The kidney’s role is to maintain a stable internal environment.

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Body fluid compartments

- **Intracellular fluid (ICF)**
  - High K+
  - Low Na+ and Cl-
  
  25L or 60% of TBF

- **Extracellular fluid (ECF)**
  - High Na+ and Cl-
  - Low K+
  
  12L interstitial fluid
  3L plasma

Total body fluid; TBF ~42L
Why & How
the body maintains fluid balance

• The volume and composition of the extracellular fluid (ECF) is maintained within narrow limits.

• This ensures that the cells have a constant environment to carry out their normal functions.

• The problem is that people have wide variations in their intake and losses of fluid.

• ECF homeostasis is primarily maintained by excretion of water and sodium through the kidneys.

• There are also some mechanisms that increase intake.
Large variations in water intake and output

**Average Water Input**
- Metabolism 10%: 250 ml
- Ingested 90%: 2250 ml

**Average Water Output**
- 4% Faeces: 100 ml
- 8% Sweat: 200 ml
- 28% Skin & lungs: 700 ml
- 60% Urine: 1500 ml

Ingested 90%: 2250 ml

Average Water Input: 2250 ml

Average Water Output: 2500 ml

Metabolism 10%: 250 ml

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Sodium is also continuously ingested and excreted

- Sodium intake comes exclusively from the diet (6-18g/day)
- The kidneys are responsible for 90-95% of the sodium output
ECF homeostasis is primarily maintained by excretion of water and sodium through the kidneys.
FUNCTIONS OF THE KIDNEY

- The basic functions of the kidney are homeostatic, including:
  - regulation of body water content (total body fluid osmolarity)
  - regulation of body sodium content (extracellular fluid volume)
  - regulation of body potassium content
  - regulation of calcium, inorganic phosphate and magnesium
  - removal of metabolic waste products from the blood (to be excreted in the urine)
  - removal of foreign chemicals from the blood (e.g. drugs, pesticides and food additives)
  - secretion of hormones:
    - renin = controls the formation of angiotensin
    - erythropoietin = stimulates red blood cell production
    - 1,25-dihydroxyvitamin D3 (vitamin D3)
  - glucogenesis = conversion of amino acids to glucose
The Kidney

renal artery & vein

medulla
cortex

capsule
apilla

Adipose tissue
calyx

Renal pelvis

ureter

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Glomeruli: the filters

Renal cortex

Glomeruli
Renal Vasculature

Glomerulus

Afferent arteriole

Efferent arteriole
The glomerular filtration barrier

- AA  afferent arteriole
- EA  efferent arteriole
- G   renin containing cells
- M   mesangial cell
- B   Bowman’s capsule
- BS  Bowman’s space
- EN  endothelial cell
- EP  epithelial cell
- F   foot processes
- BM  basement membrane
- PT  proximal tubule
The human kidney is an amazing filter

- Renal blood flow ~ 1.2 l/min (~1800 l/day!!)

- 180 litres/day filtered by the kidney
  - (total body water~42 litres)

- Approximately 0.3 to 1.5 million glomeruli

- **Glomerular filtration rate (GFR) ~ 125 ml/min**
  - (Single nephron GFR ~ 50 nl/min)
Urine Formation

1. Filtration
2. Reabsorption
3. Secretion

Excretion = Filtration - Reabsorption + Secretion
The amount of sodium and water excreted by the kidney’s is the result of two processes:

**Glomerular Filtration**

**Tubular Reabsorption**

$$SODIUM\ EXCRETION = sodium\ filtered - sodium\ reabsorbed$$
Glomerular Filtration
Fluid forced through filtration barrier by hydrostatic pressure

Glomeruli → Mechanical Filters

- Glomerular Filtration Barrier
  - Endothelial fenestrations
  - Basement Membrane (-ve charged)
  - Podocytes & slit diaphragm

- Glomerular capillaries more efficient filters than other capillaries
  - very large fenestrations
  - high hydrostatic pressures driving filtration

Filterability of solutes
Size & Charge
small molecules (<3nm or 7000MW) filtered freely
>7-9nm or 70000MW essentially blocked
Most proteins prevented due to negative charge they carry

Filtrate inside BC is virtually identical to plasma but essentially free of protein (0.02%)
Glomerular filtration rate: is determined by the net filtration pressure and the conductivity of the glomerular capillaries

- **SNGFR = NFP x Kf**
  - SNGFR = single nephron glomerular filtration rate

- **Net filtration pressure (NFP) = \( P_{GC} - (\Pi_{GC} + P_{BS}) \)**

- **Kf = glomerular filtration coefficient**
  = \( k \times S \)
  = hydraulic conductivity X glomerular capillary surface area

\( P_{GC} = \) Glomerular capillary pressure
\( P_{BS} = \) Bowmans space pressure
\( \Pi_{GC} = \) Glomerular capillary osmotic pressure
Net pressure driving filtration: the sum of hydrostatic and osmotic pressures

Blood pressure in capillary = $P_{GC}$ (55 mmHg)

Plasma osmotic pressure = $\pi_{GC}$ (30 mmHg)

Fluid pressure in capsule = $P_{BC}$ (15 mmHg)

Osmotic pressure in capsule = $\pi_{BC}$ (0 mmHg)

Net Filtration Pressure (NFP):

= $P_{GC} - (\pi_{BC} + P_{BC})$

= 55 - (30+15)

= 10 mmHg
The glomerular filtration barrier

- AA afferent arteriole
- EA efferent arteriole
- G renin containing cells
- M mesangial cell
- B Bowman’s capsule
- BS Bowman’s space
- EN endothelial cell
- EP epithelial cell
- F foot processes
- BM basement membrane
- PT proximal tubule
**RBF and GFR are “autoregulated”**

- **Autoregulation** - The ability of an organ to maintain its blood flow nearly constant despite changes in arterial pressure.

- RBF and GFR do not change when arterial pressure is between 70-150 mmHg.

- Urine and sodium output IS NOT autoregulated. Urine flow rate is directly proportional to arterial pressure. “Pressure-Natriuresis”

<table>
<thead>
<tr>
<th>Arterial pressure (mmHg)</th>
<th>RBF (ml/min)</th>
<th>GFR (ml/min)</th>
<th>Urine flow rate (ml/min)</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td>200</td>
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</tbody>
</table>
The glomerulus is unique, having two resistance beds that control the pressure within it.

The two areas of highest resistance (the points of greatest decline in blood pressure) are the afferent and efferent arterioles.
Changes in the resistances of the afferent or efferent arterioles alters RBF and GFR

\[ \text{Glomerulus} \]

\[ \text{Afferent} \quad \text{Efferent} \]

\[ \downarrow P_{gc} \quad \downarrow \text{GFR} \quad \downarrow \text{RBF} \]

\[ \uparrow P_{gc} \quad \uparrow \text{GFR} \quad \uparrow \text{RBF} \]

\[ \uparrow P_{gc} \quad \uparrow \text{GFR} \quad \downarrow \text{RBF} \]

\[ \downarrow P_{gc} \quad \downarrow \text{GFR} \quad \uparrow \text{RBF} \]
Intrarenal autoregulatory mechanisms

- GFR is very responsive to changes in glomerular forces

- Powerful mechanisms to maintain a stable environment within the kidney

- By adjusting vascular smooth muscle tone in the preglomerular vessels
Renal autoregulation mechanisms: constant filtered load

- **Myogenic mechanism**
  - Controlled constriction of the afferent and efferent arterioles opposes any changes in the systemic blood pressure so that renal blood flow and GFR remain constant. This property is known as autoregulation.

- **Tubuloglomerular feedback**
  - The filtration rate of a single nephron alters in response to changes in NaCl delivery to the macula densa
The amount of sodium and water excreted by the kidney’s is the result of two processes:

- Glomerular Filtration

- Tubular Reabsorption

SODIUM EXCRETION

= sodium filtered - sodium reabsorbed
Concentrated (hyperosmotic) urine

Desert rat

Beaver
Specialized histology of the tubular cells

Cortex
- Proximal tubule
- Distal tubule
- Principal cell
- Intercalated cell
- Cortical collecting duct

Outer medulla
- Descending thin limb

Inner medulla
- Thick ascending limb
- Inner medullary collecting duct
- Ascending thin limb
Tubule
Sodium reabsorption

- Na+ is freely filtered into the tubules
- most of the Na+ is reabsorbed in the proximal tubule
- no active transport of Na+ in the descending loop of Henle. It is impermeable to Na+
- reabsorption of Na+ by passive diffusion in the thin ascending loop of Henle
- reabsorption of Na+ by active transport in the thick ascending loop of Henle
- only a small proportion of Na+ is reabsorbed in the distal tubule and collecting ducts (and this is regulated)
- > 99% of the filtered Na+ is normally reabsorbed and returned to the plasma (none is secreted)
Water reabsorption

• H2O is freely filtered into the tubules

• H2O is reabsorbed osmotically

• most of the H2O is reabsorbed in the proximal tubule

• descending limb of the loop of Henle highly permeable to H2O

• thin and thick ascending limb of the loop of Henle impermeable to H2O

• H2O permeability of the distal tubule and collecting ducts is variable?

• > 99% of the filtered H2O is normally reabsorbed and returned to the plasma (none is secreted)

~ 1-2% filtered H2O Excreted

~ 25% • H2O • H2O • H2O • H2O

~ 67% • H2O • H2O • H2O

~ 10% filtered H2O left
Active Transport

Primary Active Transport

Transport is coupled directly to an energy source such as the hydrolysis of ATP

• Na\(^+\) Reabsorption
  - Basolateral membranes of tubular cells has extensive Na-K-ATPase
  → Hydolyses ATP & uses energy to transport Na\(^+\) out of cell into interstitium & K\(^-\) from interstitium to inside cell
  → Low intracellular vs tubular [Na\(^+\)] 12 vs 140mEq/L
  → net negative charge
  ⇒ PASSIVE diffusion of Na\(^+\) into cell by carrier-mediated facilitated diffusion
Extracellular fluid composition and volume are maintained within narrow limits

- Changes in ECF volume are sensed mainly through three receptors
Osmoreceptors and the neuro-secretion of ADH

Paraventricular nucleus

Supraoptic nucleus

Hering bodies

Optic chiasm

Posterior pituitary
Peripheral Volume Receptors

- **Baroreceptors**
  - Aortic arch
  - Carotid artery

- **Stretch receptors**
  - atrium
  - ventricles
  - pulmonary vessels
Renal Baroreceptor
Renal mechanisms controlling salt & water output

- Autoregulation
  - myogenic mechanism
  - tubulo-glomerular feedback (TGF)
- Local factors
  - nitric oxide
  - prostaglandins
  - endothelin
- Sympathetic nerves
  - arterioles
  - proximal tubule
- Hormones
  - Angiotensin II (Ang II)
  - Aldosterone
  - Antidiuretic hormone (ADH)
  - Atrial natriuretic Hormone (ANP)
The amount of sodium and water excreted by the kidney’s is the result of two processes:

- Glomerular Filtration
- Tubular Reabsorption

\[ \text{SODIUM EXCRETION} = \text{sodium filtered} - \text{sodium reabsorbed} \]
Filtration and reabsorption are controlled by neural, physical and humoral mechanisms

- **Integrated response**
  - Short term responses (seconds)
  - Medium term responses (minutes)
  - Long term responses (days)
NEURAL - Increased renal sympathetic nerve activity decreases sodium and water excretion

- Stimulates renin secretion via direct action on the $\beta_1$-receptors on the renin granular cells.

- Stimulates sodium reabsorption via a direct action on the proximal tubular cells.

- Stimulates afferent and efferent arteriole constriction.
**PHYSICAL** - Arterial pressure is one of the primary inputs acting directly on the kidneys to control sodium and water reabsorption.

- An increase in renal arterial pressure causes a rapid and marked increase in sodium and water excretion this is known as **PRESSURE NATRIURESIS/DIURESIS**. (Remember that RBF and GFR are autoregulated).
Hormonal Responses

- **Circulatory**
  (Ang II, ADH, Aldosterone, ANP)

- **Paracrine**
  (Ang II, nitric oxide, endothelin, bradykinin, prostaglandins)

- **Autocrine**
  Ang II, nitric oxide
Renin-angiotensin-aldosterone system:
Renin is the enzyme responsible for the formation of angiotensin II

- **Renin** is synthesised, stored and released by the granular cells of the afferent arteriole
- Renin release is stimulated by
  - Intrarenal baroreceptors
  - Macula densa
  - Renal sympathetic nerves
- A negative feedback system
Renin-angiotensin-aldosterone system:

Angiotensin II acts at many sites.

Activation of this system results in decreased sodium and water excretion

• Extrarenal actions
  - vasoconstriction
  - stimulates thirst
  - stimulates ADH
  - stimulates aldosterone
Renin-angiotensin-aldosterone system: Activation of this system results in decreased sodium & water excretion.

• Intrarenal actions
Atrial natriuretic peptide (ANP)
Activation of this system results in increased sodium & water excretion.

- Cells of the cardiac atria secrete ANP.
- Acts directly on the collecting ducts to inhibit sodium reabsorption.
- Indirectly, inhibits sodium reabsorption by inhibiting the secretion of renin and aldosterone.
- Dilating the afferent and constricting the efferent arteriole. Increasing GFR and the filtered load of sodium.
Aldosterone is the single most important controller of sodium reabsorption.
Activation of this system results in decreased sodium & water excretion.

- **Aldosterone**: produced by the adrenal cortex, stimulates sodium reabsorption in the collecting ducts.
  - The total quantity of sodium reabsorption dependent on aldosterone is 2% of the filtered load.
  - **Not much??** This equates to approximately 500 mmol/day or a maximum of 30g NaCl per day.
  - Therefore, sodium reabsorption can be very finely controlled.

- **Aldosterone is stimulated by**:
  - plasma potassium levels
  - **angiotensin II**
  - inhibited by ANP
ADH makes cells of late distal tubule and collecting duct water permeable

- Anti-diuretic hormone (ADH) is also known as vasopressin.
- Released in response to increased plasma osmolarity and decreased blood pressure (volume).
- ADH causes the insertion of aquaporins (water channels) into the luminal membrane.
- Low plasma ADH levels, large volume of urine is excreted (diuresis), and the urine is dilute.
- High plasma ADH levels, small volume of urine is excreted (antidiuresis), and the urine is concentrated.
The Basic Components of Cardiovascular Control

- Arterial Pressure
- Cardiac Output
- Cardiac Filling
- Blood Volume
- Autonomic Nerves and Hormones
- Total Peripheral Resistance
- Kidney
- Salt and Fluid Output
- Salt and Fluid Intake
**Na⁺ intake ↓**

- More Na⁺ excreted than eaten; ↓ ECF Na⁺ content
- ECF osmolarity ↓
- Osmoreceptor-ADH-system returns osmolarity to normal by ↑ water excretion

**ECF volume ↓**

- VR ↓ and so BP ↓

**Atrial stretch receptors**
- ↓ ANP in blood
- ↓ GFR

**Renal baroreceptors**
- ↑ renin production
- ↑ angiotensin II
- ↑ aldosterone
- ↑ Na⁺ reabsorption in the kidney
- ↓ excretion of Na⁺

**Arterial baroreceptors**
- ↑ sympathetic output
- ↓ GFR

- ↑ thirst
- ↑ intake of water
Kidney Failure

- There are more nephrons in each kidney than needed to sustain life.
- So kidney disease may not become apparent until there has been substantial loss of renal function.
- Therefore slowly progressing renal disease can be asymptomatic in the early stages.
Renal failure (GFR $= 25 \text{ ml/min}$)

- GFR normally $\sim 125 \text{ ml/min}$.
- Patients with $1/4$ normal GFR are basically symptom free.
- The kidneys have a large functional capacity that is not normally tested.
Why does renal failure go undetected until too late?

- GFR decreased, but increased SNGFR in functioning glomeruli

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>75% loss of nephrons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of nephrons</td>
<td>2,000,000</td>
<td>500,000</td>
</tr>
<tr>
<td>Total GFR (ml/min)</td>
<td>125</td>
<td>40</td>
</tr>
<tr>
<td>SNGFR (nl/min)</td>
<td>62.5</td>
<td>80</td>
</tr>
<tr>
<td>Volume excreted for all nephrons (ml/min)</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Volume excreted per nephron (nl/min)</td>
<td>.75</td>
<td>3.0</td>
</tr>
</tbody>
</table>
Renal Failure

- Acute renal failure (ARF)
- Chronic renal failure (CRF)
- End-stage renal disease (ESRD)
Acute renal failure

• **Acute renal failure (ARF) is a very serious condition**
  - 1 in 1058 people will develop ARF during their lives
  - 50% will die within 3 months

• **The majority of cases develop in Hospital**
  - fluid depletion, sepsis or drug toxicity

• **Prompt treatment can completely restore kidney function**
  - including surgery, transfusion, dialysis, antibiotics
Bob

- 52 years old
- Overweight
- tired
- hungry & thirsty
- frequent urination
- weight loss
- nausea
- loss of appetite
- blurred vision
- oedema
- tingling sensation
- decreased urine
DIABETES:

Complications:
- retinopathy
- nephropathy
- neuropathy
- peripheral artery disease
- anaemia
- fluid & electrolyte disturbance
Bob

- **CLINIC**
- Urinary analysis
  - protienuria
  - glucosuria
- Blood analysis
  - increased BUN
  - Increased Pcr
- Increased BP
Bob - Diabetic Nephropathy
Type II Diabetes or non-insulin dependent diabetes mellitus (NIDDM)

• Treatment
  - insulin therapy
  - control BP (drugs)
  - control proteinuria (diet)

• Prognosis
  - progression of disease can be slowed if BP and Proteinuria can be controlled
  - insulin (feast & famine)
Diabetes Type I (IDDM) - 5%

Diabetes Type II (NIDDM) - 90%
Type II DIABETES:

More likely to develop in people:
• over 40
• obese
• sedentary
• family history
• Aborigine, African American, Hispanic American
Clinical course of diabetes:

<table>
<thead>
<tr>
<th>Time (Years)</th>
<th>GFR (mL/min)</th>
<th>Proteinuria (mg/24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>150</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>5000</td>
</tr>
</tbody>
</table>

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Diabetes:

- 6% of Australians have Type II diabetes
- 50% are undiagnosed
- Diabetes costs over $1 billion/year
End-stage renal failure

• How do you get here?

I’VE GOT LOTS OF GLOMERULI!!
Rate of progression of renal failure

Primary kidney disease

↓ nephron number

Glomerular sclerosis

↑ Glomerular pressure and filtration

Hypertrophy & vasodilation of surviving nephrons

↑ Arterial pressure
End-stage renal disease (ESRD)

The unrelenting loss of nephrons leads to end-stage renal failure

Common causes of ESRD

- Diabetes 40%
- Hypertension 25%
- Glomerulonephritis 15%
- Polycystic kidney disease 4%
- Pyelonephritis 4%
Transplantation

• Long waiting lists
  - increasing waiting lists
  - donated kidneys decreasing

• Success of transplant
  - 5 years    73%
  - 10 years   21%
  - 20 years   4%