THE EDEMA SYNDROMES

SOME COMMON EDEMA STATES

Arterial Underfilling	Controversial	Primary renal Na retention
systolic failure	early cirrhosis	acute GN
pericardial constriction	early nephrosis	
late cirrhosis		
IVC and/or lymphatic occlusion		
third space disorders		

Na^+ BALANCE
QUANTITATIVE DILEMMAS

Variable	Na^+	FeNa
	(mEq)	(%)
Total body Na^+	~ 3000	—
extracellular	~ 2200	—
Filtered Na load/24 hours (P_{Na}) X (GFR) (140 mEq/L) (180 L/24 hrs)	~ 25000	—
Na^+ intake/24 hrs (~ 5-6 gm)	240	~ 1%

EDEMATOUS STATES: THE LINKAGE BETWEEN HEART AND KIDNEY

Let the medicine therefore be given in the doſes, and at the intervals mentioned above:—let it be continued until it either acts on the kidneys, the ſtomach, the pulſe, or the bowels; let it be ſtopped upon the firſt appearance of any one of theſe effects

" I uſe it in the Aſcites, Anaſarca, and Hydrops
" Pectoris; and ſo far as the removal of the water
" will contribute to cure the patient, ſo far may be
" expected from this medicine: but I wiſh it not to
" be tried in aſcites of female patients, believing
" that many of theſe caſes are dropſies of the ovaria

An Account of the Foxglove and Some of its Medical Uses, with Practical Remarks on Dropsy, and Other Diseases

THE EDEMA ODYSSEY

I. SOME EARLY LANDMARKS

1. "In heart failure . . . in consequence of low arterial pressure, the loss of fluids by the kidney is diminished. The ultimate result is hydremic plethora."

   Starling, 1896

THE EDEMA ODYSSEY

I. SOME EARLY LANDMARKS

1. Starling (1896): "hydremic plethora"

2. Tigerstedt and Bergmann (1898): a saline extract from kidneys, termed renin, raised b.p.

THE EDEMA ODYSSEY
I. SOME EARLY LANDMARKS

1. Starling (1896): "hydremic plethora"

2. Tigerstedt and Bergmann (1898): *renin*

3. "The kidneys react to changes in the volume of the circulating blood"
   (*arterial receptors were implicit in Peters' argument)*
   Peters (1935)

THE EDEMA ODYSSEY

THE CARDIAC EDEMA DEBATE: 1935-1945

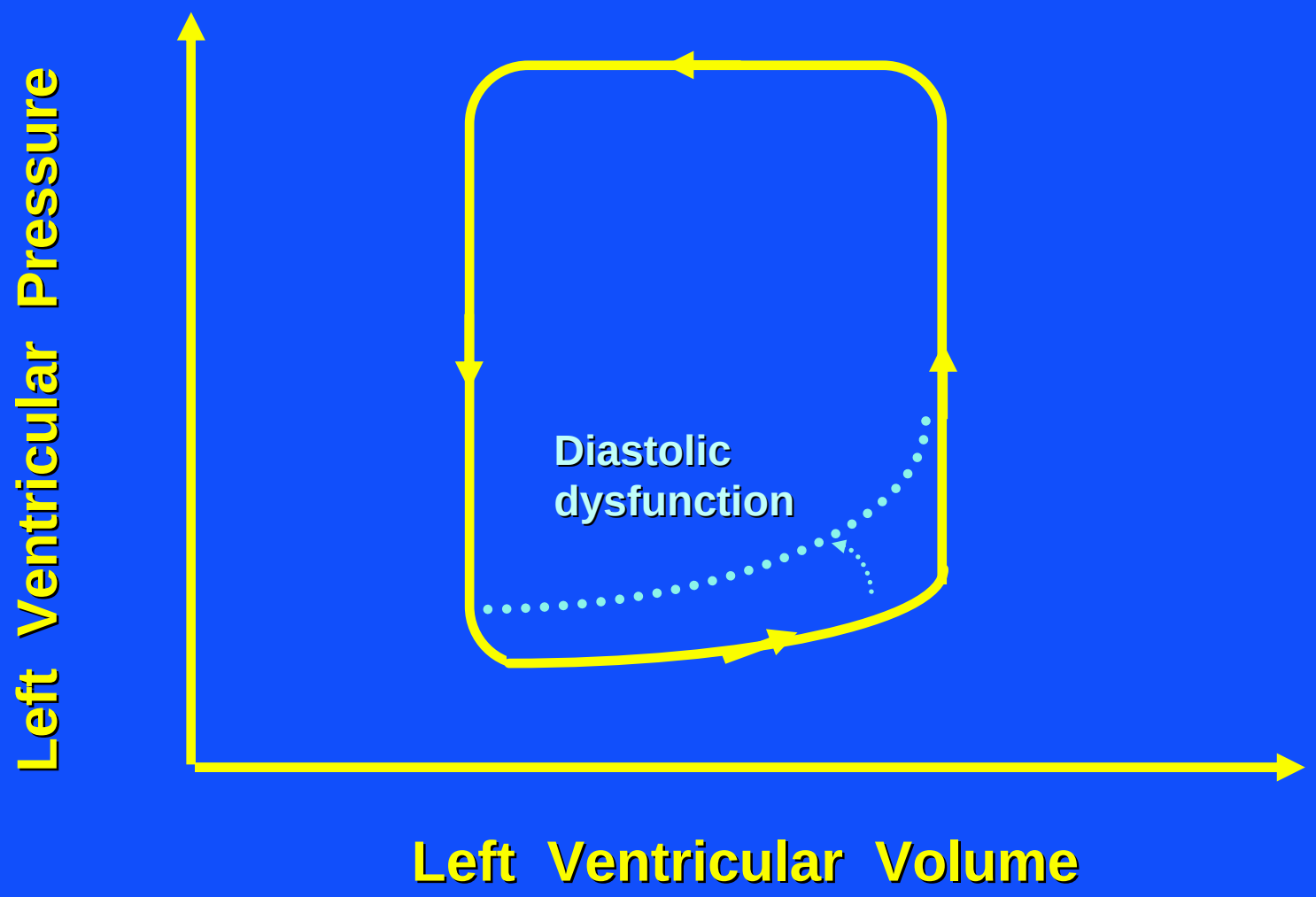
4. Harrison (1935) : backward failure

"Dyspnea and edema . . . can both be accounted for by the back-pressure theory and are not explicable on any other basis"

Harrison (1935)

HARRISON'S "BACKWARD FAILURE"

DIASTOLIC DYSFUNCTION



EDEMA

THE CARDIAC EDEMA DEBATE: 1935-1945

5. "The signs of a marked decrease in cardiac output . . . may be similar to that of shock"
   Stead and Ebert (1942)

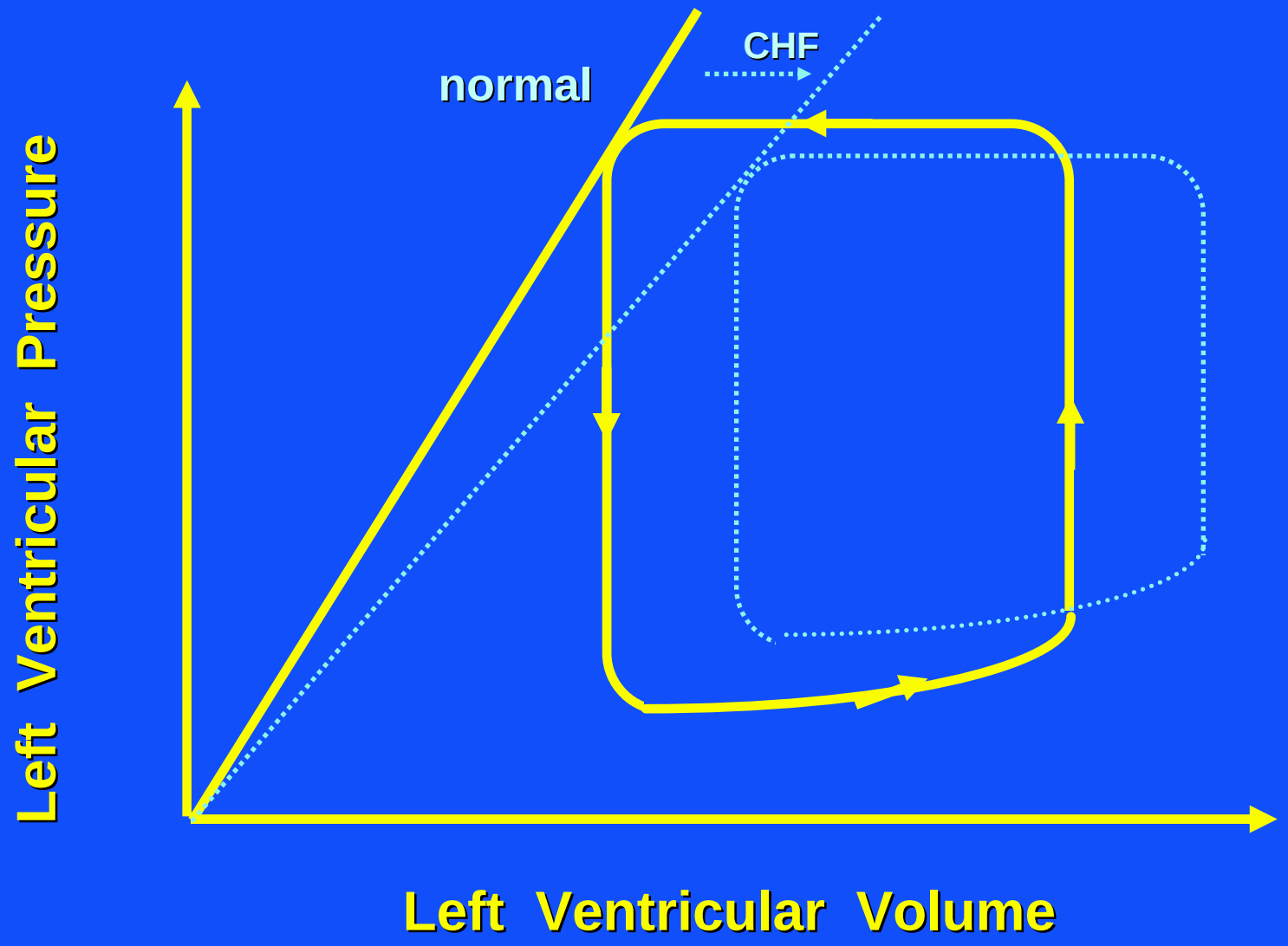
6. Warren and Stead (1944)

   observation: *CHF patients gain weight before venous pressure rises*

   conclusion: "In congestive failure the cardiac output is inadequate . . . and the kidneys are no longer able to excrete salt"

WARREN AND STEAD'S "FORWARD FAILURE"

PUMP FAILURE



THE EDEMA ODYSSEY

HORMONES AND EDEMA: 1945-1950

7. "Renin increases with a low cardiac output due to a decrease in blood available to the kidney."

   A. J. Merrill (1946)

8. Leutscher (1950): "The preliminary observations . . . indicate sodium-retaining factors in the urine of some cardiac or nephrosis patients"

THE EDEMA ODYSSEY

VOLUME RECEPTORS

9. The Gauer-Henry reflex (1947-51):
   positive pressure breathing: antidiuresis
   negative pressure breathing: water diuresis

   conclusion: non-osmotic ADH release driven by left atrial stretch receptor release

10. Hyponatremia following mitral commisurotomy

THE EDEMA ODYSSEY

VOLUME RECEPTORS

11. Epstein (1953): "Circulating states in which kidneys tend to retain sodium are characterized by inadequate filling of the arterial tree."

12. Homer Smith (1957): "Volume receptors are involved in sodium conservation . . . Where these receptors are located is moot (the Cheshire cat hypothesis)."

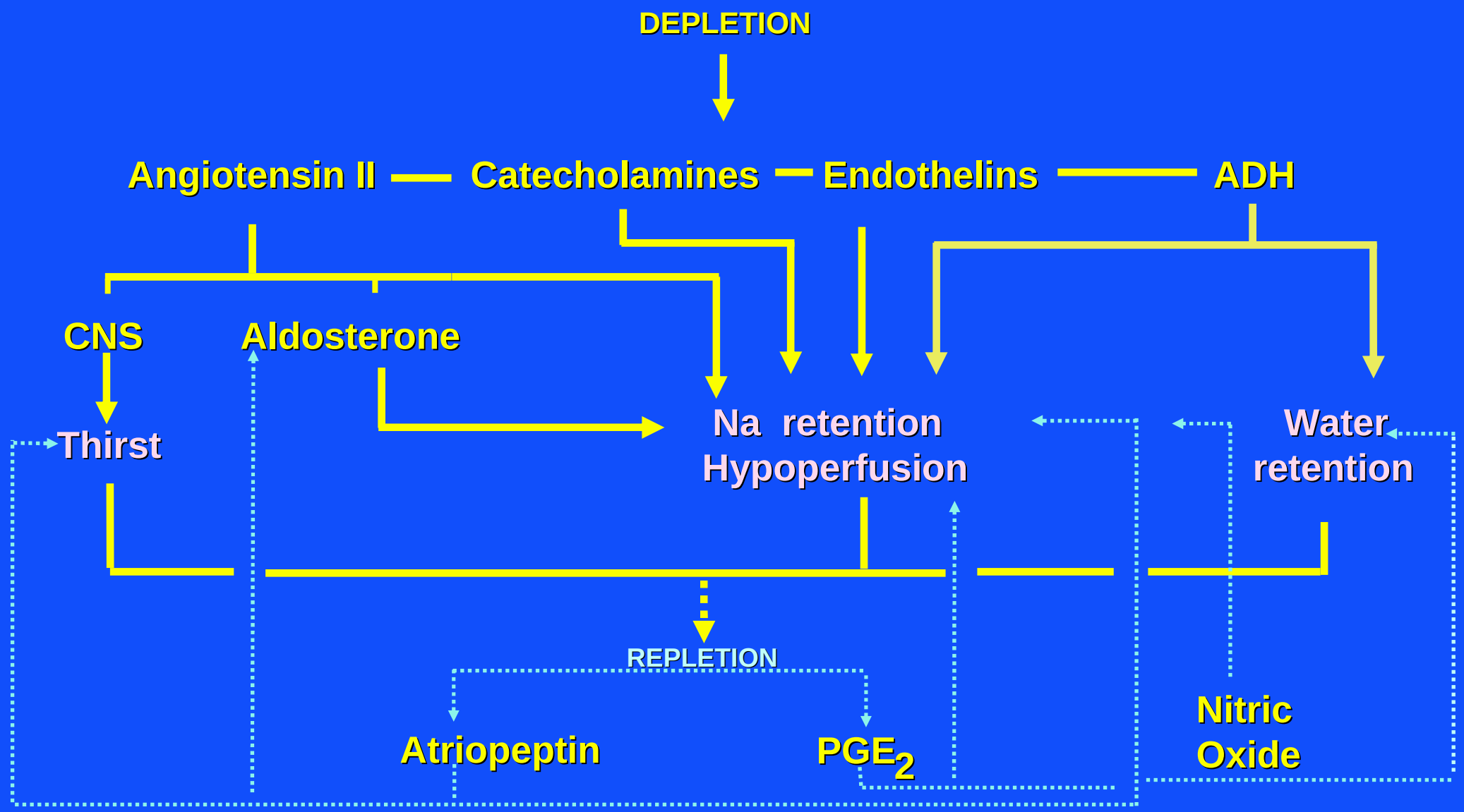
BARORECEPTORS: HOMER SMITH'S CHESHIRE CAT

High Sensitivity	Lower Sensitivity	Intrarenal	Hepatic
low pressure areas	high pressure areas	JGA	Portal vein sinusoidal
left atrium *thoracic veins*	*carotid sinus* *aortic arch*		↓
			? significance

↓

Hemodynamic changes
Na avidity

THE VOLUME REPLETION CASCADE



KEY FACTORS IN EDEMA STATES

PRECIPITATING FACTORS	***MANDATORY REQUIREMENT***
Deranged Starling Forces	steady-state
Arterial Underfilling	
Altered Volume/Capacitance Ratio	positive Na^+ balance
Primary Renal Na^+ Avidity	

DERANGED STARLING FORCES

THE STARLING EQUATION

The equation $J_V = K_f (\Delta P - \sigma \Delta \pi)$

The terms J_V = flow

σ = solute reflection coefficient
($\sigma = 0$: wholly permeable solute)
($\sigma = 1$: wholly impermeable solute)

K_f = capillary permeability
ΔP = hydrostatic pressure
$\Delta \pi$ = oncotic pressure

DERANGED STARLING FORCES

σ *DISORDERS*

Syndrome	Abnormality	Net Na^+ Balance
ARDS	leaky pulmonary capillaries	±
Rhabdomyolysis	leaky muscle capillaries	varies $\bar{c}$ magnitude of fluid sequestration
Burns	leaky capillaries loss of cutaneous barrier	massive Na^+ losses
Cyclical edema syndrome	generalized capillary leak	+

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late cirrhosis		
IVC and/or lymphatic occlusion		
third space disorders		

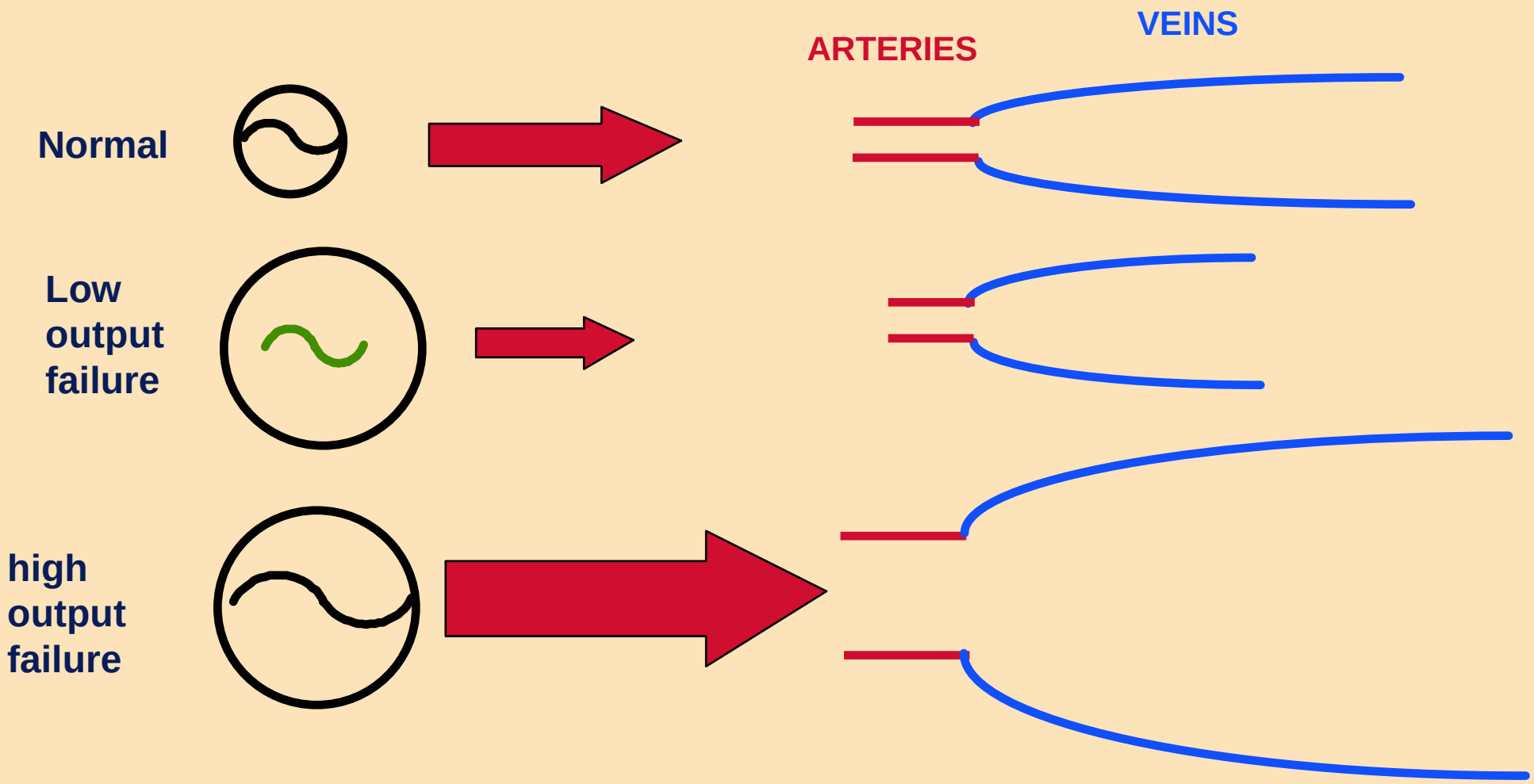
STARLING DERANGEMENTS (Δ P) WITH ARTERIAL UNDERFILLING

THE HEART FAILURE SYNDROMES

	Features
Low-output Failure	↓ contractility and EF ↑ end-diastolic volume
High-output Failure	demand > performance ↓ volume/capacitance ratio
Diastolic failure	↓ compliance and filling normal EF “flash” pulmonary edema

LOW AND HIGH OUTPUT HEART FAILURE

REDUCED ECV, BUT FOR DIFFERENT REASONS



PATHOPHYSIOLOGY OF ARTERIAL UNDERFILLING

PATHOLOGIC SEQUENCE

Local or systemic venous pressure increases

↓

Reduced venous arterial blood transfer →

↓

Reduced effective circulating volume

RESULT

Hemodynamic response (minutes)

↑ Heart rate
↓ Capacitance (venous)
↑ Systemic resistance (arterial)

Renal Response (days)

Na^+ avidity

HEART FAILURE: A SUICIDAL SYNDROME

"↓ filling . . . arterial tree"

hemodynamic changes

↓

↑ afterload

Na^+ avidity

↓

↑ preload

↑ end - diastolic volume

↓

further ↓ E. F.

PRINCIPAL SODIUM-AVID SEGMENTS IN UNDERFILLING

Segment	Normal % Na Absorbed	Factors ↑ Na absorption
proximal	60%	FF A-II catechols } ↑ TGF
late DCT; CCD	10%	ADH aldo ANP resistance (?)
IMCD	5%	ANP resistance

REDUCED ECV: GLOMERULAR AND HEMODYNAMIC RESPONSE

↓ ECV

catecholamines | AII | ADH | endothelin I

↓↓ RBF, ↓ GFR → ↑ FF

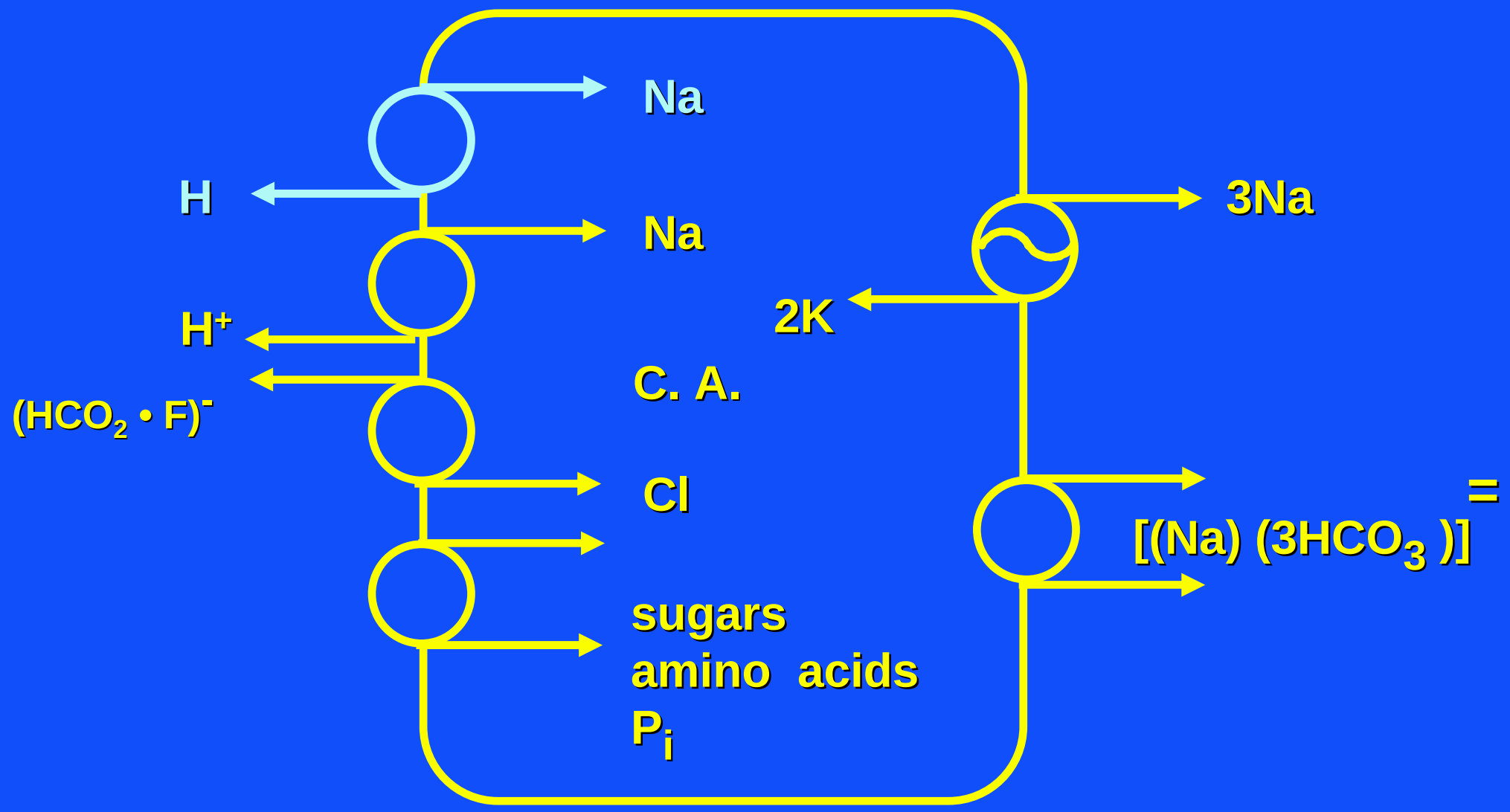
↑ net proximal absorption

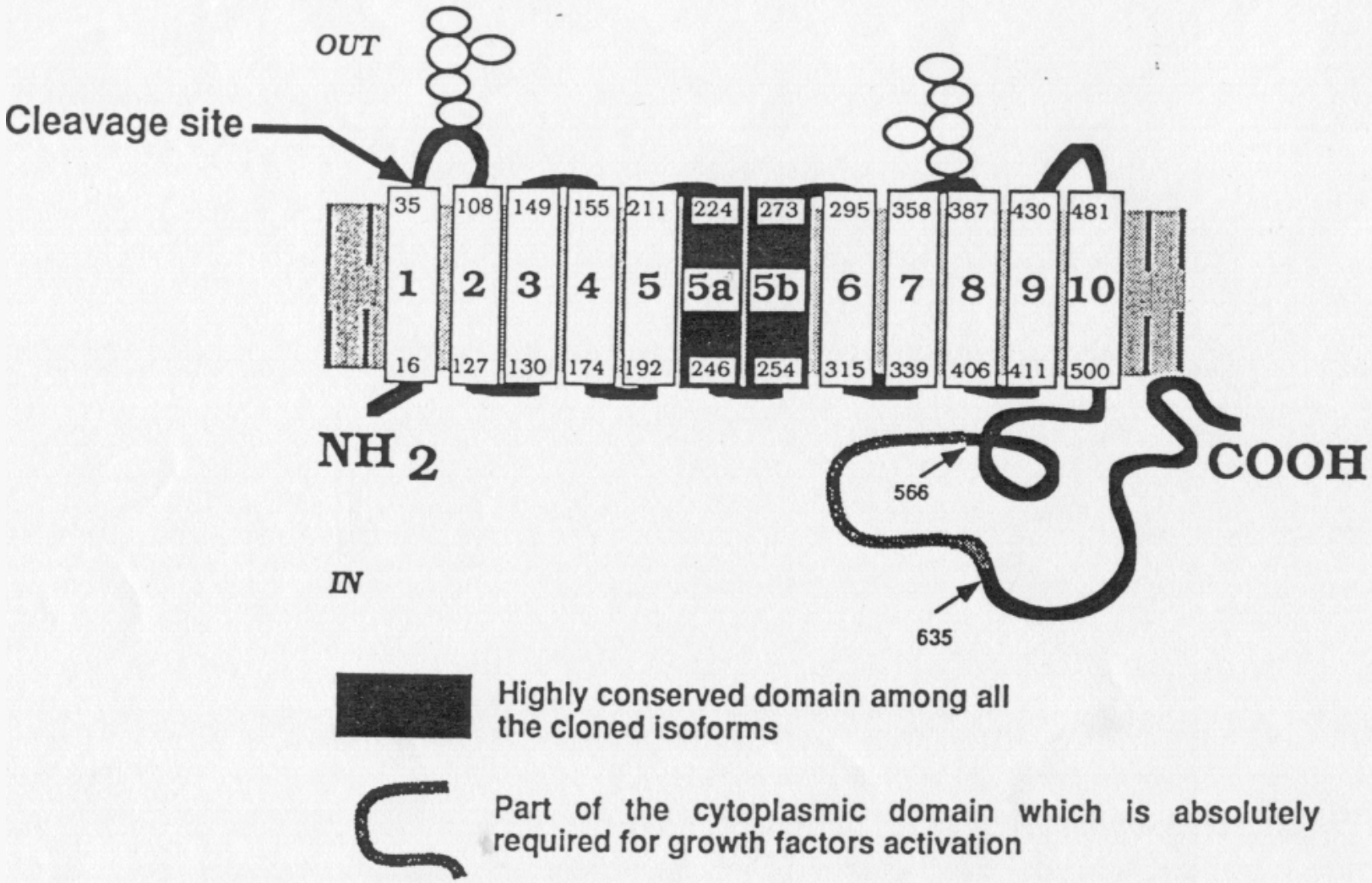
↓ distal Na^+ delivery

activation of JGA baroceptors

renin - AII

GENERAL MODEL FOR PROXIMAL TRANSPORT





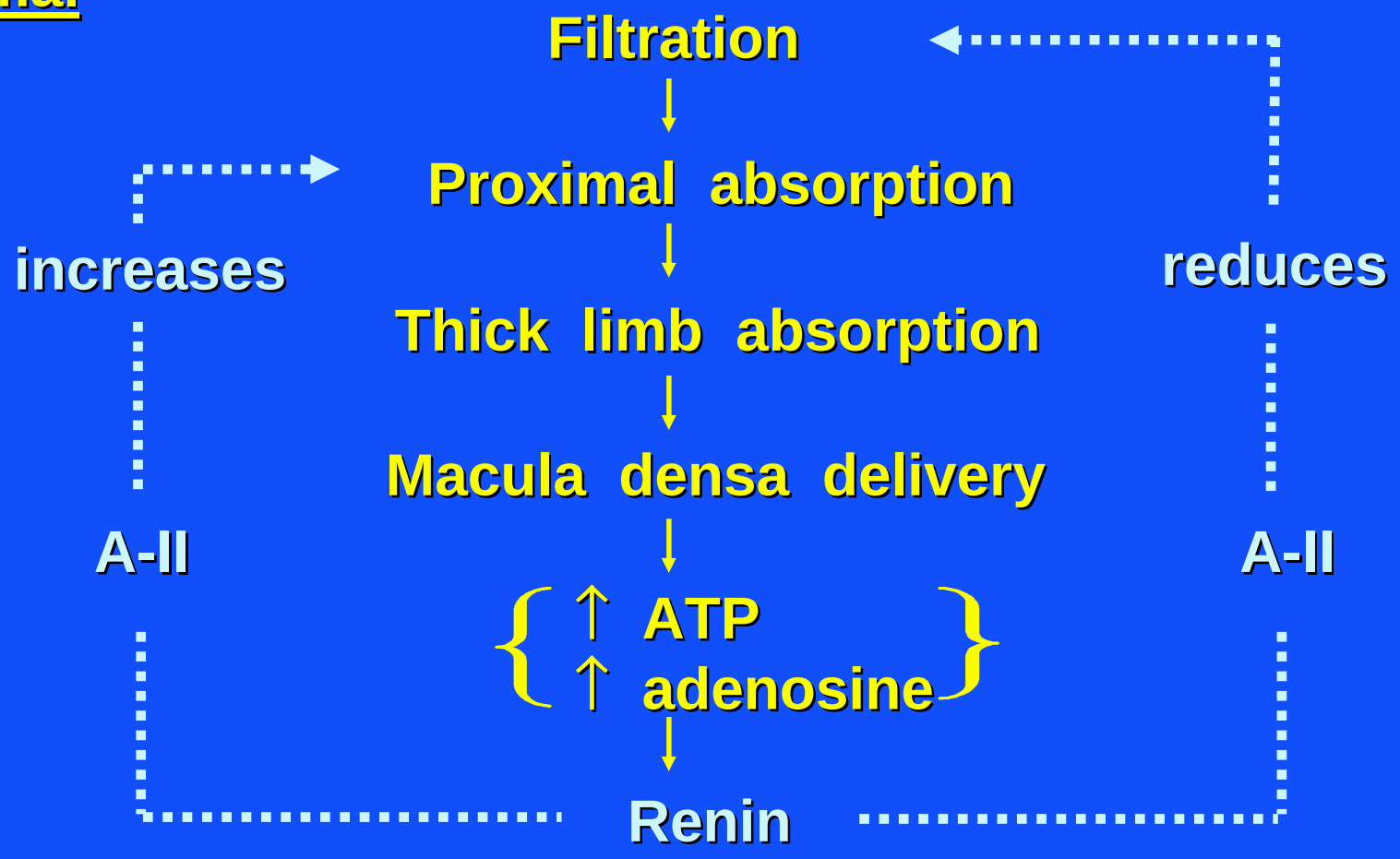
NHE_3: *Kidney- and intestine-specific*

Five NHE isoforms identified to date

STARLING DERANGEMENTS (Δ P) WITH ARTERIAL UNDERFILLING

ACTIVATION OF TGF

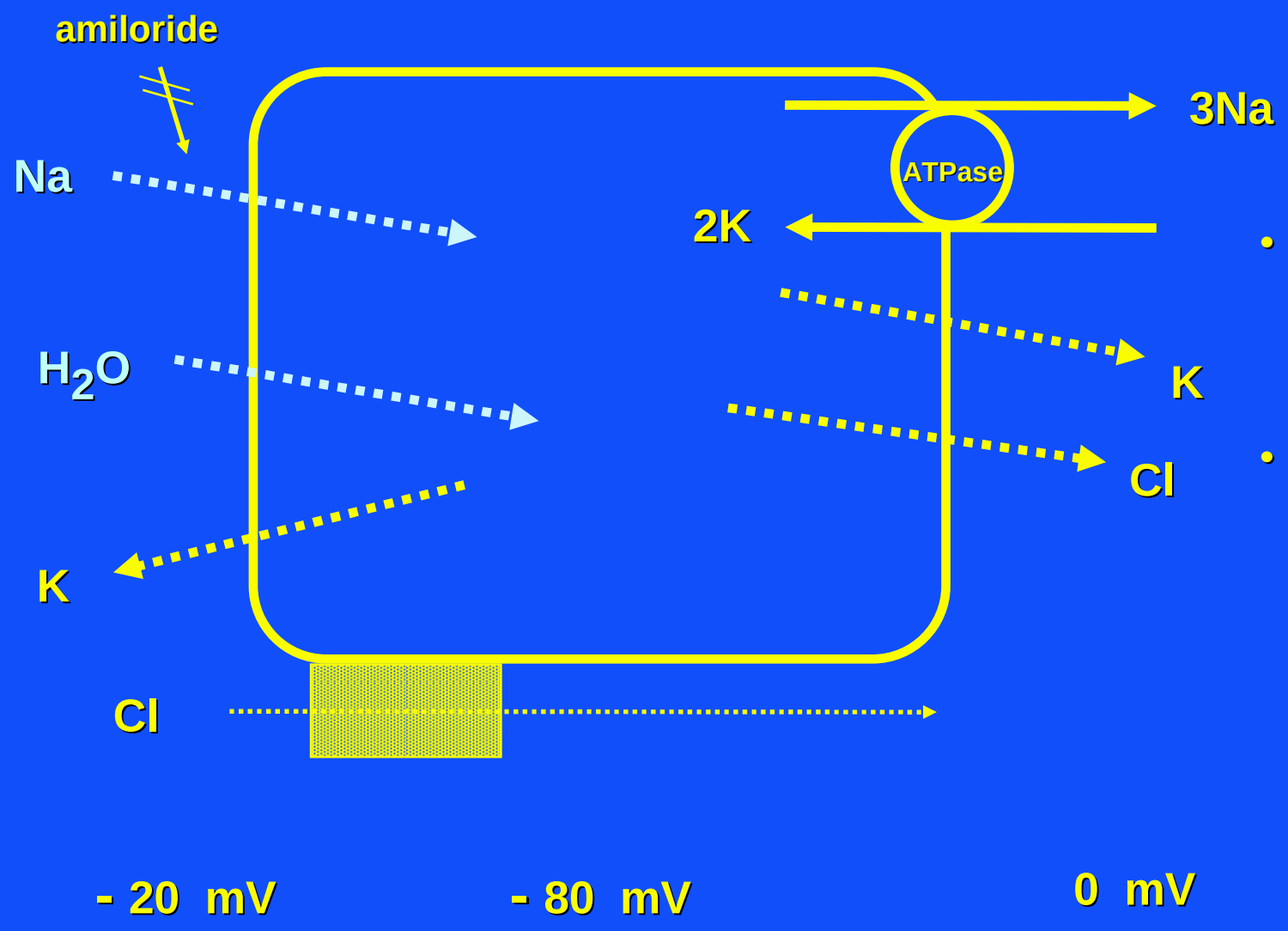
Normal



PRINCIPAL SODIUM-AVID SEGMENTS IN UNDERFILLING

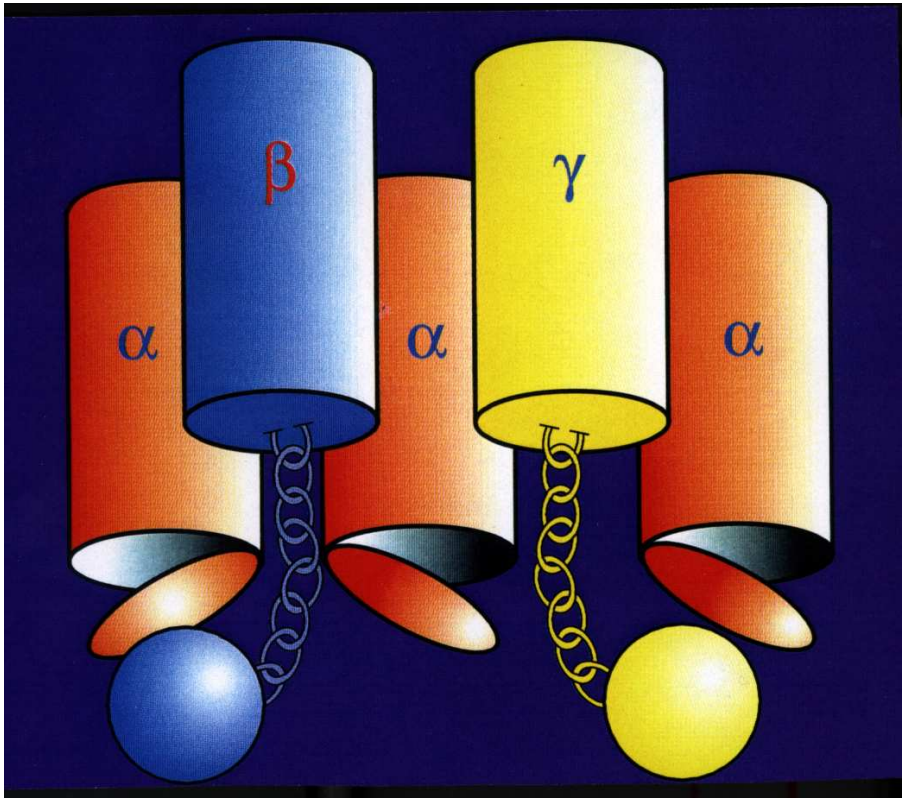
Segment	Normal % Na Absorbed	Factors ↑ Na absorption
proximal	60%	A-II, catechols } ↑ TGF
late DCT; CCD	10%	ADH, aldo
IMCD	5%	ANP resistance

THE CD PRINCIPAL CELL



- ADH, via cAMP
  ↑ ENaC
  ↑ AQP_2
- Aldo, via nuclear receptors
  ↑ ENaC

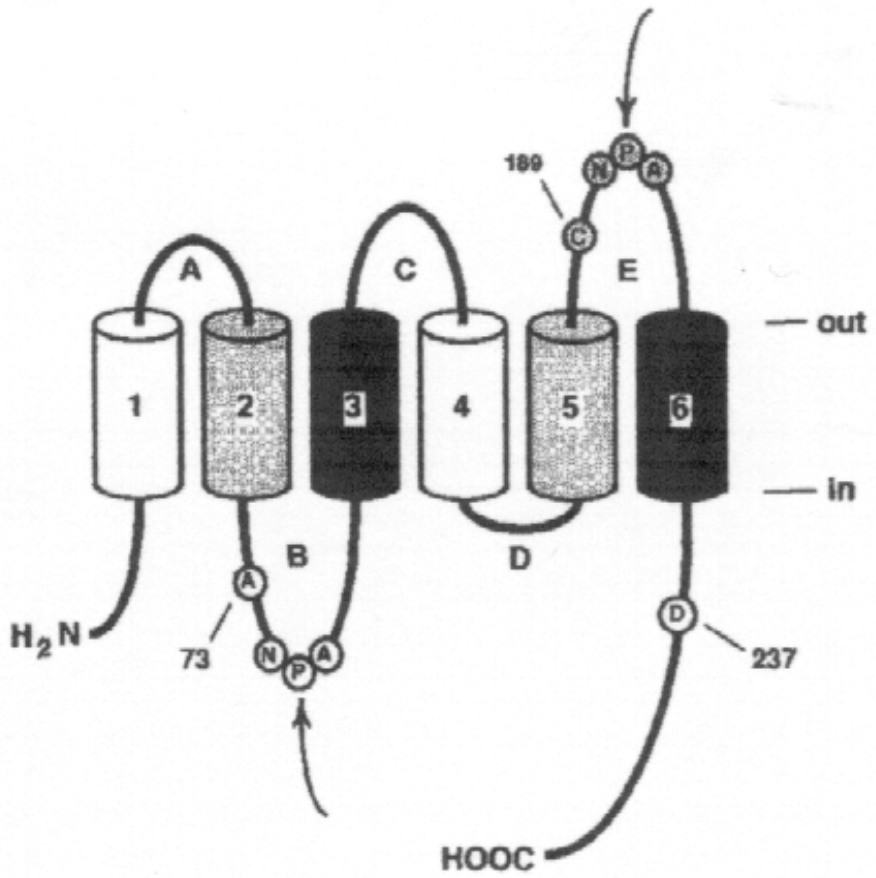
ENaC
Epithelial Na Channel

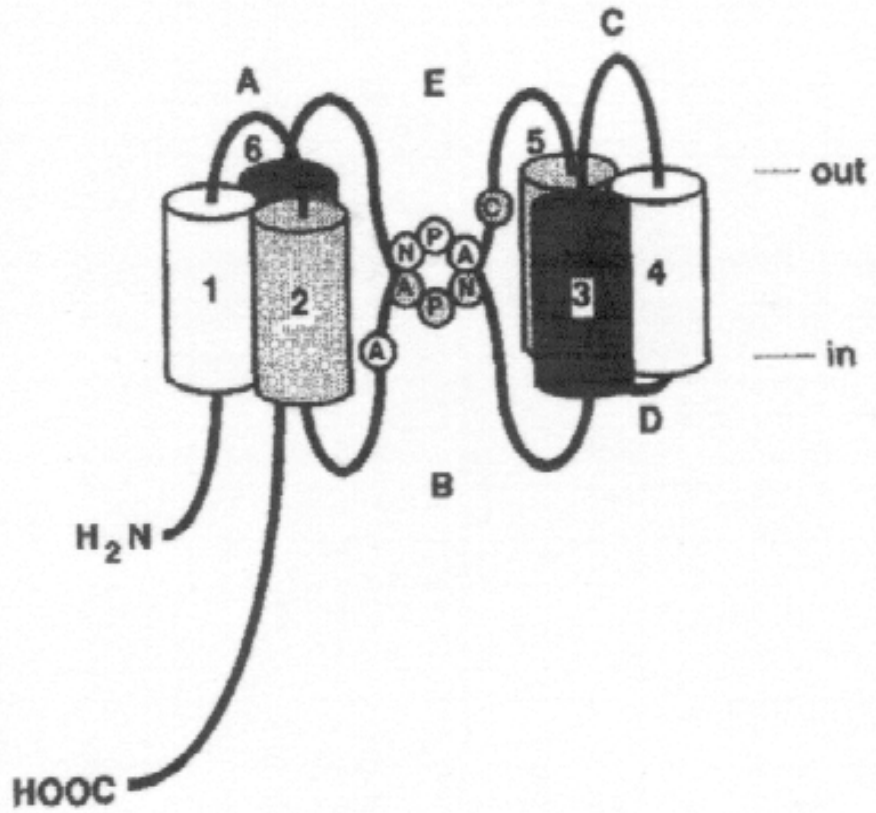


- **Each α subunit :**
  amiloride-sensitive Na channel
- **β and γ subunits:**
  ↑surface delivery of ENaC
- **Liddle's syndrome:**
  β subunit mutation
- **pseudohypoaldo I:**
  α or β subunit mutation
- **ARDS :**
  α subunit mutation

News in Physiol. Sci.
12:55, 1997

AQUAPORIN 2: AGRE'S HOURGLASS MODEL





Agre, *et al.*
JBC 269:14648, 1994

PRINCIPAL SODIUM-AVID SEGMENTS IN UNDERFILLING

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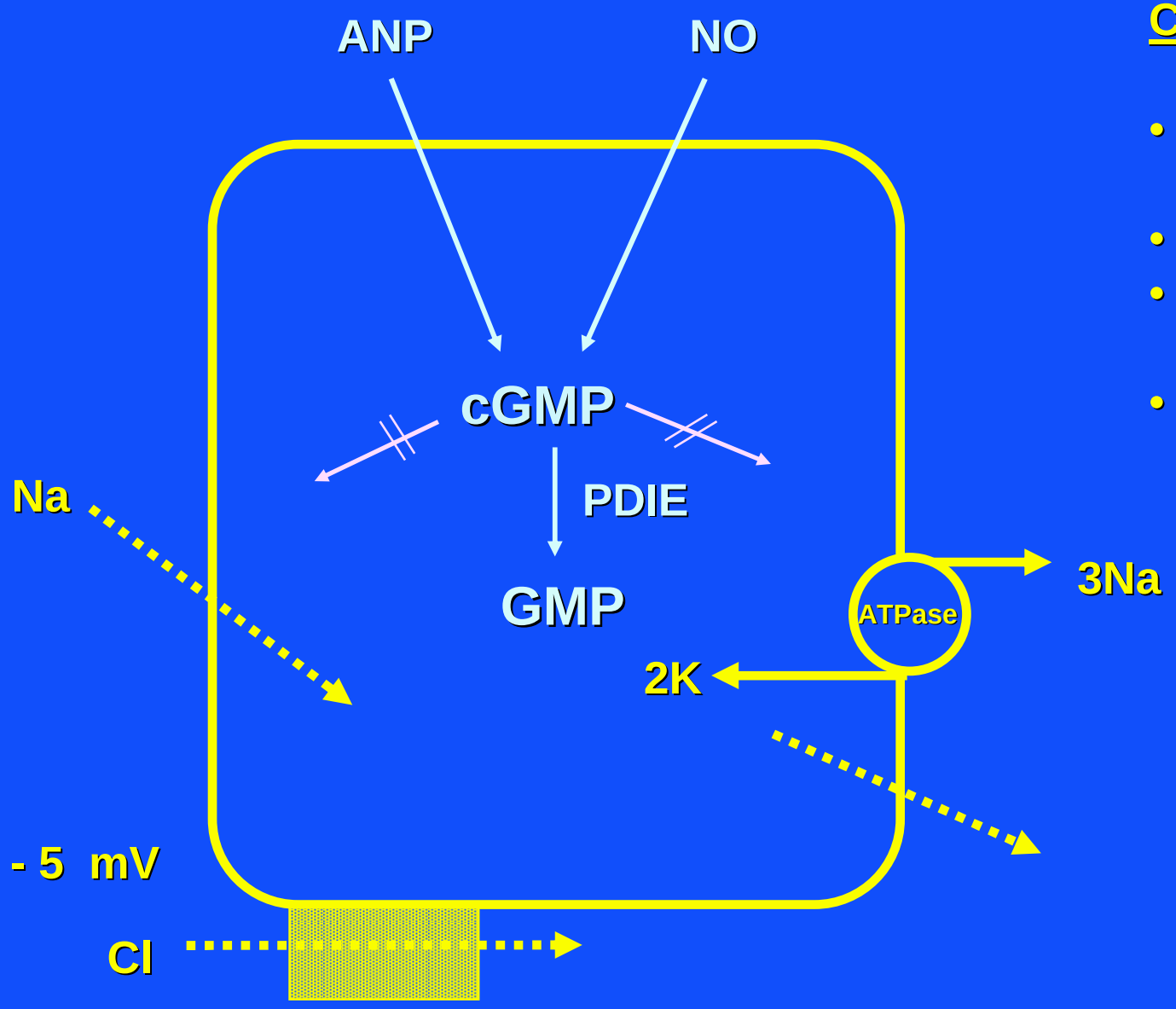
IMCD	5%	ANP resistance

THE IMCD



CHARACTERISTICS

- Classical Ussing epithelium
- Aldosterone- sensitive
- Major locus for ANP- natriuresis
- ANP-resistance in cirrhosis, CHF, nephrotic syndrome

MAJOR ACTIONS OF ANP

- ↓ Afferent arteriolar resistance
- ↓ Aldo effect in CCD
- ↓ IMCD Na^+ absorption

ANP RESISTANCE

Disorder	Mechanism
Experimental CHF	↓ ANP_A density (*AJP* 265:F119, 1993)
Experimental cirrhosis	↑ cGMP - PDIE (*AJP* 271:F3, 1996)
Experimental nephrosis	↑ cGMP - PDIE (*AJP* 271:F3, 1996)

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late cirrhosis		
IVC and/or lymphatic occlusion		
third space disorders		

EDEMATOUS STATES: CIRRHOSIS

PRECIPITATING FACTORS

Deranged Starling Forces

Arterial Underfilling

Altered Volume/Capacitance Ratio

Primary Renal Na^+ Avidity

MANDATORY REQUIREMENT

steady-state

positive Na^+ balance

CIRRHOSIS

UNDERFILLING VS. OVERFILLING

Classical Underfilling Theory

Sinusoidal Portal Hypertension

↓

Lymph Formation > Lymph Removal

↓

Ascites Formation

↓

Reduction of Plasma Volume

↓

Activation of Renin - Angiotensin, Sympathetic Nervous System and AVP Secretion

↓

SODIUM AND WATER RETENTION

OVERFLOW THEORY

Sinusoidal Portal Hypertension

↓ Hepatic Pressure Receptors

PRIMARY SODIUM AND WATER RETENTION

↓

Plasma Volume Expansion

↓

Ascites Formation

Massry and Glassock
Textbook of Nephrology
Ed. 3; Fig. 34-4

CIRRHOSIS

OVERFILLING ARGUMENTS IN EARLY DISEASE

1. In <u>some</u> experimental cirrhosis:
   Na^+ retention precedes ascites

2. In pre-ascitic cirrhosis:
   ↑ cardiac output
   ↑ blood volume
   ↑ splanchnic pooling

3. In pre-ascitic cirrhosis:
   nl renin
   nl aldo

CIRRHOSIS

KEY STRUCTURAL DERANGEMENTS

Normal	Cirrhotic
Symmetrically placed hepatic lobules	Asymmetrically distributed regenerating nodules
Portal triad → sinusoid → central vein	Regenerating nodules *no central vein* *sinusoidal compression*

CIRRHOSIS

CONSEQUENCES OF ABNORMAL REGENERATIVE NODULES

high inflow resistance

↓

↓ portal / arterial flow

↓

portal hypertension

↓

splanchnic pooling

compression of adjacent sinusoids

↓

↑ intrasinusoidal pressure

↓

ascites
(a weeping liver)

SOME COMMON EDEMA STATES

Arterial Underfilling	Controversial	Primary renal Na retention
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NEPHRITIC AND NEPHROTIC SYNDROMES

GENERAL FEATURES

	Acute Nephritis	Nephrotic Syndrome
Hematuria	++++	±
Proteinuria	++	++++
Hypoalbuminemia	±	++++
↓ GFR	++++	±
Hypertension	+++	±
Dilutional anemia	+++	±

THE NEPHROTIC SYNDROME

THE EDEMA CONTROVERSY

"Underfilling"

Proteinuria and hypoalbuminemia

↓

Reduced effective volume

↓

Activation of:
Renin-angiotensin system
Sympathetic nervous system
AVP secretion

↓

Sodium and water retention

↓

EDEMA FORMATION

"OVERFILLING"

Primary renal sodium retention

↓

Increased plasma volume
and arterial pressure

↓ Hypoalbuminemia

EDEMA FORMATION

Adapted from
Massry and Glassock
Textbook of Nephrology
Ed. 3; Fig. 34-4

NEPHROTIC SYNDROME

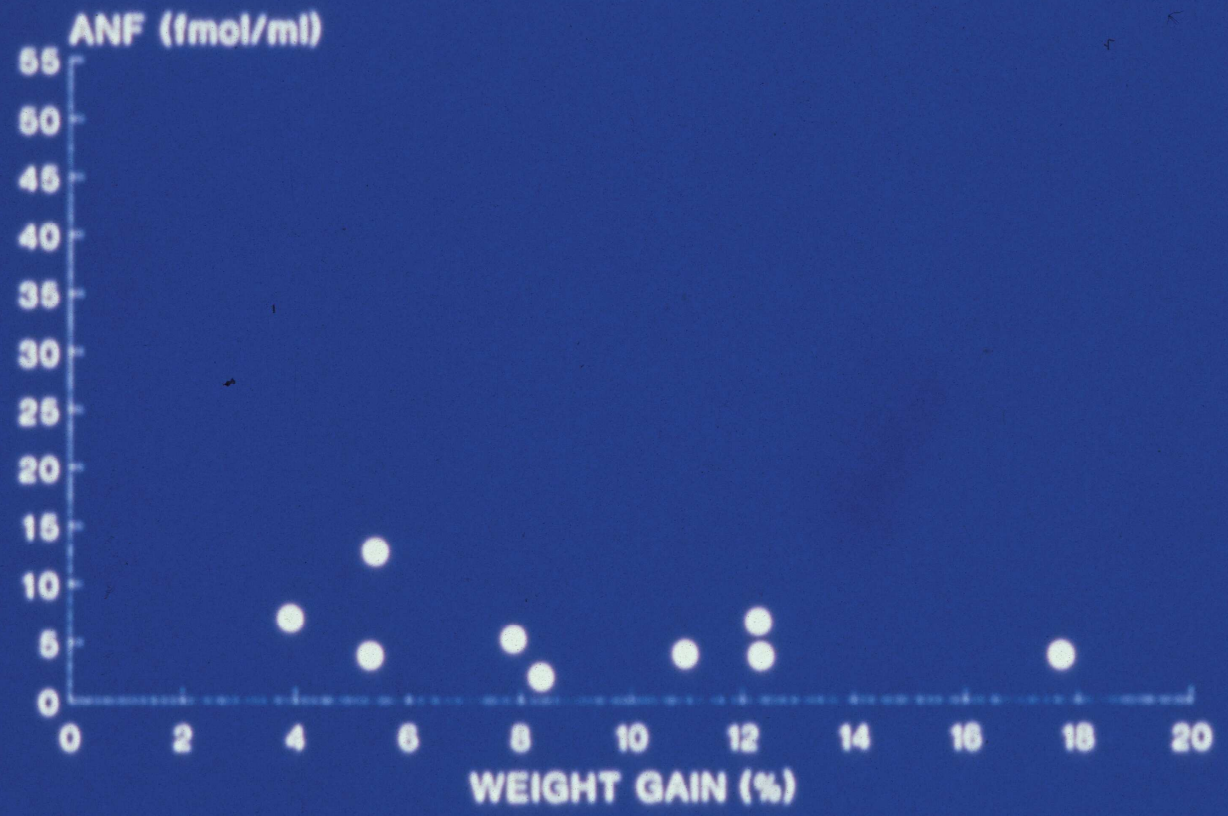
ARGUMENTS FAVORING PRIMARY RENAL Na AVIDITY

1. Congenital hypoalbuminemia: generally edema-free
2. Nephrotic edema can resolve $\bar{c}$ hypoalbuminemia
3. ↑ cGMP-PDIE levels; ↓ ANP levels with edema

IMCD: putative locus
for primary Na avidity

THE NEPHROTIC SYNDROME

3. *ANP LEVELS AND NEPHROTIC SYNDROME*



Kidney International
38:512, 1990

THE NEPHROTIC SYNDROME

A CLINICAL SPECTRUM

1. Nephrotic syndrome is a clinical and hemodynamic spectrum:

↑ blood volume		↓ or normal volume
older patients		younger patients
glomerular inflammation		little inflammation
↓ GFR	→	normal GFR
↑ b. p.	←	normal b. p.
↓ renin/AII		nl or ↑ aldo.

2. Most nephrotics without glomerular inflammation act underfilled.

THE NEPHROTIC SYNDROME

SOME GENERAL CONCLUSIONS

1. **Primary renal Na^+ retention occurs:**
   ANP resistance
   ? other factors

2. **↓ albumin contributes to vascular/interstitial distribution of accumulated fluid**

3. **↓ GFR:** ***resemble nephritic syndrome***
   NL GFR: ***resemble "pure" nephrosis***

EDEMATOUS STATES

PRECIPITATING FACTORS	***MANDATORY REQUIREMENT***
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Altered Volume/Capacitance Ratio	
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THE NEPHRITIC SYNDROME

ACUTE GN → PRIMARY Na^+ RETENTION

1. Glomerular Inflammation

   ↓ K_f
   Normal RPF } → ↓ FF

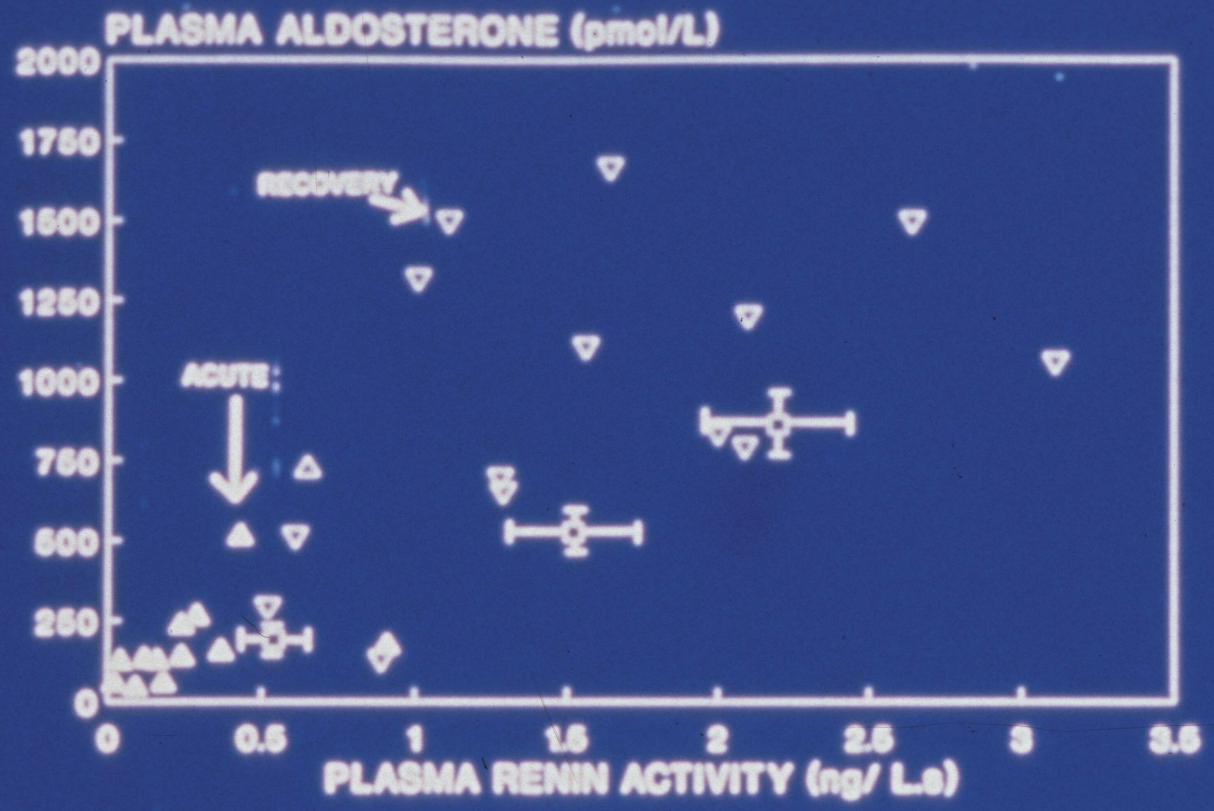
2. ↓ GFR → ↓ axial delivery → ↑ proximal Na^+ absorption

3. Continued Na^+ intake:

   Plasma expansion → dilutional edema
   Hypertension → edema; pulmonary congestion
   ↑ ANP
   ↓ renin / aldosterone

THE NEPHRITIC SYNDROME

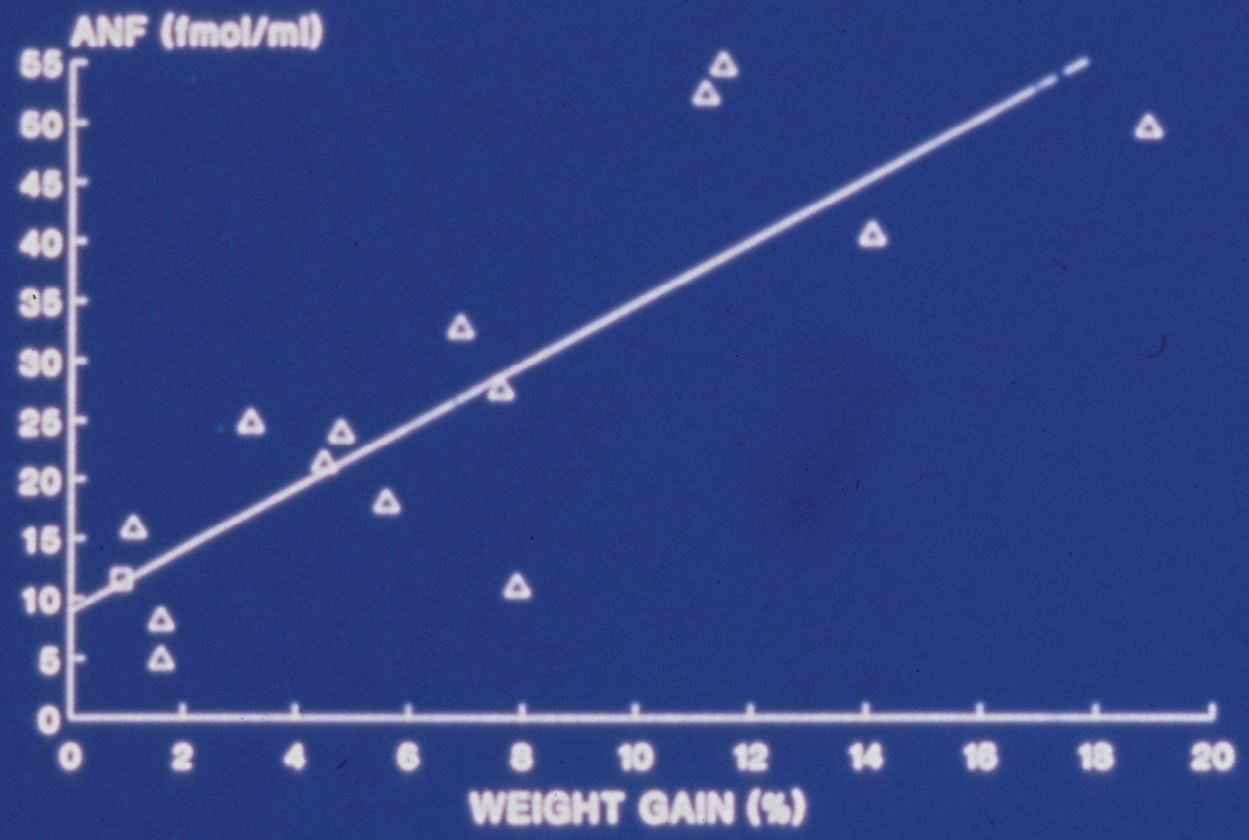
2. *RENIN-ALDOSTERONE LEVELS*



Schrier and Gottschalk
Diseases of the Kidney
Ed. 5, Fig. 63-2

THE NEPHRITIC SYNDROME

3. *ANP LEVELS*



Adapted from:
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