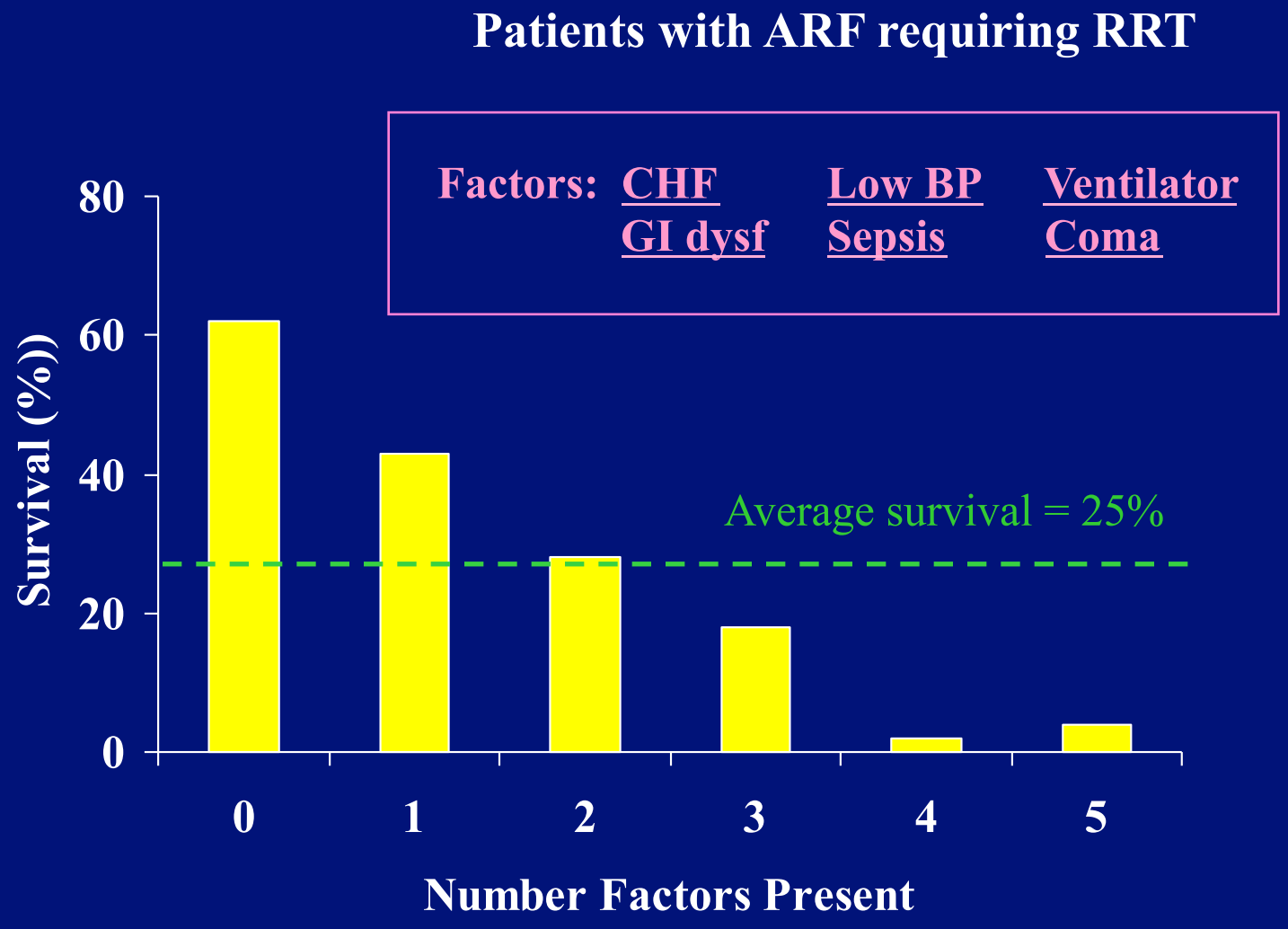


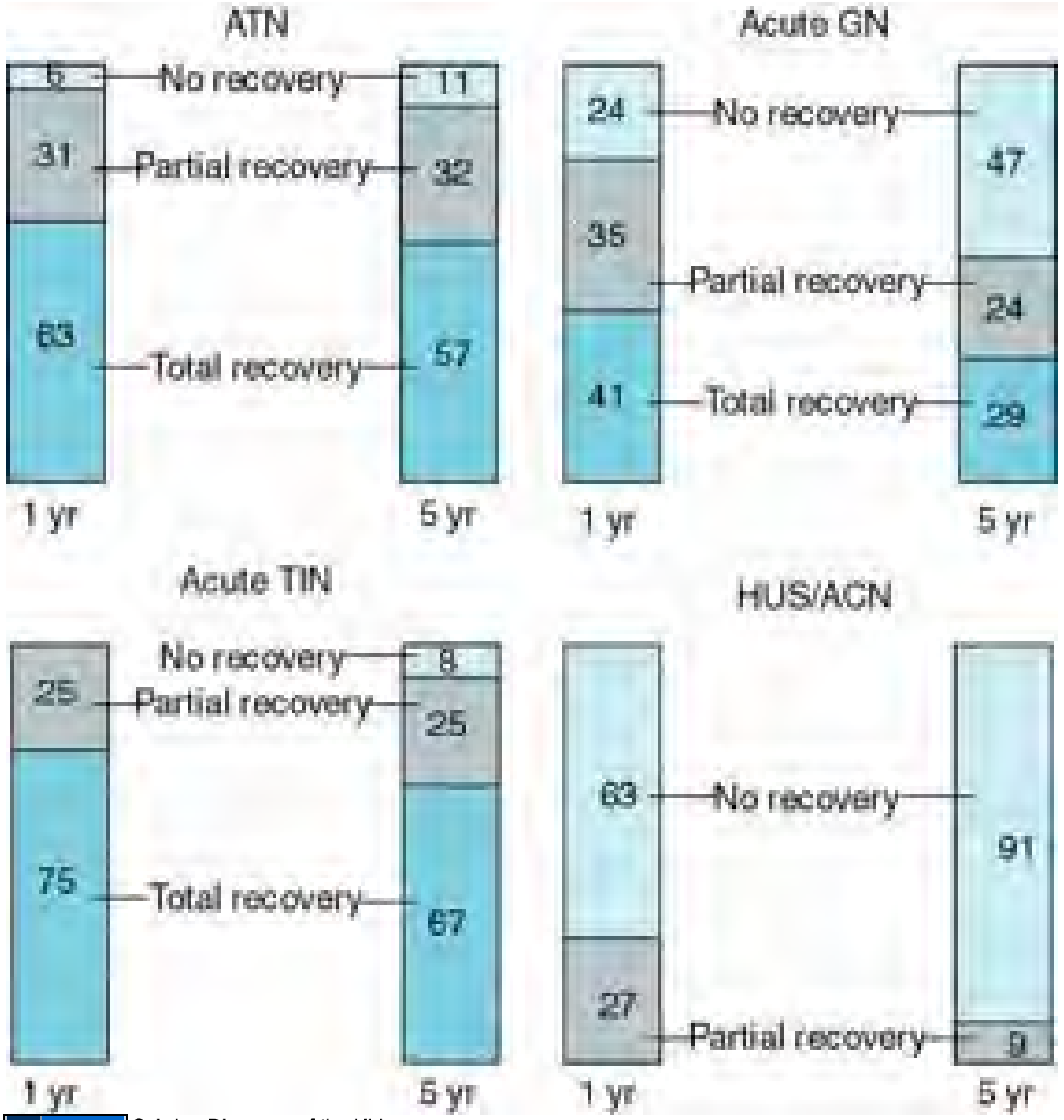
R.D. Swartz

Continuous renal replacement therapy during ARF with CVVHD using citrate anticoagulation

Organ System Disease & Outcome

Lohr et al, Am J Kid Dis, 1988





PD-JNEL Schrier, Diseases of the Kidney

CONSIDERATIONS FOR SOME SPECIFIC DISEASE ENTITIES

Intravenous Contrast

- ‘RENAL’ form of ARF in that the agents are direct tubule toxins and the renal dysfunction is not immediately reversible.

- ‘PRERENAL’ form of ARF in that FE_{Na} is often low and vasoconstriction is a major factor.

-High risk groups - Diabetics > other causes of CRF.

CONTRAST NEPHROPATHY

- Serum creatinine increase ≥ 0.5 mg/dl in 3.3% of 7586 patients.
- Cre < 1.1 – 3.7% in diabetics, 2% in nondiabetics
- Cre 1.2-1.9 – 4.5% in diabetics, 1.9% in nondiabetics
- Cre 2–2.9 – 22.4%
- Cre > 3 – 30.6%
- 22% mortality with ARF, 1.4% without, odds ratio 10.3

GROUPS AT RISK FOR CONTRAST NEPHROPATHY

- GFR < 60 estimated by MDRD or Cockroft Gault
- Diabetics
- Repeat administration within 36 hours
- Emergent studies
- Shock

PREVENTING CONTRAST NEPHROPATHY

- Hold NSAIDs, diuretics, ? ACEI/ARB

- Diuretics, mannitol non-specific endothelin blockade ineffective and possibly deleterious.

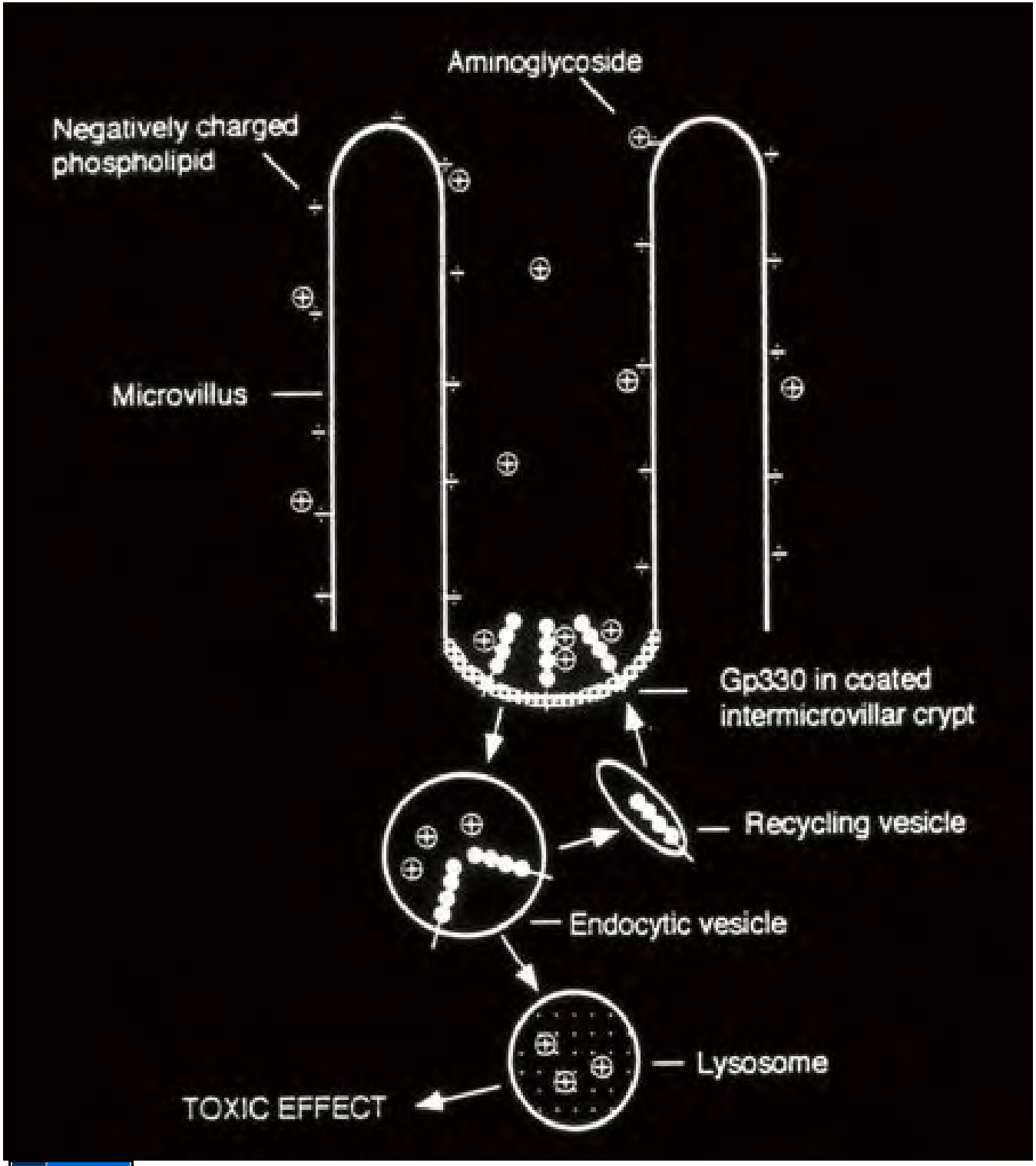
- Volume expansion prior to and following procedure has well established benefit – $NaHCO_3 \geq$ isotonic NaCl $\geq$ ½ NS.

- Minimize amount of contrast used.

- Risk from low osmolarity contrast $\leq$ isosmolar contrast << high osmolarity contrast.

- Oral N-acetylcysteine of uncertain benefit, but inexpensive, nontoxic.

- Benefit of fenoldopam, theophylline not established.



Aminoglycosides

- Every course is toxic. Hypotension or ischemia plus aminoglycosides are potentially synergistic in their toxicity. Don't use unless absolutely necessary. Switch if cultures and clinical condition allow you to.

- Dose by the estimated clearance taking into account size (muscle mass), age, and sex, not the absolute level of creatinine.

- Dose adjustments for decreased renal function should be by lengthening the interval as opposed to reducing the dose.

- Levels are important as a guide to how you are doing, but high troughs frequently indicate that problems that are destined to be progressive have already begun.

- If you must continue dosing despite nephrotoxicity, use levels as a guide to when to next dose.

- Course of nephrotoxicity - anticipate full expression of acute renal failure well after you have stopped dosing.

Additional Source Information

for more information see: http://open.umich.edu/wiki/CitationPolicy

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