THE EDEMA SYNDROMES
### SOME COMMON EDEMA STATES

<table>
<thead>
<tr>
<th>Arterial Underfilling</th>
<th>Controversial</th>
<th>Primary renal Na retention</th>
</tr>
</thead>
<tbody>
<tr>
<td>systolic failure</td>
<td>early cirrhosis</td>
<td>acute GN</td>
</tr>
<tr>
<td>pericardial constriction</td>
<td>early nephrosis</td>
<td></td>
</tr>
<tr>
<td>late cirrhosis</td>
<td></td>
<td></td>
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<tr>
<td>IVC and/or lymphatic occlusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>third space disorders</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Na⁺ BALANCE

### QUANTITATIVE DILEMMAS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Na⁺</th>
<th>FeNa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mEq)</td>
<td>(%)</td>
</tr>
<tr>
<td><strong>Total body Na⁺</strong></td>
<td>~ 3000</td>
<td>—</td>
</tr>
<tr>
<td><strong>extracellular</strong></td>
<td>~ 2200</td>
<td>—</td>
</tr>
<tr>
<td><strong>Filtered Na load/24 hours</strong></td>
<td>~ 25000</td>
<td>—</td>
</tr>
<tr>
<td>(P&lt;sub&gt;Na&lt;/sub&gt;) X (GFR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(140 mEq/L) (180 L/24 hrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Na⁺ intake/24 hrs</strong></td>
<td>240</td>
<td>~ 1%</td>
</tr>
<tr>
<td>(≈ 5-6 gm)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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)

“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

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

Left Ventricular Pressure

normal

CHF

Left Ventricular Volume

normal
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”
c

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

10. Hyponatremia following mitral commissurotomy
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 CHERISHIRE CAT

High Sensitivity

Lower Sensitivity

Intrarenal

Hepatic

low pressure areas  high pressure areas  JGA  Portal vein sinusoidal

left atrium  carotid sinus  aortic arch

thoracic veins

Hemodynamic changes

Na avidity

? significance
THE VOLUME REPLETION CASCADE

DEPLETION

Angiotensin II — Catecholamines — Endothelins — ADH

CNS

Aldosterone

Thirst

Na retention

Hypoperfusion

Water retention

REPLETION

Atropeptin

PGE₂

Nitric Oxide
KEY FACTORS IN EDEMA STATES

**PRECIPITATING FACTORS**

- Deranged Starling Forces
- Arterial Underfilling
- Altered Volume/Capacitance Ratio
- Primary Renal Na⁺ Avidity

**MANDATORY REQUIREMENT**

- steady-state
- positive Na⁺ balance
The equation

\[ J_V = K_f (\Delta P - \sigma \Delta \pi) \]

The terms

\( J_V \) = flow

\( \sigma \) = solute reflection coefficient

(\( \sigma = 0 \): wholly permeable solute)

(\( \sigma = 1 \): wholly impermeable solute)

\( K_f \) = capillary permeability

\( \Delta P \) = hydrostatic pressure

\( \Delta \pi \) = oncotic pressure
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Abnormality</th>
<th>Net Na(^+) Balance</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS</td>
<td>leaky pulmonary capillaries</td>
<td>(\pm)</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>leaky muscle capillaries</td>
<td>varies (\bar{c}) magnitude of fluid sequestration</td>
</tr>
<tr>
<td>Burns</td>
<td>{ leaky capillaries, loss of cutaneous barrier }</td>
<td>massive Na(^+) losses</td>
</tr>
<tr>
<td>Cyclical edema syndrome</td>
<td>generalized capillary leak</td>
<td>+</td>
</tr>
</tbody>
</table>
KEY FACTORS IN EDEMA STATES

**PRECIPITATING FACTORS**

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SOME COMMON EDEMA STATES

- Arterial Underfilling
- systolic failure
- pericardial constriction
- late cirrhosis
- IVC and/or lymphatic occlusion
- third space disorders

Controversial

Primary renal Na retention

early cirrhosis
early nephrosis
acute GN
**STARLING DERANGEMENTS (Δ P) WITH ARTERIAL UNDERFILLING**

**THE HEART FAILURE SYNDROMES**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-output Failure</td>
<td>↓ contractility and EF</td>
</tr>
<tr>
<td></td>
<td>↑ end-diastolic volume</td>
</tr>
<tr>
<td>High-output Failure</td>
<td>demand &gt; performance</td>
</tr>
<tr>
<td></td>
<td>↓ volume/capacitance ratio</td>
</tr>
<tr>
<td>Diastolic failure</td>
<td>↓ compliance and filling</td>
</tr>
<tr>
<td></td>
<td>normal EF</td>
</tr>
<tr>
<td></td>
<td>“flash” pulmonary edema</td>
</tr>
</tbody>
</table>
LOW AND HIGH OUTPUT HEART FAILURE
REDUCED ECV, BUT FOR DIFFERENT REASONS

Normal

Low output failure

high output failure

ARTERIES

VEINS
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

<table>
<thead>
<tr>
<th>Segment</th>
<th>Normal % Na Absorbed</th>
<th>Factors</th>
<th>↑ Na absorption</th>
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<tbody>
<tr>
<td>proximal</td>
<td>60%</td>
<td>FF</td>
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<td>late DCT; CCD</td>
<td>10%</td>
<td>A-II, catechols</td>
<td>↑TGF</td>
</tr>
<tr>
<td>IMCD</td>
<td>5%</td>
<td>ADH, aldo, ANP resistance (?)</td>
<td></td>
</tr>
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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 - All
NHE$_3$: Kidney- and intestine-specific
Five NHE isoforms identified to date
Filtration

Proximal absorption

Thick limb absorption

Macula densa delivery

\{ \text{\(\uparrow\) ATP, \(\uparrow\) adenosine} \}

Renin

\text{A-II}

\text{Normal}

\text{\(\uparrow\) \(\uparrow\) \(\uparrow\) \(\uparrow\) ATP}

\text{\(\uparrow\) \(\uparrow\) \(\uparrow\) \(\uparrow\) adenosine}

\text{\(\uparrow\) \(\uparrow\) \(\uparrow\) \(\uparrow\) Renin}

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<td>ADHaldo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ANP resistance</td>
</tr>
</tbody>
</table>
THE CD PRINCIPAL CELL

- Na
- K
- Cl
- H₂O
- ATPase
- Amiloride
- 3Na
- 2K
- K
- Cl
- ADH, via cAMP
  - ENaC
- Aldo, via nuclear receptors
  - AQP₂
  - ENaC

-20 mV  -80 mV  0 mV
ENaC
Epithelial Na Channel

• Each $\alpha$ subunit: amiloride-sensitive Na channel
• $\beta$ and $\gamma$ subunits:
  $\uparrow$ surface delivery of ENaC
• Liddle's syndrome:
  $\beta$ subunit mutation
• pseudohypoaldol I:
  $\alpha$ or $\beta$ subunit mutation
• ARDS:
  $\alpha$ subunit mutation

*News in Physiol. Sci.*
12:55, 1997
AQUAPORIN 2: AGRE’S HOURGLASS MODEL

Agre, et al.
JBC 269:14648, 1994
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</tbody>
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TGF
THE IMCD

CHARACTERISTICS

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

ANP

NO

cGMP

PDIE

GMP

Na

2K

ATPase

3Na

Na

Cl

-5 mV
MAJOR ACTIONS OF ANP

- ↓ Afferent arteriolar resistance
- ↓ Aldo effect in CCD
- ↓ IMCD Na⁺ absorption
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental CHF</td>
<td>↓ ANP$_A$ density</td>
</tr>
<tr>
<td></td>
<td>(AJP 265:F119, 1993)</td>
</tr>
<tr>
<td>Experimental cirrhosis</td>
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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
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 some 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
Symmetrically placed hepatic lobules
Portal triad → sinusoid → central vein

Cirrhotic
Asymmetrically distributed regenerating nodules
Regenerating nodules no central vein
sinusoidal compression
CIRRHOSIS
CONSEQUENCES OF ABNORMAL REGENERATIVE NODULES

- High inflow resistance
  - Portal/arterial flow decreases
  - Portal hypertension
  - Splanchnic pooling

- Compression of adjacent sinusoids
  - Intrasinusoidal pressure increases
  - Ascites (a weeping liver)
SOME COMMON EDEMA STATES

**Arterial Underfilling**
- systolic failure
- pericardial constriction
- late cirrhosis
- IVC and/or lymphatic occlusion
- third space disorders

**Controversial**
- early cirrhosis
- early nephrosis

**Primary renal Na retention**
- acute GN
### NEPHRITIC AND NEPHROTIC SYNDROMES

#### GENERAL FEATURES

<table>
<thead>
<tr>
<th></th>
<th>Acute Nephritis</th>
<th>Nephrotic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematuria</td>
<td>++++</td>
<td>±</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>±</td>
<td>++++</td>
</tr>
<tr>
<td>↓ GFR</td>
<td>++++</td>
<td>±</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+++</td>
<td>±</td>
</tr>
<tr>
<td>Dilutional anemia</td>
<td>+++</td>
<td>±</td>
</tr>
</tbody>
</table>
THE NEPHROTIC SYNDROME

THE EDEMA CONTROVERSY

“Underfilling”
Proteinuria and hypoalbuminemia

Reduction of 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 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

ANF (fmol/ml)

WEIGHT GAIN (%)

Kidney International
38:512, 1990
THE NEPHROTIC SYNDROME
A CLINICAL SPECTRUM

1. Nephrotic syndrome is a clinical and hemodynamic spectrum:

- ↑ blood volume
  - older patients
- ↓ or normal volume
  - younger patients
- glomerular inflammation
- ↓ GFR
- ↑ b. p.
- ↓ renin/AII

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. $\downarrow$ albumin contributes to vascular/interstitial distribution of accumulated fluid

3. $\downarrow$ GFR: resemble *nephritic syndrome*
   NL GFR: resemble *“pure” nephrosis*
EDEMATOUS STATES

**PRECIPITATING FACTORS**

- Deranged Starling Forces
- Arterial Underfilling
- Altered Volume/Capacitance Ratio
- Primary Renal Na\(^+\) Avidity

**MANDATORY REQUIREMENT**

- steady-state
- positive Na\(^+\) balance
THE NEPHRITIC SYNDROME

ACUTE GN $\rightarrow$ PRIMARY Na$^+$ RETENTION

1. Glomerular Inflammation
   $\downarrow$ $K_f$
   $\{$
   Normal RPF
   $\rightarrow$
   $\downarrow$ FF

2. $\downarrow$ GFR $\rightarrow$ $\downarrow$ axial delivery $\rightarrow$ $\uparrow$ proximal Na$^+$ absorption

3. Continued Na$^+$ intake:
   Plasma expansion $\rightarrow$ dilutional edema
   Hypertension $\rightarrow$ edema; pulmonary congestion
   $\uparrow$ ANP
   $\downarrow$ renin / aldosterone
THE NEPHRITIC SYNDROME

2. RENIN-ALDOSTERONE LEVELS

![Graph showing plasma aldosterone levels vs. plasma renin activity.]

Schrier and Gottschalk: Diseases of the Kidney
Ed.6, Fig. 63-2
THE NEPHRITIC SYNDROME

3. ANP LEVELS

ANF (fmol/ml) vs WEIGHT GAIN (%)

Adapted from:
Schrier and Gottschalk
Diseases of the Kidney
Ed. 6, Fig. 63-2
SOME COMMON EDEMA STATES

Arterial Underfilling
systolic failure
pericardial constriction
late cirrhosis
IVC and/or lymphatic occlusion
third space disorders

Controversial
early cirrhosis
early nephrosis

Primary renal
Na retention
acute GN
KEY FACTORS IN EDEMA FORMATION

**PRECIPITATING FACTORS**

- Deranged Starling Forces
- Arterial Underfilling
- Altered Volume/Capacitance Ratio
- Primary Renal Na\(^+\) Avidity

**MANDATORY REQUIREMENT**

- steady-state
- positive Na\(^+\) balance