Objectives

By the end of the chapter you should be able to:

• Describe the location and composition of the kidneys
• Summarize the main functions of the kidney
• Name the different fluid compartments within the body, stating their relative proportions and values
• Distinguish between osmolarity and osmolality, defining the units of measurement for each
• Explain how the following influence the distribution of ions across a semi-permeable membrane:
  • Concentration gradient
  • Electrical gradient
  • Proteins
• Understand the role of the lymphatic system in fluid movement
• Describe the routes by which water and ions enter and leave the body, giving the relevant values
• Outline the difference between the two methods used in the dilution principle
• Discuss why it is important to use high-molecular-weight plasma proteins when measuring plasma volume
• Explain why interstitial fluid must be measured indirectly.

OVERVIEW OF THE KIDNEY AND URINARY TRACT

Structural organization of the kidney and urinary tract

The kidneys lie in the retroperitoneum on the posterior abdominal wall on either side of the vertebral column (T11–L3). The right kidney is displaced by the liver, so it is 12 mm lower than the left kidney. The adult kidney is approximately 11 cm long and 6 cm wide, with a mass of 140 g. Each kidney is composed of two main regions:

• An outer dark brown cortex
• An inner pale medulla and renal pelvis.

The renal pelvis contains the major renal blood vessels and the origins of the ureter. Each kidney consists of 1 million nephrons, which span the cortex and medulla and are bound together by connective tissue containing blood vessels, nerves and lymphatics.

The kidneys form the upper part of the urinary tract. The urine produced by the kidneys is transported to the bladder by two ureters. The lower urinary tract consists of the bladder and the urethra.

Approximately 1–1.5 L of urine is produced by the kidneys each day – the volume and osmolality vary according to fluid intake and fluid loss.

The urinary tract epithelium is impermeable to water and solutes unlike the nephrons in the kidney, so the composition of urine is not altered as it is transported to the bladder. The bladder contents are emptied via the urethra, expulsion from the body being controlled by an external sphincter. Both the upper and the lower urinary tracts are innervated by the autonomic nervous system.
Basic principles

Figure 1.1 shows the anatomy of the kidneys and urinary tract.

Functions of the kidney and the urinary tract

1. **Excretion**: of waste products and drugs – this involves selective reabsorption and excretion of substances as they pass through the nephron.
2. **Regulation**: of body fluid volume and ionic composition. The kidneys have a major role in homeostasis (the maintenance of a constant internal environment) and are also involved in maintaining the acid–base balance.
3. **Endocrine**: the kidneys are involved in the synthesis of renin (which generates angiotensin I from angiotensinogen, and thus has a role in blood pressure and sodium balance), erythropoietin (which controls erythrocyte production) and prostaglandins (involved in vasodilation).
4. **Metabolism**: Vitamin D is metabolized to its active form. The kidney is a major site for the catabolism of low-molecular-weight proteins including several hormones such as insulin, parathyroid hormone and calcitonin.

**FLUID COMPARTMENTS OF THE BODY**

**Body fluids**

Body fluids are divided into:

- Intracellular fluid (ICF), the fluid within cells
- Extracellular fluid (ECF).

ECF is divided into:

- Plasma – ECF within the vascular system, i.e. the non-cellular component of blood.
- Interstitial fluid (ISF) – ECF outside the vascular system (and separated from plasma by the capillary endothelium).
- Transcellular fluid (TCF) – ECF (e.g. synovial fluid, aqueous and vitreous humour,
Osmolarity versus osmolality

Osmolarity is the molar concentration of solute particles per litre of solution (mOsmol/L). Osmolality is the molar concentration of solute particles per kilogram of solvent (water) (mOsmol/kg H₂O). Figure 1.3 illustrates the differences between osmolality and osmolarity.

- Normal body fluid osmolality is between 285 and 295 mOsmol/kg H₂O.
- Urine osmolality may vary between 60 and 1400 mOsmol/kg H₂O.

Plasma osmolality can be calculated from sodium ion (Na⁺⁺), potassium ion (K⁺⁺), urea, and glucose concentrations using the formula:

\[
\text{Plasma osmolality} = 2(\text{Na}^{++} + \text{K}^{++}) + \text{urea} + \text{glucose}
\]

Isotonicity and isosmoticity

Changes in the extracellular osmolality can cause cells to shrink or swell because water will move across the plasma membrane by osmosis into or out of the cells to maintain equilibrium. Therefore, an important function of the kidneys is to regulate the excretion of water in the urine so that the osmolality of the ECF remains nearly constant despite wide variations in intake or extrarenal losses of salt and water. This prevents damage to the cells from excess swelling and shrinkage:

- If cells are placed in a solution over 295 mOsmol (hypertonic solution), they shrink as water moves out into the solution.

Water is a major component of the human body. Approximately 63% of an adult male and 52% of an adult female is water (i.e. 45 L in a 70 kg male, 36 L in a 70 kg female). This difference is due to the fact that females have a higher proportion of body fat, which has a low water content. One-third of total body water (TBW) is ECF (about 15 L in a 70 kg male) and two-thirds is ICF (about 30 L in a 70 kg male).

Osmolarity and osmolality

Basic concepts

Osmosis is the net passage of a solvent through a semi-permeable membrane from a less concentrated solution to a more concentrated solution. This occurs until both solutions reach the same concentration (equilibrium). The osmotic effect can be measured as an osmotic pressure. This is the pressure at which water is drawn into a solution across a semi-permeable membrane. Thus, the more concentrated the solution (i.e. the higher the solute content), the greater the osmotic pressure. Hydrostatic pressure is the pressure needed to be applied to the region containing the solute to prevent the net entry of water.

Osmolarity is the total solute concentration of a solution – the number of osmotically active particles in solution. The higher the osmolarity, the lower the water concentration.

1 Osmole (Osmol) = 1 mole of solute particles.
Basic principles

Fig. 1.3 Osmolarity can be described as 1 mole of glucose added to water, and dissolved to make up to 1 L. Osmolarity is the addition of 1 L of water to one mole of glucose (adapted from Lote CJ 2000 Principles of renal physiology, 4th edn. Kluwer Academic Publishers, p 4–5).

- If cells are placed in a solution of 285–295 mOsmol/kg H₂O (isotonic solution, i.e. 0.9% saline), there is no net movement of water by osmosis and no swelling or shrinkage. This is because an isotonic solution has the same osmolarity as normal body fluid.
- If cells are placed in a solution less than 285 mOsmol (hypotonic solution), they swell as water enters from the solution.

Figure 1.4 shows the changes in the cells brought about by hypertonic, isotonic and hypotonic solutions.

**Diffusion of ions across biological membranes**

Passive transport

Biological membranes (e.g. cell membranes) are selectively permeable, allowing only small molecules and ions to diffuse through them. The concentration gradient and electrical gradient influence the movement of these molecules into or out of cells.

The rate of diffusion of different molecules depends upon their shape, size, weight and electrical charge. When solutions either side of a membrane contain diffusible ions only, ions move passively from an area of high ionic concentration down the electrical gradient to an area of lower ionic concentration. This occurs until equilibrium is reached, when the ion distribution on either side of the membrane will be as follows:

- **Isosmoticity**: this refers to solutions with the same solution concentration per kilogram water (e.g. 0.9% saline and 5% dextrose).
- **Isotonicity**: this refers to solutions that do not cause any change in cell volume (e.g. 285–295 mOsmol/L of non-permeable solute).

Thus, different isotonic solutions are isosmotic, but solutions that are isosmotic to plasma are not necessarily isotonic.
Active transport

Na⁺ permeability is 1/50th K⁺ permeability. The primary active transport mechanism uses energy in the form of adenosine triphosphate (ATP) to actively pump Na⁺ out of and K⁺ into the cells against a concentration gradient. Three Na⁺ ions are exchanged for every two K⁺ ions. This sodium pump is composed of several proteins and lies within the cell membrane of all cells. Cl⁻ ions diffuse passively out of the cell across the cell membrane because there is an overall negative charge within the cell. This leads to a higher concentration of Cl⁻ ions outside the cells.

According to the Gibbs–Donnan effect, there should be more ions inside the cell than outside because of the effects of anionic proteins. This is balanced in biological systems by the sodium pump as Na⁺ is effectively non-diffusible.

The Gibbs–Donnan effect

Proteins are negatively charged molecules, which are so large that they cannot diffuse across membranes. Thus, if proteins are present on one side of the membrane (side A), they act as anions and attract positive ions (cations) from side B. Cations diffuse across the membrane to the more negative side A, and thus maintain electrical neutrality. As a result, side A will not only contain non-diffusible proteins, but also the cations from side B – and therefore will have a greater number of total ions. Consequently, the osmotic pressure on side A will be greater. This encourages the entry of water, unless the osmotic pressure difference is counterbalanced by hydrostatic pressure on side B (Fig. 1.5).

Cell membranes are permeable to:

- Potassium ions (K⁺)
- Chloride ions (Cl⁻)
- Sodium ions (Na⁺).

Side A (diffusible cations × diffusible anions) = Side B (diffusible cations × diffusible anions)

Fig. 1.4 Cell changes induced by hypotonic, isotonic and hypertonic solutions.

Cell membranes are permeable to:

- Potassium ions (K⁺)
- Chloride ions (Cl⁻)
- Sodium ions (Na⁺).
Basic principles

Fluid movement between body compartments

At any one moment, body fluid compartments have a relatively constant yet dynamic composition. Equilibrium is maintained by the continual transfer of fluid between the different compartments.

Exchange between ECF and ICF

Water diffuses freely across cell membranes so that equilibrium is reached between the ICF and ECF. Any change in the ionic concentration of the ICF or ECF is followed by the movement of water between these compartments.

- Na⁺ is the most important extracellular osmotically active ion
- K⁺ is the most important intracellular osmotically active ion.

Exchange between plasma and ISF

The capillary endothelium separates plasma (within the circulatory system) from the ISF (outside the circulatory system). Water and ions move between these two compartments – 90% of ions by simple diffusion and 10% by filtration.

Ion filtration between plasma and ISF relies on:

- The arterial end of the capillary, which has a hydrostatic pressure of 32 mmHg, forcing fluid out of the capillary plasma into the ISF.
- Proteins that are too large to cross the capillary endothelial cells, and therefore remain in the plasma, creating a colloid osmotic (or oncotic) pressure (25 mmHg).
- The venous end of the capillary having an osmotic pressure of 25 mmHg. This is greater than the hydrostatic pressure (12 mmHg), causing fluid to move out of the ISF and re-enter the capillary plasma.

It is very important that water and ions (salt) are kept in balance within the body. Dehydration (loss of water from body tissues) will disrupt these mechanisms. There are three types of dehydration:

- Isosmotic – water loss equals ions loss (diarrhoea, vomiting, burns)
- Hyposmotic – ion loss exceeds water loss (adrenal insufficiency)
- Hyperosmotic – water loss exceeds ion loss (diabetes insipidus, diabetes mellitus).

Fig. 1.5 The Gibbs–Donnan effect. +, diffusible cation; –, diffusible anion; P, impermeable molecule (e.g. protein).
Exchange between interstitial fluid and lymphatic vessels

Plasma proteins and fluid lost from the vascular system are filtered into the ISF and taken up by the lymphatic system. The lymphatic system is composed of a network of lymphatic capillaries in all organs and tissues, which eventually drain into the venous system via the thoracic duct in the neck. These lymphatic capillaries are very permeable to protein and thus return both the fluid and plasma proteins to the circulatory system.

The movement of fluid across a capillary wall between the plasma and ISF is illustrated in Figure 1.6. Hydrostatic pressure depends upon:

- Arteriole blood pressure
- Arteriole resistance (which determines the extent to which blood pressure is transferred to the capillary)
- Venous blood pressure.

Osmotic pressure (25 mmHg) is produced by plasma proteins (17 mmHg – oncotic pressure) and the imbalance of ions – there are more ions (e.g. Na⁺) within the capillary than outside. This is due to the presence of negatively charged proteins and the Gibbs–Donnan effect.

Water diffusion is controlled by two forces:

- Hydrostatic pressure (within the vascular system only)
- Osmotic pressure (from plasma proteins).

Albumin is the main plasma protein responsible for maintaining osmotic pressure and plasma volume. Abnormally low levels may result in a loss of oncotic pressure in the blood vessels. This results in the retention of fluid in the ISF, causing swelling of the tissue, a clinical sign called oedema.

The ionic composition of the fluid compartments is shown in Figure 1.7.
Basic principles

**Fluid and ion movement between the body and the external environment**

There is a continuous exchange of body fluids with the external environment, but there must be a balance between intake and output, as body weight is consistent from day to day.

Daily water intake and output are shown in Figure 1.8. Water loss from the lungs varies with the climate (e.g. in very dry climates over 400 mL per day is lost). Insensible losses are those due to evaporation of water from the skin (i.e. not sweat). Sweating (‘sensible perspiration’) is an additional loss, which acts as a homeostatic mechanism to maintain constant body temperature. Urinary loss can be adjusted according to the needs of the body and the water intake. The amount of water lost in defaecation can also vary, and is increased greatly in diarrhoea. Daily water intake can fluctuate considerably and can be altered according to need (i.e. thirst mechanism). Water derived from metabolism is the result of oxidation of food. Despite these variations, the body’s ionic concentration is maintained within the normal range by the kidney’s homeostatic mechanisms, which include control of tubular reabsorption of filtered Na⁺ and to a lesser extent K⁺ – as well as regulating water reabsorption.

Whereas water intake can be controlled, normally, the minimum water loss from urine, lungs, skin and faeces cannot fall below 1200 mL/day. Thus, if there is no water intake, dehydration occurs, eventually resulting in death within a few days.

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**Measuring body fluid compartments**

**Dilution principle**

The dilution principle is used to measure fluid volume if fluids cannot be directly measured or extracted from the container or compartment holding them. This allows measuring in situ. A substance that will mix completely and uniformly in the fluid compartment is used to allow all of the volume present to be measured, e.g. a dye. Allowances must be made for the excretion and metabolism of the selected indicator by the body.

\[
V_D = \frac{(Q_A - Q_M)}{C}
\]

Where \(V_D\) = volume of distribution; \(Q_A\) = quantity administered; \(Q_M\) = quantity metabolized after 10 h; \(C\) = concentration.

Two methods are used:
- Single injection method
- Constant infusion method.

**Single injection method**

This is used for test substances with a slow rate of excretion from the compartment being measured and is carried out as follows:

1. A known amount of test substance is injected intravenously
2. Plasma concentration is determined at intervals
3. A graph (log concentration against time scale) is plotted (Fig. 1.9)
4. The linear portion is extrapolated back to the start (i.e. time 0) – this gives the concentration of substance assuming it had distributed evenly and instantly.

Using this method:

\[
\text{Compartment volume} = \frac{\text{Amount injected}}{\text{Concentration at zero time}}
\]

**Constant infusion method**

This is used for test substances that are excreted rapidly and is carried out as follows:

1. A loading dose of the test substance is injected intravenously
2. The test substance is infused at a rate to match the excretion rate
3. Plasma concentration is measured at intervals
Blood volume: is derived from the kidney plasma volume and the haematocrit (% of red blood cells in total blood volume). For example, if the haematocrit is 45%, the plasma volume is 55% of blood volume (measure plasma volume as above and blood volume = plasma volume $\times \frac{100}{55}$).

Normal blood volume = 5 L.

Red cell volume: can be derived from plasma volume and haematocrit or measured by direct dilution, using radiolabelled red blood cells.

Measurement of extracellular fluid

As ECF is made up of several compartments (plasma, ISF and TCF), it is difficult to measure accurately. A substance that will diffuse quickly across the endothelial barriers into the ISF, but not into the cells, is required. Substances used include:

- Inulin (can be excluded from bone and cartilage)
- Mannitol
- Thiosulphate (most commonly used)
- Radiosulphate
- Thiocyanate
- Radiochloride or radiosodium (these substances cannot be completely excluded from cells).

Measurement of plasma volume, red cell volume and blood volume

Plasma volume, blood volume and red cell volume are measured as follows:

- **Plasma volume**: is measured using the dilution principle. The test substance needs to remain within the vascular system (e.g. high-molecular-weight substance). Radio-iodinated human serum albumin and Evans Blue dye are commonly used.

  Normal plasma volume = 3 L.

- **Blood volume**: is derived from the kidney plasma volume and the haematocrit (% of red blood cells in total blood volume). For example, if the haematocrit is 45%, the plasma volume is 55% of blood volume (measure plasma volume as above and blood volume = plasma volume $\times \frac{100}{55}$).

  Normal blood volume = 5 L.

4. When the substance comes to equilibrium, the plasma concentration is constant (Fig. 1.10).

5. The infusion is stopped and urine collected until all the test substance has been excreted. Using this method:

   Amount excreted = Amount present in the body at the time the infusion was stopped

   and:

   $\text{Compartment volume (L)} = \frac{\text{Amount excreted (mg)}}{\text{Plasma concentration (mg/L)}}$

   - $C = \text{plasma concentration at time 0}$
   - $X = \text{plasma concentration of injected substance}$
   - $C = \text{plasma concentration at time 0}$
   - $X = \text{plasma concentration of infused substance}$
   - $C = \text{plasma concentration at time 0}$
   - $X = \text{plasma concentration of infused substance}$

   Fig. 1.9 The dilution principle: single injection method, showing the plasma concentration of an injected substance.

   Fig. 1.10 The dilution principle: constant infusion method, showing the plasma concentration of an infused substance.
A known amount of the selected indicator is injected intravenously and the ECF volume is calculated using the dilution principle. It is difficult to measure the TCF because it is separated from the capillaries by another membrane in addition to the capillary membrane.

Normal ECF volume = 15 L.

Measurement of interstitial fluid
The ISF cannot be measured directly, and it is calculated using the following equation:

ISF (12 L) = ECF (15 L) – plasma volume (3 L)

Measurement of total body water
Isotopes of water are used as markers (deuterium oxide or tritiated water) to measure TBW. The normal value in a 70 kg man is 63% (i.e. 45 L) and in a 70 kg woman, 52% (36 L), being lower in women because of their greater proportion of body fat.

Measurement of transcellular fluid
As this compartment is separated from the rest of the ECF by a membrane, the substances used to measure the ECF do not cross into this compartment. Thus TCF is included in the TBW, but excluded from the ECF:

TBW = ECF + ICF + TCF

There is a large turnover – about 20 L/day in the gastrointestinal tract. Figure 1.11 summarizes the methods used to measure the different fluid volumes.

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<th>Summary of fluid volume measurements in a 70 kg individual</th>
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<tr>
<td>Fluid volume</td>
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<tr>
<td>plasma volume</td>
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<tr>
<td>blood volume</td>
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<tr>
<td>red cell volume</td>
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<td>TCF = TBW – ECF – ICF</td>
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<tr>
<td>extracellular fluid (ECF)</td>
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<td>intracellular fluid</td>
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<tr>
<td>interstitial fluid (ISF)</td>
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<tr>
<td>total body water (TBW)</td>
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<td>transcellular fluid (TCF)</td>
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Fig. 1.11 Summary of fluid compartments and their measurement in an individual weighing 70 kg.