Blood pressure increases with aging only in civilizations with high salt intake.

**Cook islands**
- Difference in BP and HT between highland and coast
- Emigrants to Hawaii – prevalence of HT higher (30%)
ANIMAL ANALOGY

- Philogenetic similarities
- 99.6% coding exons
- Same amount of NaCl in milk

- no stress, same potassium intake
  BP increase with higher salt intake
- salt sensitivity in chimpanzees

Denton, 1995
Correlation between blood pressure and salt intake

Salt intake determines BP in hypertensive and normotensive subjects

![Graph showing the correlation between NaCl intake and blood pressure changes.]

**INTERSALT study**

$\Delta$ intake NaCl 100 mmol $= \Delta$ BP of 10/6 mmHg/30 years

Cutler, 1997
Correlation of systolic AMBP and salt intake in Croatia

Spearmanova rang korelacija: $r = 0.217; p = 0.0069$

Pezo-Nikolić, Jelaković, 2008 unpublished data
Correlation of systolic AMBP and salt intake in Croatia

<table>
<thead>
<tr>
<th></th>
<th>Normotension (N=62)</th>
<th>White coat HT (N=64)</th>
<th>Essential HT (N=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spearmanova rang korelacija: r = 0,154; p = 0,2712</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spearmanova rang korelacija: r = 0,100; p = 0,5234</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spearmanova rang korelacija: r = 0,170; p = 0,2192</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pezo-Nikolić, Jelaković, 2008 unpublished data
24 hour sodium excretion (mmol/dU) and BP categories in Croatia

Kruskal-Wallis ANOVA: p = 0.0055

<table>
<thead>
<tr>
<th>Category</th>
<th>Median (Min-Max)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotension (N=62)</td>
<td>168 (68-384)</td>
<td>0.82</td>
</tr>
<tr>
<td>White coat HT (N=64)</td>
<td>198 (64-490)</td>
<td>0.0089</td>
</tr>
<tr>
<td>Essential HT (N=55)</td>
<td>210 (39-524)</td>
<td>0.0035</td>
</tr>
</tbody>
</table>

Pezo-Nikolić, Jelaković, 2008 unpublished data
Elementary, My Dear Watson

Alimentary, My Dear Watson

Doyle, Journal of Sherlock Holmes, 1898
Guytons' Pressure-Natriuresis relationship

Central role played by the kidneys

Arterial pressure $\uparrow$

Urine Flow

- Normal
- Hypertension

Arterial Pressure (mmHg)

50 100 150 200 250

Blood Volume $\downarrow$

Hereditary:
- SHR
- Dahl S
- TGR

Secondary:
- Goldblatt
- RRM + salt
- All
- V1 agonist
- DOCA + salt
- ALDO + salt
Interaction of the Modern Western Diet and the Kidneys in the Pathogenesis of Essential Hypertension

High sodium intake +
Lack of renal adaptation and other defects in Na excretion

\[ \text{Retention of Na by the kidneys} \]

\[ \text{Excess of Na in the body} \]

\[ \text{Extracellular fluid volume expansion} \]

\[ \text{Release of digitalis like factor} \]

\[ \text{Na/K ATPase} \]

\[ \text{Excess of cellular Na} \]

\[ \text{Vascular smooth muscle cell contraction} \]

\[ \text{Increased peripheral vascular resistance} \]

\[ \text{HYPERTENSION} \]
Final, common pathway in hypertension

- Kidney sodium retention
- Intravascular volume
- Cardiac output
- Autoregulation
- Normal peripheral vascular resistance
- Normal cardiac output
- Blood pressure

Hypertension
Renal mechanisms of diminished sodium excretion

- Molecular error in sodium transport
- Less nephrons
- Decreased medullary circulation
- Loss of peritubular blood vessels and interstitial fibrosis
# Renal mechanisms of diminished sodium excretion

## Mechanisms

<table>
<thead>
<tr>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced ultrafiltration capability</td>
</tr>
<tr>
<td>Enhanced tubular Na reabsorption</td>
</tr>
</tbody>
</table>

## Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Hypertension in blacks</td>
</tr>
<tr>
<td>Sodium sensitive EH</td>
</tr>
<tr>
<td>Primary aldosteronism</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
</tr>
</tbody>
</table>

---
Hypertension 'follows' a transplanted kidney

REMISSION OF ESSENTIAL HYPERTENSION AFTER RENAL TRANSPLANTATION


with comments by
Robert G. Luke, and Eberhard Ritz

Table 1. Clinical Characteristics and Results of Blood-Pressure and Renal-Function

Studies the First Time Both Were Obtained Simultaneously in Six Black Patients

with a Family History of Hypertension (See Appendix).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Blood Pressure</th>
<th>Serum Urea Nitrogen</th>
<th>Urine Protein</th>
<th>No. of Blood &amp; Urine Tests</th>
<th>ESRD Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>M</td>
<td>240/170</td>
<td>131.2</td>
<td>4</td>
<td>180 mg/24 hr</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>M</td>
<td>180/150</td>
<td>281.1</td>
<td>Negative by dipstick</td>
<td>180 mg/24 hr</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>M</td>
<td>150/100</td>
<td>121.0</td>
<td>Negative by dipstick</td>
<td>C=88 mg/24 hr</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>M</td>
<td>150/120</td>
<td>381.3</td>
<td>Negative by dipstick</td>
<td>C=100 mg/24 hr</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>F</td>
<td>250/100</td>
<td>281.1</td>
<td>Negative by dipstick</td>
<td>180 mg/24 hr</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>M</td>
<td>300/160</td>
<td>150.1</td>
<td>(diabetes)</td>
<td>C=60 mg/24 hr</td>
<td>2</td>
</tr>
</tbody>
</table>

*ESRD denotes blood urea nitrogen level, and ESRD anti-epinephrine.

Table 2. Evidence of Resolution of Cardiac Hypertrophy from Electrocardiograms and Chest X-Ray Films before and after Renal Transplantation.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Score for Vascular Hypertrophy</th>
<th>Diameter of Heart &quot;T&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

Mean ± S.E.M. 5.3 ± 0.6 0.5 ± 0.3 17.0 ± 0.2 13.8 ± 0.3

(P<0.001)

Figure 1. Photomicrograph of the Nephrectomy Specimen from a Patient Typical of Those Considered to Have Nephrosclerosis.
Monogenic hypertensions & hypotensions

Modifi. after Lifton at al, Cell 2001
Central Role for ENaC in Development of Hypertension

J. Howard Pratt

Lumen

γ €442V
(8–10–30%; W=0%)

β T594M
(8–5%; W=0%)

PY motif

α A663T
(8–15%; W=30%)

Intracellular
Increased sodium absorption in renal tubules:
- Hypertrophy of cardiomiocytes and VSM in blood vessels
- Enhanced expression of AT1 receptor
- Activation of NF-κB in proximal tubule (inflammation)
- Enhanced stimulation of central sympatheticus (via AII)
- Increased synthesis of TGF beta
- Increased NAD(P)H – oxidative stress – inflammation
  - less NO
  - diminished medullary flow
Increased sodium intake = increased total cardiovascular risk

- increased reactivity of platelets
  \[ \rightarrow \text{via Na:Ca exchanger} \]
  \[ \text{Gow, 1992, Nara, 1984} \]

- increased hypertrophy and fibrosis
  \[ \rightarrow \text{via TGF}\beta \]
  \[ \text{Gu, 1998} \]

- ↑ expression of AT1 R and ↓ AT2 R
  \[ \rightarrow \text{via local RAS} \]
  \[ \text{Schmid, 1997} \]

- ↑ ET 1
  \[ \text{Ferri, 1997} \]

- endothelial dysfunction
  \[ \rightarrow \text{via NO, EDHF} \]
  \[ \text{Miyoshi, 1997} \]

- ↑ insulin resistance
  \[ \text{Campese, 1994} \]
Increased sodium intake = increased total cardiovascular risk, independently of blood pressure

Sodium excretion and left ventricle hypertrophy and albuminuria

Schmieder, 1990   du Cailar, 2002
Salt-sensitive hypertension—update on novel findings

Bernardo Rodriguez-Iturbe\textsuperscript{1} and Nosratola D. Vaziri\textsuperscript{2}


Fig. 1. Antithromogenic and salutary effects of dietary salt restriction. The different pathways for the development of salt-sensitive hypertension in the 1960s and 2000s are depicted. Na retention and increased cardiac output (ECV) lead to increased PVR and hypertension. Genetic mutations and polymorphisms affecting Na reabsorption in the kidney induce Na retention, SNS activity, TGF-β, ROS formation, Ang II, and inflammation, leading to vasoconstriction and LVH, which contribute to the development of hypertension.
Insulin resistance and salt-sensitive hypertension in metabolic syndrome

Toshiro Fujita


**Diagram:**

- **Angio II**
  - IRS1 deficit
  - Insulin resistance
  - Hyperinsulinaemia
  - Sympathetic
  - IRS2
  - PI3 kinase
  - Na reabsorption
  - NAD(P)H
  - Compression of the kidney by the abdominal fat
    - Reduced medullary blood flow
    - Reabsorption in the ascend. limb of the loop of Henle
    - Mechanism for hyperinsulinaemia-induced sodium retention in metabolic syndrome
    - + uric acid

**Key Points:**

- Leptin
- Angio II
- NHE3 - PT
- NaHCO3 co-transport - PT
No kidney, 
No cry!
Since the 1930s, Kempner and his associates have employed the Rice Diet to treat more than 18,000 patients from all around the world. Walter Kempner retired from Duke University in 1974 and from the Rice Diet program in 1994. He died in 1997 at the age of 93.
DASH Sodium Trial

Sacks, 2001
Long term effects (after 15 years) of 3 g lower salt intake

Cardiovascular risk 25% in TOHP I

Total mortality 20% in TOHP I
Wisdom begins in wonder.

Socrates