Book 1

Clinical Chemistry of the Kidney and Renal Associated Physiology

Written Material for CHM 651/751, Clinical Chemistry I

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Chapter 1
Kidney Anatomy and Function

1A. Overview of the functions of the kidney

a) Regulation of H₂O balance

b) Regulation of electrolyte balance

c) Endocrine function and actions
   1') Prostaglandins are produced by the kidney and act on the kidney
   2') Renin - Angiotensin

d) Elimination of waste products
   1') Metabolic (urea, NH₃, creatinine)
   2') Toxins

e) Regulation of red blood cell production - Erythropoietin [a glycoprotein hormone secreted chiefly by the kidneys, which acts on the stem cell of bone marrow to stimulate red blood cell production (Ref 16)]

f) Bone Growth
   1') Excretion of Ca²⁺, PO₄³⁻
   2') Vitamin D regulation

g) Acid-base regulation

1B. The kidney is part of the urinary system that consists of (Ref. 1, p. 538) (see Figure 1):

a) 2 kidneys

b) 2 ureters

c) 1 bladder

d) 1 urethra

Urine is formed in the kidneys, collected in the bladder via the ureters and released from the bladder into the urethra. Ureters are tubes that are 25-30 cm in length and 4-5 mm in diameter (Ref. 4, p. 507). There are three layers: a fibrous outer, a muscular middle, and a mucous inner layer. Urine does not run down the ureter by gravity alone. The urine is also forced down the passage by peristaltic waves of contraction (Ref. 2, p. 179). The bladder is a "collapsible bag" that can contain up to 500 mL of urine (Ref. 2, p. 179). Bladder activity is controlled by the parasympathetic nervous system (Ref 4, p. 507)
1C. (See Figure 1) The "cap" on top of the kidney is the adrenal gland. Notice that the right kidney is lower than the left, presumably because the liver takes up space above the right kidney (Ref. 1, pp. 539-40).

2. The kidney resembles a big lima bean - average size 11.25 cm long x 5-7.5 cm wide x 2.5 cm deep (Ref. 1, p. 538).

3. The kidneys are located on the posterior wall of the abdominal cavity, one on each side of the vertebral column (Ref. 3, p. 707), just above the waistline. The figure below (Figure 2) shows location on the posterior side, one kidney on each side of the vertebral column (Ref. 3, p. 708).
4. (See Figure 2) A heavy cushion of fat surrounds the kidney (adipose capsule) (Ref. 3, p. 708) and connective tissue (renal fascia) hold the kidneys in place (Ref. 1, p. 540). Encasing the kidney is a smooth transparent fibrous membrane called the renal capsule (Ref. 3, p. 708) (Ref. 4, p. 495).

Ref. 5, p. 393

5. A logical approach to a discussion of the anatomy of the kidneys is to describe it from the point of view of function. So let’s summarize the function of the kidneys. There are two basic functions:

   a) To excrete end-products of body metabolism

   b) To control concentrations of most constituents in body fluids. This includes:

      1') acid-base homeostasis (i.e., hydrogen ion concentration)
      2') electrolyte concentration
      3') water volume

6. To perform this function blood must be directed through the kidneys. In a gross over simplification (Figure 3) the kidney has been likened to a filter - in which the end-products of metabolism are filtered by the kidney - with the end-products of metabolism passing through the kidney filter (to be removed from the body in the urine), while all the other components are not filtered.
7. This is a poor description of how the kidney actually operates. In actuality there are three processes going on: filtration, reabsorption, and secretion (see Figure 4).
Thus, end-products of metabolism are not reabsorbed to any large extent and exit the body through the urine. All other components such as water, electrolytes, and other small molecules are reabsorbed. This reabsorption process is the key to the kidney’s ability to control the concentration of constituents in the body. The amount reabsorbed increases or decreases to increase or decrease the amount of constituent in the body, respectively.

**Figure 5 (Ref. 4, p. 494)**

8. Let's see how function is translated into anatomy (see Figure 5).
   a) One-fifth of the cardiac output is directed through the kidneys (can vary between as low as 12 percent to as high as 30 percent of the output). The flow rate of blood through the kidney is 1200 mL/min (Ref. 5, p. 395).
   b) Blood enters kidney from renal artery which comes off the abdominal aorta. Blood leaves the kidney (with the constituent concentration adjusted and a portion of the end-products of metabolism removed) through the renal vein, which empties into the inferior vena cava.
Urine comes out of the kidney through the ureter.

9. Gross anatomy of kidney (see Figure 6)
   The kidney tissue parenchyma (parenchyma is defined as the fundamental cells of a tissue, as distinguished from supportive or connecting tissue cells) consists of two types:
   a) **Medulla** - in the inner portion of the kidney (Ref. 1, p. 541), has the shape of a cone, has a darker color than the cortex, and has a striated appearance (Ref. 6, p. 5). Each cone is called a renal pyramid (Ref. 3, p. 709). There are 8-18 renal pyramids in the kidney (Ref. 6, p. 5). The medulla contains the loop of Henle and collecting duct structures (Ref. 2, p. 173).
   b) **Cortex** - on the outer portion of the kidney and in between the renal pyramids, has a brownish-pink color (Ref. 6, p. 5) and is granular in appearance (Ref. 2, p. 172). Seventy-five percent of kidney tissue is cortex (Ref. 13, p. 37). In general, the cortex contains glomeruli, proximal tubules, and distal convoluted tubules (Ref. 2, p. 173).
   It should be noted that the terms medulla and cortex are not unique terms to the kidney, but are general terms for the inner and outer layer of an organ or other structure, respectively (Ref. 16).

![Figure 6 (Ref. 6, p. 5)](image)

10. Let's work backwards from the ureter (Ref. 2, p. 172) (see Figure 6)
   a) The upper portion of the ureter expands into the renal pelvis.
   b) The renal pelvis is composed of three funnel-shaped ducts called major calyces (plural of calyx).
c) Each major calyx receives 2 to 3 smaller ducts known as minor calyces. There are 7-14 minor calyces (Ref. 7, p. 426).

11. Urine drains into the minor calyces from the medulla. Each minor calyx receives urine from one or more renal pyramids (Ref. 6, p. 5).

12. Other notes:
   a) The apex of the pyramid is called the papilla, which fits into one of the minor calyces (Ref. 7, p. 427). There are 10-25 minute openings in the papilla through which urine enters into the minor calyx (Ref. 8, p. 510).
   b) The cortex arches over the renal pyramids (called cortical arches) (Ref. 6, p. 5) and dips in between adjacent pyramids (called renal columns) (Ref. 8, p. 511).

13. Vasculature (See Figure 7)
   The renal artery comes from the abdominal aorta and divides into five segmental arteries (Ref. 6, p. 16). These segmental arteries divide again and eventually supply the interlobar arteries which ascend between the medullary pyramids (area known as the renal columns) (Ref. 6, p. 16). At level of corticomедullary junction, the interlobar arteries “arch” over the base of renal pyramid; hence the name arcuate (because an arc is formed over the renal pyramids) (Ref. 8, p. 516). The arcuate arteries terminally branch into interlobular arteries which extend into the cortex, to the surface of the kidney (Ref. 6, p. 16).

![Figure 7 (Ref. 6, p. 16)](image)

14. (See Figure 8). From the interlobular branch arises afferent arteriole which goes into the glomerulus.
15. It is in the glomerulus that process of filtration takes place. The glomerulus is a tuft of capillaries as shown in Figure 8 (Ref. 9, p. 511). A portion of the blood plasma (which is the fluid portion of the blood) is filtered into the tubular system, the rest exits through the efferent artery. Water and small molecules will pass through capillary walls into the tubular structure shown in Figure 8. Not all of the components of blood pass into the tubular network. Large molecules, such as proteins, will not be able to. Not all of the liquid and small molecules pass through the capillary walls of glomerulus into the tubular system. Only 20% of the water volume is filtered, with most of the blood volume exiting through the efferent arteriole.

This process is shown schematically in Figure 9. The filtrate has essentially the same composition as plasma except for one significant difference, there is no significant amount of large proteins in the filtrate (Ref. 5, 6th edition, p. 408). [Note: small proteins are filtered but do not appear in the urine because 100% of these small proteins are reabsorbed by the tubular system at the normal concentrations that these small proteins are at in the plasma.]
Figure 9 (ref. 6, p. 39)

16. Definition of terms
   a) Glomerulus - capillaries
   b) Bowman's capsule - cup-like structure that receives filtrate (Ref. 3, p. 709)
   c) The glomerulus and Bowman's capsule together is referred to as the renal corpuscle. (Ref. 3, p. 710).

17A. The glomerular membrane is shown in Figure 10 and 11.
17B. The glomerular membrane consists of three layers:

a) Capillary endothelial cells are present as sheets on the inside of the capillary wall and are perforated by thousands of small holes called fenestrae (Latin for window - Dorland's Dictionary). The fenestrae are 500 - 1000 Å in diameter (Ref. 5, p. 397; Ref. 9, p. 8).
b) Basement membrane. Composed mainly of a meshwork of proteoglycan fibrillae, collagen and glycoproteins, that have large spaces through which fluid can filter (Ref. 10, p. 12). Proteoglycan fibrillae consist of chains of heteropolysaccharide attached to a protein core (looks like a brush with bristles).

Ref. 10

c) Epithelial cells called podocytes (Dorland's Dictionary - podocyte is Greek: podos meaning foot; cyte comes from kytos meaning hollow vessel). Podocytes protrude into branches, which further branch into small-club shaped processes called pedicels (also called foot processes). These interdigitate with other pedicels from adjacent podocyte cells. There are narrow slits between pedicels called slit pores (Ref. 5, p. 397) which are 250 to 400 A in width (Ref. 9, p. 12). This is bridged by a layer 40-60 A thick (less than the thickness of a cell membrane) of a material of unknown composition called a filtration-slit membrane. Staggered rod-like units project from the podocyte and connect to a centrally linear bar - delineating rectangular pores 40-140 A within the slit membrane. This is approximately the size of an albumin molecule. This layer (filtration-slit membrane) provides the greatest barrier to molecules passing through the glomerulus, on the basis of size exclusion (Ref. 10, p. 14).

Ref. 5, p. 398

18. Permeability of various substances through glomerular membrane (Table I).

Table I (Ref. 5, p. 398)
Permeability of various substances through the glomerular membrane

<table>
<thead>
<tr>
<th>Molecular Weight</th>
<th>Permeability</th>
<th>Example Substance</th>
</tr>
</thead>
<tbody>
<tr>
<td>5200</td>
<td>1.00</td>
<td>Inulin</td>
</tr>
<tr>
<td>30,000</td>
<td>0.5</td>
<td>Very small protein</td>
</tr>
<tr>
<td>69,000</td>
<td>0.005</td>
<td>Albumin</td>
</tr>
</tbody>
</table>

a) Inulin is a polymer of fructofuranose - a vegetable starch having the formula \((C_{12}H_{22}O_{11})_4\).

b) Permeability is a ratio of the concentration of the dissolved substance in the filtrate to the concentration of the substance in the plasma. The glomerular membrane is completely impermeable to most all plasma proteins and is highly permeable to essentially all small-sized dissolved substances.
19. a) There are two factors which affect permeability characteristics of a compound through the glomerular membrane. One factor affecting permeability is the size of the molecule. Permeability goes down as you increase the size of the molecule. Pores in membrane are large enough to allow passage of molecules up to diameter 80 A. Albumin has diameter 60 A - yet it is excluded. This is explained by invoking the second factor influencing permeability, electrostatic effects. The glomerular pores are lined with glycoproteins which have negative charge, due to sialoproteins and heparin sulfate present in the glomerular capillary pores (Ref. 12, p. 58). Plasma proteins have negative charge and are thus repelled by electrostatic repulsion.

b) Small solutes are transported across glomerular capillaries by the process of convection. There are no concentration gradients. The filtered load of materials is strictly proportional to the glomerular filtration rate (GFR) and determined only by forces affecting fluid filtration (Ref. 12, p. 57).

20. Review and overview:

a) Blood enters glomerulus from arterial system - filters at the glomerulus, with the filtrate proceeding through the tubular system. Twenty percent of the plasma is filtered into Bowman's capsule; 80% of the plasma continues through to the efferent arteriole.

b) Fluid from tubular system enters the collecting ducts which traverses the medulla to the papilla. Fluid then exits the kidney as urine through the calyces, through the renal pelvis, through the ureter to the bladder.

c) The major purpose of tortuous tubular system between the glomerulus and the collecting ducts is to reabsorb necessary components. Think what would happen if reabsorption did not occur and the filtrate passed direction into the ureter (Ref. 5, p. 398). The average plasma flow into both kidneys is 650 ml/min, with the average filtration fraction being 19%. On an average, a person forms filtrate at 125 ml/min (this is for both kidneys). If there was no reabsorption constant replenishing of fluid and electrolytes would be necessary. How would you like to drink 1 L every 10 minutes? As it is, 99% of the filtrate is reabsorbed from the tubules back into the blood vessels.

d) There is another process performed by the tubules. Secretion of a substance from the blood after it has passed through the glomerulus into the tubules (Ref. 5, p. 41).

21. The structure of the renal corpuscle and the tubular system up to and including the collecting tubules is called the nephron (Ref. 4, p. 496, Ref. 16).

22. The tubular system of the nephron consists of different tubular sections (see Figure 12).

a) Proximal tubule (Ref. 15, pp. 51-52).

This is the first section of the tubule system. The proximal tube is subdivided into a proximal convoluted section (which is further subdivided into an early and late segment) and a proximal straight segment. The convoluted section is named because the tubules are looped, while the straight segment is straight (or is slightly spiraled).
b) **Loop of Henle**  
Consists of:  
1') **Thin Limb of Loop of Henle**  
a'') Descending portion  
b'') Ascending portion  
2') **Thick Limb of Loop of Henle**  
a''') This segment starts after the ascending limb of the loop and ends at the portion of the tubule system where it passes by the renal corpuscle.  
b''') The point where tube comes in contact with renal corpuscle is very important in the control of filtration rate (Ref. 5, p. 411) as will be discussed later.  
c) **Distal Convoluted Tubule**  
1') Starts at the point where the tubule passes by the renal corpuscle and ends at the connecting segment (Ref. 5, p. 403).  
2') It is high convoluted (Ref. 6, p. 13)  
d) **Connecting Segment**  
1') Ends at the collecting tubule.  
e) **Collecting Tubule**  
1') **Cortical collecting tubule**  
2') **Medullary collecting tubule** - starts at the cortex/medulla interface

**Figure 12 (Ref. 17, p. 32)**

23. Successive collecting ducts coalesce to form progressively larger collecting ducts which penetrate the medulla to the papilla. In each kidney there are 250 of these large collecting ducts which empty into the renal pelvis (Ref. 5, p. 394). These large collecting ducts are called papillary ducts of Bellini (Ref. 6, p. 6) (see Figure 13).
24. The nephron is the functional unit of the kidney. There are 2.5 million nephrons in the two kidneys (Ref. 5, p. 393). Each nephron 3 to 4 cm long and the total length of the nephron tubular system in the kidneys is 75 miles (Ref. 8, p. 511).

Ref. 5, p. 394

25. For the most part nephrons are classified into two categories (see Figure 13).

a) **Cortical nephron** - glomerulus lies close to the kidney surface. These nephrons have very short thin limbs of loop of Henle and penetrate only the outer zone of the medulla. These predominate in man - making up 85% of the nephrons of the kidney (Ref. 14, p. 27).

b) **Juxtamedullary nephron** - glomerulus is still in the cortex, however, long loops of Henle penetrate deep into the inner zone of the medulla, with many reaching all the way to the papilla.

c) Note, there is also a classification of the nephron that has a location of the nephron intermediate to the cortical and juxtamedullary nephrons.

26. Let’s pick up with the vasculature again. Recapping, blood enters the glomerulus from the afferent arteriole, passes though the glomerulus (where part of the fluid passes into the tubular system) and enters the efferent arteriole (see Figure 14).
27. Two different capillary systems arise from the efferent arteriole, depending on the type of nephron. These two are (Ref. 5, p. 394) (see Figure 15):

a) Peritubular Capillary Network (peri is greek, meaning around)

b) Vasa Recta
28. Peritubular Capillary Network

The efferent arteriole of a majority of the glomeruli (except for the juxtamedullary and a small percentage of the intermediate nephrons) divide and form the peritubular network as shown in Figure 15. This capillary system surrounds the proximal and distal convoluted tubules (Ref. 11, p. 1399). The pathway of blood flow is from the peritubular network into the interlobular vein, into the arcuate vein, into the interlobar vein, which ultimately goes into the renal vein (see Figure 16).
29. **Vasa Recta**

   a) The capillary vascular system supplying the medulla is the vasa recta which arises from:

   Ref. 6, p. 19
   Ref. 11, p. 1401

   1') Efferent arterioles of the juxtamedullary glomeruli
   2') Efferent arterioles from intermediate nephrons which supply branches for peritubular capillary networks as well as branches which descend into the medulla.
   3') A glomerular arterioles or shunts (which arise from glomerulus degeneration). Less than 10% of blood going into medulla arise from this route. These exist in healthy people but are not common. They increase in number with age (Ref. 6, p. 19).
b) The efferent arterioles destined for the medulla:
   1') contribute side branches for the capillary network before entering the medulla
   2') each then divides into 12-25 descending vasa recta (Latin - for straight (recta) vessel (vasa)). These pursue straight courses to various depths in the medulla. Gives rise to a radially elongated capillary network having hairpin turns. This capillary system is closely associated with the loop of Henle and the collecting ducts.

30. Figure 17 shows the various capillary networks arising from juxtamedullary nephrons.

31. The pathway of blood after the vasa recta is into the arcuate vein, into the interlobar vein, which ultimately goes into the renal vein (see Figure 16).

32. The vascular and tubular components lead to the appearance of the regions (Ref. 4, p. 496):
   a) Renal corpuscles give granular appearance to the cortex.
   b) Collecting ducts and vasa recta give the striated appearance to the medulla.

33. Anatomical units of the kidney (see Figure 17).

Ref. 2, p. 174
   a) Lobe - is the area between the interlobar arteries, consisting of the renal pyramid and the cortical arch. One human kidney has 12 or more lobes (Ref. 8, p. 511).
   b) Lobule - the area between the interlobular arteries. This part of the kidney contains all the nephrons that drain into the same collecting duct (Ref. 8, p. 511).

Ref. 4, pp. 397-8

34. Kidney regeneration
   a) Only 25% of the total renal mass is necessary for survival.
   b) When one kidney is removed, the opposite undergoes enlargement because of an increased size in the nephron (not increased number).
   c) Nephrons do not regenerate; epithelial cells of renal tubules can however.
Figure 17 (Ref. 2, p. 174)

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References


Chapter 2
Overview of Water in the Body

1. Water is important to the body because (Ref. 1, p. 315):
   a) it is abundant, averaging 60% of body weight (depending on body fat content, running the range from 50% for a fat individual to 70% for a thin individual);
   b) it is the medium in which all metabolic reactions take place.

Ref. 1, p. 315

2. (See Figure 1) To get into a discussion about the regulation of the water content in the body we need to have an appreciation of the location of water in the body. Basically there are two types of water compartments; inside the cell (intracellular water) and outside the cell (extracellular water). A third compartment, which is much smaller, is the transcellular water compartment.

3. Amounts of water in the various compartments (Ref. 1, p. 316)
   a) Intracellular (ICF) - 2/3 of the total body water (28 liters)
   b) Extracellular (ECF) - 1/3 of the total body water
      1') Plasma - 3.5 liters (8% of the total body water)
      2') Interstitial Fluid (ISF) - 10.5 liters (25% of the total body water)

3A. The normal adult has approximately 5 L of blood, with 3 L being plasma and 2 L being red blood cells (Ref. 3, p. 383).
4. Let's look at the pathway by which water moves outside the cells (extracellular water). In an overview, extracellular water flows in the circulatory system, with some of it entering the ISF, which empties into the lymph system, which empties back into the circulatory system.

5. The circulatory system is diagramed in Figures 2 and 3. It consists of the left ventricle of the heart pumping oxygenated blood from the lungs (received by the left atrium of the heart) through the arteries of the body. The blood is then returned through the veins to the right atrium of the heart and then subsequently pumped through the pulmonary (lung) arteries and veins by the right ventricle of the heart. This cycle repeats. Coming off the arteries and leading into the veins are smaller vessels called arterioles and venules, respectively. Between the arterioles and venules are the capillaries, where the exchange of components between the blood and tissue takes place (nutrients and oxygen from the blood to the tissue and end-products of metabolism from the tissue to the blood).

Figure 2 (Ref. 3, p. 206)
6. (Figure 4) Arterial pressure in the capillaries causes the water to flow from the capillaries into the interstitium (region between cells). Nine-tenths of this fluid is reabsorbed at the venous ends of the capillaries.
7. Composition of the interstitium (See Figure 5)
   a) Water
   b) Collagen fiber bundles (collagen is protein)
      · purpose is to provide tension strength to the interstitium
   c) Proteoglycan filaments (98% hyaluronic acid; 2% protein)
      · forms a fine mat which fills all the interstitial space; these filaments are so thin that they are hard to see even with an electron microscope

Ref. 3, Ch. 30

7A. Fluid in the interstitium is entrapped in the small spaces between the proteoglycan filaments. Fluid diffuses through the interstitium, and does not flow at any appreciable rate because of the proteoglycan filaments. The diffusion rate of water in the interstitium is 95-99% of that of free water. Thus there is rapid transport of water, electrolytes, etc. There are also pockets of free fluid. These expand tremendously in edema.

8. What happens to the 1/10 of the water that enters the interstitium but does not return to the capillaries? This water has to eventually return to the circulatory system, otherwise there would be a build up of water in the tissue. This 1/10 water component that does not re-enter the capillaries enters the lymphatic capillaries (see Figure 6) which is the entry point to the lymph system that eventually empties into the venous system. The lymph is considered to be a part of the ISF (Ref. 2, p. 5).
9. The lymphatic system is diagramed in Figure 7.

10. The lymphatic system is diagramed in Figure 7.
Ref. 3, p. 361

a) The lymph system is the route by which fluid flows from the interstitial space to the blood.

b) A very important function of the lymphatics is to carry proteins and large particulate matter out of the tissue spaces.

c) With a few exceptions, all tissues have lymphatic channels draining the interstitial space. The exceptions are the superficial portion of the skin, the central nervous system, the deeper portions of the peripheral nerves, the endomysium of muscles [sheathed, delicate reticular fibrils which surround each muscle (Ref 7)], and the bones. These tissues have other channels (prelymphatics) which eventually drain into the lymphatic vessels or the cerebrospinal fluid (in the case of the central nervous system).

d) The normal flow rate of the lymph is 120 mL/hour.

Ref. 8, p. 350

9A. The pathway of lymph fluid in the lymphatics is summarized below

a) The ISF enters the lymphatic system where the fluid is called lymph. Lymph flows from the smallest vessels, called lymphatic capillaries, into larger vessels, called lymphatic venules, into larger vessels called lymphatic veins. The lymphatic veins then empty into one of the two largest lymphatic vessels: the right lymphatic duct (carries lymph from the right upper extremity and from the right side of the head, neck, and upper torso) or the thoracic duct (carries lymph from the rest of the body). The right lymphatic duct and thoracic duct empty into the blood system by emptying into the veins in the neck region [junctures of the internal jugular veins and the subclavian veins (Ref 3, Ch. 31)].

Like the blood capillaries, the lymphatic capillaries are lined with endothelial cells. However the fit of the endothelial cells is not as tight in the lymphatic capillaries, allowing passage of proteins and larger components between them from the ISF.

Along the lymphatic pathway are lymph nodes. The nodes perform a very important function of defense by degrading bacteria, cancer cells, etc., to prevent the spread of these agents from the local tissues where they are present. This defense function is accomplished by macrophages present in the lymph nodes, utilizing the process of phagocytosis. [Phagocytosis is a process by which the material is taken into the macrophage cell and degraded through various chemical processes (Ref 7)].

Ref. 3, Ch. 31

9B. Other facts about the lymphatics

a) Two thirds of the lymph originates from the liver and the intestine.

b) Lymph is derived from ISF that flows into the lymphatics. Thus lymph has almost the same composition as the ISF of the part of the body from which the lymph flows.
c) The concentration of protein in the lymph usually increases after it goes through the lymph nodes (the afferent lymph is lymph before it enters the lymph node, while the efferent lymph is lymph after it exits the lymph node), as a significant amount of water is absorbed into the blood. There is an extensive network of blood capillaries in the lymph node into which a significant amount of water and small molecules (but not proteins) are absorbed. The efferent lymph protein concentration is greater than the afferent lymph protein concentration; except in the case of the afferent lymph originating from the liver, where the lymph is diluted after passing through the node because of the high concentration of protein present in the lymph.

d) The lymphatic system is one of the major routes of absorption of nutrients from the GI tract, being the principal location for the absorption of fats.

e) A critical function of the lymphatics is to maintain a low concentration of protein in the interstitium. Protein continually leaks from the capillaries into the ISF. Protein must be removed from the ISF, otherwise the tissue colloid osmotic pressure will become so high that normal capillary hydrodynamics can no longer continue (see Chapter 3, points 35-39).

f) Lymphatic flow occurs according to the mechanisms given below.

1') Flow occurs by an intrinsic pumping mechanism in which there is a stretching of the lymph vessel as the fluid enters, which causes a contraction of the smooth muscle on the wall of the vessel, which subsequently causes a pumping of the lymph. In addition, each segment of the lymph vessel has a valve system, as shown in Figure 7a, which causes flow to occur in one direction (fluid can only flow one way through the valve).

![Figure 7a](image)

2') External compression of lymph vessels also causes flow. This can occur by:

a') contraction of muscles
b') movement of the body
c') arterial pulsations
d') external compression of tissues by objects pressing the outside of the body

Lymph flow can increase by a factor of 10- to 30-fold during exercise.

3') A lymphatic capillary pump mechanism has also been proposed. When tissues swell with excess fluid, the fluid flows into the lymphatic capillaries because they are pulled open through anchoring filaments which are attached to the lymphatic capillaries and tissue cells. Compression of the tissue moves the fluid forward in the capillary.
10. The last water compartment to consider is the transcellular water compartment. Although it could be considered a part of the ECF, it is not conventionally considered so (Ref. 1, p. 315). It is thus considered a third compartment, different from the ICF and the ECF.

   a) The most important of transcellular water compartments are (Ref. 2, pp. 5-6):
      1') gastrointestinal (fluid in the stomach and intestines)
      2') genitourinary (intratubular fluid and urine present in the kidneys and lower urinary tract; fluid in the genital tract)

   b) Others transcellular water compartments are (Ref. 1, p. 315):
      1') cerebrospinal fluid (CSF)
      2') aqueous humor of eye

Ref. 1, p. 315

11. Fluid in the body cavities [pericardial (surrounding the heart), pleural (surrounding the lungs), peritoneal (surrounding the abdominal organs), and synovial (surrounding the joints)] is considered ISF. These are normally empty and contain only a few mLs of viscous lubricating fluid.

Ref. 1, pp. 316-317

12. The composition of water in the various locations is shown in Figure 8 and Table I. The difference between plasma and plasma water is the following: plasma contains lipids and other components which do not contain ions (in addition to the aqueous solution), while plasma water consists solely of the aqueous portion (no lipids). The additional volume that these lipids occupy (which is void of ions) leads to a lower concentration of these ions in the plasma (7% lower). Plasma water represents 93% of total plasma volume, thus the concentration of ions in plasma is 93% of that in the plasma water. It is the concentration of ions in plasma that is conventionally measured in the laboratory (except when ion-selective electrode techniques are used). However, it should be noted that it is the concentration of ions in plasma water which is physiologically important. In conditions in which there is an abnormally high concentration of lipids in the plasma, the concentration of ions in the plasma will be measured to be lower than normal, implying a hypo-concentration state. However, there is no physiological problem since the concentration of ions in the plasma water is unchanged from normal (since the body regulates the plasma water compartment, not the plasma compartment).

Table I (Ref. 1, p. 316)
13. Comments about ions of the ECF

a) The main cation is sodium. It accounts for most of the osmolarity of the ECF (both plasma and ISF). It is very important in the regulation of the volume of water in the body.

b) Potassium, calcium, and magnesium are present at a much lower molar concentration than sodium, but have extremely important functions:
   - \( K^+ \) influences the electrical potential of cells
   - \( Ca^{2+} \) affects the neuromuscular excitability

c) \( Cl^- \) and \( HCO_3^- \) are the principle anions. These ions serve as osmolarity determinants of the ECF. In addition, \( HCO_3^- \) has the important function of serving as a buffer component, maintaining the pH of the ECF.

d) Phosphate is present at low concentrations. It plays an important role in the renal excretion of acid.
14. Compositional differences between plasma and ISF

   a) There is a higher concentration of protein in plasma (most proteins are unable to pass
   between the capillary endothelial cells).

   b) One would expect the same concentration for each particular small molecule in the plasma
   when compared to its concentration in the ISF [since there is no size barrier for these small
   molecules to diffuse through the intercellular clefts between the capillary endothelial cells (see
   points 30-34 of Chapter 3 for background material on the transfer of components between the
   plasma and the ISF in the capillaries)]. However, this is only true for uncharged molecules.
   For charged species, there is a slight difference in the concentration of ions across a capillary
   membrane due to the Gibbs-Donnan equilibrium (explained below). In comparing the
   concentration of ions of plasma water to that of ISF, the following is found:

   1') There is a slightly greater concentration of cations in plasma water

   2') There is a slightly lower concentration of anions in plasma water

   3') There is a higher concentration of divalent cations in plasma water, because of the
   partial binding of the divalent cations to plasma proteins (in addition to a Gibbs-
   Donnan explanation)

15. Intracellular fluid (ICF) composition (Ref. 2, p. 8).

   a) The principle cation is potassium (serves as the principal osmolarity determinant of the cell)

   NOTE: the large differences in the potassium concentration of the ECF and ICF, combined
   with the selective permeability of the cell membrane to potassium, results in
   an electrical potential difference across the cell membrane. For most cases the cell potential is
   a negative 50-90 mV compared to the ECF.

   b) Magnesium is far more concentrated in the ICF than in the ECF, being the cation of second
   highest concentration

   c) The major anions are organic phosphate and proteins

16. There are four processes that govern the movement of substances across membranes as described
   below. These processes are:

   a) Diffusion

   b) Osmotic pressure

   c) Active transport

   d) Electrostatic force
17. Diffusion (Concentration Gradient Force) (net transfer of a solute down its concentration gradient)

If the membrane is permeable to a solute and there is a concentration difference across the membrane for the solute, then there is a net movement of the solute across the membrane from the higher to the lower concentration side, until the concentration is equal on both sides of the membrane (unless there is a counteracting force that opposes this process). The rate of flux of solute across the membrane will be greater with higher concentration differences across the membrane, as seen by Fick’s Law given by Equation 1 (Ref. 5, p. IV):

$$N_{\text{diff}} = D \frac{dc}{dx}$$ (1)

where \(c\) is the concentration (moles/mL), \(x\) is distance (cm), \(D\) is the diffusion coefficient (cm\(^2\)/sec) and \(N\) is the flux (moles/cm\(^2\)-sec).

18. Osmotic pressure (net transfer of water down its osmolarity gradient)

Another principle guiding the movement of substances across the membrane is the total solute concentration (not just of one particular solute molecule). There is a bulk flow of solution (i.e., movement of water and solutes that are permeable to the membrane) from the low osmolarity compartment to the high osmolarity compartment separated by a semipermeable membrane. This process is described in detail below.

a) (Ref. 1, p. 314) What is osmolarity? It is the measure of the total number of solute molecules of any kind dissolved in solution. An osmole is a mole of solute molecules in solution after dissociation. For example, a monovalent ionic compound will have two osmoles per one mole since it has one positive and one negative species.

b) The process of osmosis is the transfer of water across a semipermeable membrane (permeable to water but not to certain solutes that are present) in an attempt to equalize the osmolarity difference across the membrane (Ref. 1, p. 314). The principle explaining osmosis is that the chemical potential of the water is greater on the lower osmolarity side of the membrane (i.e., water molecules strike each pore of the membrane at a higher rate for the solution having a lower concentration of solutes and thus there is a net diffusion of water to the higher concentration side) (Ref. 3, p. 387).

Only solute molecules which are impermeable (or have hindered permeability) to the membrane cause osmosis to occur. Permeable ions only participate as “spectators” to the process, being carried through the membrane as the water solution is transferred through it (see point 18.f)

d) The effect of osmosis on cell size is illustrated in Figure 9, in which water enters or exits the cell to equalize the osmolarity of the ICF and ECF, causing the cell to increase or decrease in size.

e) Osmotic pressure is the quantitative measure of the osmosis process. It is the force necessary to exactly oppose osmosis. Osmotic pressure is measured in two ways (Ref. 2, pp. 24-25): 1') It is measured as the pressure needed to prevent a net transfer of water (i.e., as shown in Figure 10, the pressure needed over compartment 1 to prevent an increase of water volume in this compartment).
Solutions of solute X separated by a membrane permeable to water but not to solute X. Compartment 1 has a higher osmolarity than compartment 2. The pressure exerted over compartment 1 to prevent water transfer equals the osmotic pressure.

2) (See Figure 11) Alternatively, osmotic pressure can be measured by letting osmosis occur. Osmosis will occur at the starting point given in Figure 10 if there is no differential pressure exerted over compartment 1. This causes the osmotic pressure to decrease (since water is being transferred into compartment 1, diluting this solution)
while the hydrostatic pressure of compartment 1 increases (i.e., the solution level of compartment 1 increases). At some point, the hydrostatic pressure will equal the osmotic pressure and there is no more net transfer of solution from compartment 2 to 1. At this point the hydrostatic pressure is a measure of the beginning osmotic pressure. Although there is still an osmolarity difference between the compartments at this equilibrium point, there is no net force causing transfer of water (hydrostatic pressure equals the osmotic pressure). Figure 11 shows the equilibrium endpoint of Figure 10 (in the case where there is no differential pressure exerted over compartment 1).

**Figure 11 (Ref. 2, p. 25)**

Hydrostatic pressure measurement of the osmotic pressure. Equilibrium endpoint of Figure 10 in which there is no differential pressure exerted over compartment 1.

f) The process of osmosis causes a bulk flow of water, which means that water molecules drag solute molecules across the membrane with it [only those solute molecules permeable to the membrane (Ref. 2, p. 24)].

Ref. 2, p. 27

NOTE: osmotic pressure and osmosis only result from solute molecules that are impermeable to (or hindered by) the membrane. No osmosis takes place when the membrane does not hinder diffusion of the solute. Let's discuss the case where compartment 1 contains a solution of a solute in water while compartment 2 contains water but no solute. The membrane is permeable to both the solute and water. In this case, the equilibrium result would be solutions of equal concentration in compartments 1 and 2. Any transfer of water at this point would be...
opposed by an increase in osmolarity in the compartment from which the water came, pulling the water back. There is thus no net transfer of water and hence, no osmosis.

h) Definition of terms:
Ref. 3, p. 389; Ref. 1, p. 318
1') Osmotic Pressure: theoretical pressure difference between a solution and water if the membrane is impermeable to all solute molecules while being completely permeable to water. Plasma has an osmotic pressure of 5453 mm Hg. [Conversion factor is (19.3 mm Hg)/mOsm/L].

Ref. 1, pp. 314, 318
2') Effective Osmotic Pressure: the pressure difference across the membrane between a solution and water that is actually measured (due to solutes that are impermeable or semipermeable to the membrane). The effective osmotic pressure is thus dependent on:
a') solute concentration
b') permeability of the membrane to the solute (solutions that are completely permeable do not add to the effective osmotic pressure)

The effective osmotic pressure in the ECF is called the colloid osmotic pressure and is due to components that cannot pass through the capillary membrane (most notably proteins). Values for the colloid osmotic pressure of plasma and interstitial fluid are 28 mm Hg and 6 mm Hg, respectively.

Ref. 2, p. 28
19. Active Transport (net transfer of a solute against its concentration gradient)

Active transport is the process by which a solute goes from a solution at low concentration of this solute to a solution at high concentration of this solute. This process requires energy. Examples of active transport are:
a) the pumping of Na\(^+\) out of the cell and K\(^+\) into the cell by Na,K ATPase
b) absorption of glucose by the intestine and renal tubular cells

20 A. Electrostatic Force (net transfer of a charged species down its electrostatic gradient)

Electrostatic force promotes the transfer of charged species across the membrane according to the principle that like charges repel and opposite charges attract. Thus if a compartment has a negative charge it will promote the exit of negatively-charged species and the entrance of positively-charged species (as long as these chemical species are permeable to the membrane). One example of an electrostatic force employed in physiological processes is the uptake of cations and the release of anions by negatively charged cells (as long as the cell membrane is permeable to the ions). How the cell develops a negative potential is described below.
20 B. Mechanism by which a cell establishes a negative potential

a) The ions establishing the cell’s potential have the property of being permeable to the membrane. The ion that is the main determinant of a cell’s potential is potassium, because of the potassium concentration difference that exists between the ECF and ICF and because cells are far more permeable to this ion compared to any other ion (Ref. 2, p. 32). The cell has a potential of negative 50-90 mV with respect to the ECF (Ref. 2, p. 8).

b) The mechanism by which a cell’s potential is established is described below, with the aid of Figures 12, 13 and 14.

c) The major factors in the establishment of a negative potential for the cell are the concentration of the potassium ions outside the cell (at a concentration of 4 mEq/L) and inside the cell (at a concentration of 140 m Eq/L), and the permeability properties of the cell membrane (having permeability to potassium but not to other cations and impermeability to the principal anions in the ICF, namely organic phosphate and proteins).

d) Figure 12 shows the "initial" conditions

Accept the beginning condition that the ICF has a higher concentration of potassium than the ECF (established by the Na,K ATPase protein present on the cell membrane as described in point 20C.b.c). Also, start with the reasonable condition that there are an equal number of + and - charges in the ECF. Ditto for the ICF. At this point, then, there is no potential difference across the membrane. However this condition is not the equilibrium condition. The concentration difference of K⁺ ions that exists between the ECF and ICF (combined with the fact that the membrane is permeable to K⁺) provides a force driving K⁺ ions from the high concentration side to the low concentration side, as represented by the arrow. Even though there is a great concentration difference of anions (proteins and organic phosphates) between the ICF and ECF, there is no force driving these anions out of the cell because of the lack of permeability of the membrane to these anions.

Figure 12
e) (See Figure 13) The concentration gradient force (diffusion force) causes a net movement of K\(^+\) through the membrane to the outside of the cell, leaving negative charges behind in the cell. The negative potential of the cell is developing: excess positive charges are accumulating on the outside of the cell and excess negative charges are accumulating on the inside of the cell.

![Figure 13](image)

f) If the concentration gradient were the only force operating, then diffusion of K\(^+\) across the membrane would occur until \([K^+]_{ECF} = [K^+]_{ICF}\). However, this does not occur because as K\(^+\) migrates across the membrane another force opposing the concentration gradient force develops. This force is an electrostatic force, resulting from the positive charge building up on the outside of the cell (a repelling force hindering K\(^+\) ions from exiting the cell) and a negative charge building up on the inside of the cell (an attraction force favoring the retention of K\(^+\) in the cell). This electrostatic force is represented by the arrow pointing to the right in Figure 13.

g) (See Figure 14) Finally after the magic number of K\(^+\) ions have diffused through the membrane, there is an equalization of the electrostatic and concentration gradient forces (represented in Figure 14 by the equal-sized opposing arrows) resulting in no more net transfer of K\(^+\). The cell develops a negative potential on the order of -50 mV to -90 mV. Only a small number of K\(^+\) ions are actually transferred to reach the equilibrium condition depicted in Figure 14 (1/(500,000)) of the total positive charges in the cell are transferred (at
least for nerve cells). Thus, the concentration of $K^+$ inside and outside the cell does not change to any significant degree.

![Figure 14](image-url)

**Figure 14**

Ref. 3, pp. 102-103; Ref. 2, p. 32

20C. More details on the potential of cells

a) The above example assumes that it is only the potassium ion which establishes the cell potential. In actuality, other ions have concentration differences between the ECF and ICF, to which the membrane is slightly permeable. These ions would thus influence the membrane potential. The quantitative relationship between ion concentration ($C$) inside (i) and outside (o) the cell and the permeability of the ion through the membrane ($P$) for the ions $Na^+$, $K^+$, $Cl^-$ are given by the Goldman-Hodgkin-Katz equation below.

$$EMF(mV) = -61 \cdot \log \left( \frac{C_{Na^+} P_{Na^+} + C_{K^+} P_{K^+} + C_{Cl^-} P_{Cl^-}}{C_{Na^+} P_{Na^+} + C_{K^+} P_{K^+} + C_{Cl^-} P_{Cl^-}} \right)$$

and $Cl^-$ are given by the Goldman-Hodgkin-Katz equation below. The concentration and permeability (measured for squid giant axon cells at rest) for each ion is given in Table II.
### Table II (Ref. 1, p. 316; Ref. 6, p. 57)

<table>
<thead>
<tr>
<th>Ion</th>
<th>ECF (mEq/L)</th>
<th>ICF (mEq/L)</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>142</td>
<td>10</td>
<td>0.04</td>
</tr>
<tr>
<td>K⁺</td>
<td>4</td>
<td>156</td>
<td>1.0</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>103</td>
<td>2</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Some comments. Potassium has the greatest influence on the cell’s potential because of its high permeability through the membrane. Sodium does not have a significant influence on the cell’s potential because of the membrane’s lack of permeability to this ion. Chloride has moderate permeability through the membrane, however it’s effect does not change the cell’s potential from what is established by potassium, because the ratio of the ECF to the ICF chloride concentration is close to the ratio of the ICF to the ECF potassium concentration. (That and the fact that chloride has half the permeability of potassium means that the cell potential is not shifted significantly by the chloride ion.)

**b)** How is the ion concentration difference between the ECF and the ICF established?

Ref. 3, p. 103

Limiting the discussion to Na⁺ and K⁺, the large concentration difference of these ions between the ECF and ICF is established and maintained by active transport, which is accomplished by the Na-K, ATPase pump (which is a protein present on the cell membrane). This "pump" pumps Na⁺ out of the cell while K⁺ is pumped into the cell, both against their concentration gradients.

**c)** The Na-K, ATPase plays a role in establishing the cell potential through two effects (Ref. 2, p. 32):

1') by setting up the Na⁺ and K⁺ concentration differences between the ECF and the ICF, which establishes the diffusion potential;

2') by pumping out of the cell three positive sodium ions for every two positive potassium ions that it pumps into the cell (the Na-K, ATPase thus acts as an electrogenic pump, since negative ions cannot follow Na⁺ from the cell).

The relative contributions of the diffusion potential and the electrogenic pump potential are -86mV and -4mV, respectively (Ref. 3, pp. 103, 106).

**21.** As has been pointed out, the major compositional differences between plasma water and ISF are a significantly higher concentration of protein, a slightly greater concentration of cations, and a slightly lower concentration of anions, in the plasma water compared to the ISF. The difference in ion concentration between plasma water and the ISF is explained by the Gibbs-Donnan equilibrium (see below).
22. To explain the Gibbs-Donnan equilibrium effect, let’s present a simplified model of two compartments with a limited number of solute components, separated by a semipermeable membrane (the two compartments are the plasma water and the ISF (see Figures 15 and 16)). Na\(^+\) and Cl\(^-\) are contained in the ISF compartment and Na\(^+\) and P\(^-\) (where P\(^-\) is protein) are contained in the plasma water compartment. Initially the concentration of Na\(^+\) is the same in each compartment. The membrane is permeable to Na\(^+\) and Cl\(^-\) but not to P\(^-\). The process by which the ions re-equilibrate is explained below.

Ref. 2, pp. 29-30

23. As shown in Figure 15, a concentration difference (i.e., diffusion force) causes a flux of Cl\(^-\) from compartment 1 (ISF) to compartment 2 (plasma water). There is no flux of P\(^-\) from compartment 2 to 1 because of the impermeability of the membrane to P\(^-\).

![Figure 15 (Ref. 2, p. 29)](image)

24. (See Figure 16) There is an excess of negative charges in compartment 2 with the flux of Cl\(^-\) into the compartment. This negative charge drives Na\(^+\) from compartment 1 into compartment 2 (Ref. 2, pp. 29-30).
25. The Cl⁻ flux followed by Na⁺ flux will continue until the Na⁺ concentration gradient opposing Na⁺ transfer from compartment 1 to compartment 2 equals the concentration gradient driving the transfer of Cl⁻ from compartment 1 to compartment 2. At this point only a small number of Cl⁻ ions would transfer into compartment 2 due to a building electrostatic force resulting from the transfer of each Cl⁻ ion (which is now unaccompanied by any positively-charged ion). Quantitatively, the NaCl flux will continue until \([\text{Na}^+][\text{Cl}^-] = [\text{Na}^+]_1[\text{Cl}^-]_1\), where the subscripts refer to the compartment number (Ref. 2, p. 30).

Table III (Ref. 3, p. 389)
26. Summary of the composition of the components in water in the body (see Table III).

a) Four-fifths of the total osmolarity of the ECF (plasma and ISF) results from Na$^+$ and Cl$^-$ (Ref. 3, p. 388).

b) One-half of the total osmolarity of the ICF results from K$^+$ (Ref. 3, p. 388).

Ref. 2, p. 32

c) The difference in the potassium concentrations between the ECF and the ICF is very important. It is the concentration difference of K$^+$ inside and outside the cell and the permeability of the cell membrane to K$^+$ (and not other ions, such as sodium) which makes the cell have a negative potential.

Ref. 3, pp. 388

d) The total osmolarity of the ECF is approximately 300 milliosmoles per liter. The corrected osmolarity is calculated using solute activities, not concentrations. In general, there is an intermolecular attraction between solute molecules which leads to an osmotic activity that is 93% of what would be calculated based on the uncorrected osmolarity. The corrected osmolarity of the ECF is approximately 280 milliosmoles/liter. The corrected osmolarity is used in the calculation of osmotic pressure.

Ref. 3, pp. 388-9

e) Plasma is 1.3 milliosmolar activity units greater in corrected osmolarity than that of the ISF or ICF. This slight difference in osmolarity between plasma and ISF is mostly due to plasma proteins. The resulting osmotic pressure between plasma and ISF is 25 mm Hg.

f) The presence of protein in the plasma water, but not in the ISF, leads to the Gibbs-Donnan equilibrium effect, in which there is an increased concentration of cations, and a decreased concentration of anions, in the plasma water compared to the ISF. These differences are slight.

Ref. 3, pp. 356, 389

g) Protein does leak into the ISF to a small extent and is removed through the lymphatics. The concentration of protein in plasma is 3-6 times greater than that of the ISF.
References


5. D. C. Johnson, "Electrochemistry in Chemical Analysis".


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Chapter 3
Control of Blood Flow and Blood Pressure

1. The body needs to control the flow rate of blood through tissues, regulating it according to the needs of the tissue.
   a) There is a need to supply tissue with O₂ and nutrients, as well as a need to remove end-products of metabolism, during periods of high activity.
   b) Why is a control mechanism necessary? Why not have the blood flow at such a rate as to meet any possible needs? Answer, there is not enough blood to maintain such a flow through all tissues. The blood flow is regulated to a minimum level, sufficient to meet the needs of the tissue.

2. An overview of the circulation of blood is given in chapter 2, page 2. Shown in Figure 1 is a diagram of the capillary bed. From the arteriole, the blood enters the metarterioles and proceeds to the true capillaries (where the exchange of components between the blood and tissue takes place). The blood drains from the capillaries into the venules. At the point where the capillary arises from the metarteriole there is a precapillary sphincter (which consists of a single smooth muscle fiber surrounding the entrance to the capillary). The precapillary sphincter plays an important role in the regulation of blood flow through the tissue. It should be noted that skeletal muscles do not have precapillary sphincters. The preferential channels are very large capillaries which course directly from the arterioles to the venules.

![Figure 1](Ref. 1, p. 231)

3. Muscle coats surrounding various blood vessels
   a) Arterioles - have dense muscle coat
b) Metarterioles - have sparse but highly active smooth muscle fibers

c) Venules - have smooth muscular coats that are less extensive than the arterioles

d) Precapillary sphincter - is a single smooth muscle fiber that surrounds the beginning point of the capillary

e) True capillaries - have no muscular coats

4. The muscles on vessels play an important role in the regulation of blood flow by constricting or dilating the blood vessels diameter; constricting lessens the flow, while dilating increases the flow. Control of the contraction of muscles around the vessels occurs via the nervous system and/or via factors present in the blood of the tissue.

5. Blood flow is controlled in the short term by different mechanisms categorized before short term blood control.

a) Intrinsic
   • Factors within the tissue control the blood flow through the tissue

b) Extrinsic
   1') Nervous System

   The nervous system is a general control which affects blood flow in large segments of the systemic circulation. For example blood is shifted from non-muscular to muscular vascular beds during exercise and blood flow is regulated in the skin to control the body temperature, via the central nervous system.

   2') Hormones

6. Intrinsic Control of Bloodflow

e) Intrinsic control of the blood flow is discussed below. This control acts within minutes. There are two theories as to how this local control is accomplished.

   1') Vasodilator Theory - Some metabolic products act as vasodilator, causing relaxation of the arterioles, metarterioles, and precapillary sphincters. The vasodilator theory of blood flow control is based on the logic that an increased presence of end-products of metabolism in the tissue's blood signals a need for increased blood flow, in order for an adequate supply of oxygen and nutrients. Substances hypothesized are CO₂, lactic acid, and adenosine phosphate, histamine, potassium and hydrogen ions. Evidence contrary to the feasibility this hypothesis is that none of these substances has been detected at a sufficient concentration in the tissue to cause the vasodilation effect noted.

   2') Oxygen Demand Theory - Oxygen is required to maintain muscle contraction. Lack of O₂ in the blood vessel causes a relaxation of the muscle surrounding the vessel and
hence dilation of the vessel. This theory is based on the logic that lower oxygen (a in the tissue’s blood nutrient) levels signal a need for increased blood flow. Evidence contrary to this hypothesis is that smooth muscle can remain contracted for long periods of time in very low oxygen concentrations.

b) Experimental Verification

Figures 2 and 3 show local control effects on blood flow. Figure 2 shows an increase blood flow with increased metabolism, while Figure 3 shows an increase in blood flow with a decrease in blood oxygen concentration. Other evidence implicating oxygen as an important factor, is an experiment which demonstrated an increase in blood flow of up to seven times normal after cyanide poisoning in the local tissue.

![Figure 2 (Ref. 1, p. 232)](image)

**Figure 2 (Ref. 1, p. 232)**

![Figure 3 (Ref. 1, p. 232)](image)

**Figure 3 (Ref. 1, p. 232)**

6. Extrinsic Control of short-term blood flow
The nervous system controls the blood flow through:

a) nerve impulses sent to the muscles surrounding blood vessels, causing a change in diameter of the vessel;

b) nerve impulses sent to the heart; causing a change in heart rate and contractility;

c) nerve impulses sent to the adrenal gland, causing the adrenal medulla to release epinephrine and norepinephrine.

2') Primer on nerves

a") There are two classifications of nerves: autonomic, which controls involuntary body functions and somatic motor, which controls voluntary skeletal muscle movement. The system pertinent to the control of blood flow is the autonomic system.

b") Within the autonomic nervous system there are two types of nerves: parasympathetic and sympathetic. Stimulation of each type of nerve leads to opposite effects, as given below:

1") Parasympathetic nerve stimulation - leads to the energy conservation actions.

2") Sympathetic nerve stimulation - leads to energy expending actions.

3") Vasomotor Center
The center which controls regulation of blood flow is the vasomotor center. Figure 4 shows the location of the vasomotor center in the brain.

a') The vasomotor center controls blood flow through:

1') contraction of blood vessels by sending sympathetic signals down vasoconstrictor of nerves fibers that are connected to blood vessels.

2') control of heart rate and strength of contractility through sympathetic (stimulation leads to increased heart rate and increased strength of contractility) and parasympathetic (through control of the vagus nerve) (stimulation leads to decreased heart rate and decreased strength contractility) nerve stimulation;

3') stimulation of the adrenal medulla causing the release of the vasoconstrictors epinephrine and norepinephrine.
b')  Facts about the vasomotor center control of contraction of muscles surrounding the blood vessels which carry vasoconstrictor fibers from the vasomotor center.

1')  Blood vessels are enervated by sympathetic nerves (See Figure 5).

2')  All blood vessels are innervated except the capillaries, and most of the metarterioles. The precapillary sphincters are also not enervated. Some tissues have a greater distribution of sympathetic vasoconstrictor fibers however, including the kidney, the gut, the spleen and the skin, while the skeletal muscle, cardiac muscle, and brain have less of a distribution of these vasoconstrictor fibers.

3')  The most important sympathetic control is the control of the contraction of the arterioles, which are extensively enervated. The control of the contraction of the venules by the sympathetic nerves is the second most important control. The venules are innervated to less of an extent compared to the innervation of the arterioles.

4')  Sympathetic nerves from the vasomotor center to the blood vessel carry both vasoconstrictor and vasodilator fibers, however, the vasoconstrictor fibers are more important to blood flow.

Figure 4 (Ref. 1, p. 238)
Chapter 3
Control of Blood Flow and Blood Pressure

**Figure 5 (p. 238)**

1') How are signals sent to the vasomotor center to control the blood flow?

1") The vasomotor center is controlled by higher centers in the brain

2") Feedback receptors in cardiovascular system send signals to the vasomotor center

a") **Baroreceptors** - These are spray-type nerve ending receptors lying on the walls of the thoracic and neck arteries, and are stimulated when they are stretched by increased pressure. These receptors are extremely abundant in the internal carotid (principal artery in the neck) and the wall of the aortic arch (see Figure 6). Increased arterial pressure is translated by the baroreceptors into an increase in inhibitory signal sent to the vasomotor center causing decrease in arterial pressure.

b") **Chemoreceptors** - These receptors are located in the aorta and carotid arteries and are stimulated by an increased concentration of end-products of metabolism and by a decreased concentration of oxygen in the blood. When blood pressure is low (less than 80mm Hg) chemoreceptors transmit increased signal to the vasomotor center to excite the causing an increase in arterial vasomotor center pressure.

c") **Stretch receptors** - These receptors are located in the atria and the pulmonary arteries and are sensitive to blood volume. These stretch receptor do not monitor the arterial pressure per se (i.e. high pressure area) but rather monitors the low pressure areas of the pulmonary arteries and the atria. Pressure increases in these low pressure areas are mainly caused by increase volume (thus these receptors
detect an increase in blood volume) which a cause the stretch receptor to send an increased inhibitory signal to the vasomotor center which causes a decrease in arterial pressure. In addition to the action on the vasomotor center, some stretch receptors cause an increased urine output via direct action on the kidney (cause dilation of afferent arteriole in the kidney(see chapter 4 as to how this increases urine production through increased GFR) and an indirect action on the kidney [by stimulating the hypothalamus to decrease the rate of antidiuretic hormone (see chapter 6 on how decreased ADH production leads to increases urine production)]. It should also be noted that increase pressure of the atrium also causes an increased heart rate through stimulation of the S A mode of the heart (the heart’s pacemaker) and increased heart rate and strength of contraction elicited by the stretch receptors in the area sending a signal through the vagus nerve to the medulla of the brain - which then sends a signal back to the heart through both the vagal and sympathetic to cause the above mentioned responses.

Figure 6 (Ref. 1, p. 247)

b) Hormonal control of blood flow.
1') Vasoconstrictors
   a') Epinephrine and norepinephrine
       These hormones also cause increased activity of the heart. See point 4 for more details.
   b') Angiotensin II
   c') Antidiuretic hormone (ADH) (also called vasopressin)

c) Vasodilator substances
   a') Bradykinin
   b') Serotonin
   c') Histamine
   d') Prostaglandins

7. Long term control of blood flow
The controls of blood flow discussed above are short-term controls. The mechanism by which blood flow is controlled at an abnormal level for the long-term is a change of vascularity of the tissue (more or less vessels). Oxygen is speculated to have a key role in the amount of vasculature in a tissue. Supporting this contention is:
   a) the increased vasculature seen in animals living at high altitudes;
   b) the onset of retrolental fibroplasia in premature babies removed from an oxygen tent too quickly. (While in the tent there is a cessation of new vasculature growth in the retina. If the baby is taken out of the oxygen tent too quickly, then there is a sudden decrease in oxygen, leading to an explosive growth of new vessels in the eye, leading to blindness.)

8. Importance for the body in keeping arterial pressure constant
The importance of local control of blood flow through a tissue was discussed above. The main mechanism of this control is the constriction or dilation of blood vessels in the tissue. In order for this mechanism to work quantitatively, there must be a control of the arterial pressure to keep it constant.

Why a constant arterial pressure is necessary for the diameter of the blood vessel to have quantitative control of blood flow is seen by making an analogy to electronics.

In electronics, current (I) through a material is proportional to the voltage across that material (\( V \)) and inversely proportional to resistance (R) of the material. This is expressed mathematically as \( V = IR \). Thus, in electronics, if it is desired to have resistance be the sole determining factor of current, then it is necessary to keep the voltage across the material constant. In the same way, one can view blood flow through a tissue (see Figure 7), with the blood flow being analogous to current, pressure...
across the tissue (\(\Delta P\)) being analogous to the voltage differential, and resistance in the tissue being analogous to the resistance in the material. The mathematical relationship is:

\[
\Delta P \ (\text{Arterial - Venous}) \propto (\text{Blood Flow through tissue}) \times (\text{Resistance of the tissue}) \quad (1)
\]

This rearranges to:

\[
\frac{\Delta P}{\text{Resistance}} \propto \text{Blood Flow} \quad (2)
\]

Thus, in order for there to be sole control of blood flow through resistance, a constant arterial pressure must be maintained.

---

Figure 7

9. **Normal Arterial pressure values**

a) **Mean pressure** - 95-100 mm Hg

b) **Systolic pressure** (maximum pressure in the heart cycle after contraction of the left ventricle) - 120 mm Hg

c) **Diastolic pressure** (minimum pressure in the heart cycle when all 4 chambers of the heart are relaxed (Ref. 2, p. 494) - 80 mm Hg

The body has multiple systems for the control of arterial pressure, to maintain it within a tight range.

10. **How the body controls arterial pressure** can be seen from the relationship below:

\[
\text{Arterial pressure} \propto (\text{cardiac output}) \times (\text{total peripheral resistance}) \quad (3)
\]

[The above equation underscores a very important point. The various mechanisms of arterial pressure regulation regulate by either modulating vascular resistance or cardiac output.]
Thus, according to the relationship above, if arterial pressure goes down, the pressure can be maintained by:

a) Increasing the cardiac output, which is accomplished by:
   1') Increasing the strength and/or rate of contraction of the heart
   2') Increasing the volume of the blood delivered to the heart

b) Increasing the peripheral resistance, which is accomplished by constricting the vasculature

11. Difference in mechanism by which constriction of arterioles and venules (or veins) affects arterial pressure: constriction of arterioles causes an increase in arterial pressure by increasing the resistance. The mechanism by which blood pressure changes are caused by constriction of veins and venules is different than that caused by constriction of the arterioles, as detailed below.

   a) Veins offer little resistance to flow like arteries and arterioles, so constriction will not change overall total peripheral resistance.

   b) The important effect of constriction of the muscle coat around the veins and venules is to decrease the capacity of the vessel for blood.

   c) This decreased capacity causes movement of more blood into the heart.

   d) Distension of the heart causes the heart to pump more blood (i.e., there is increased cardiac output), according to the Frank-Starling Law. As has been discussed previously, an increased cardiac output leads to an increased arterial pressure.

   e) The Frank-Starling Law states that the heart will pump at such a rate as to pump out all the blood it receives, such that there is not a damming of blood in the veins. Thus, as the venous return increases, the cardiac output also increases. The mechanism by which increased venous return increases the cardiac output is that the cardiac muscle gets stretched. The stretched muscle contracts with greater force than the unstretched muscle, thereby pumping more blood out. The stretching of the heart muscle can also increase the heart rate by as much as 10 to 30%.

12. The mechanism of control of arterial pressure depends on the time frame needed.

   f) Short-term - regulates pressure through constriction of vessels, changing the heart rate and changing the heart contractility.

   b) Long-term - regulates the pressure through changing the cardiac output (which is accomplished through the regulation of the volume of the blood).

13. Details concerning short-term and long-term mechanisms of arterial pressure control

   g) Short-term mechanisms
1') Speed: Has rapid action, acts within seconds to minutes, with an immediate reestablishment of blood pressure in an emergency situation.

2') Frequency of fluctuations controlled: Maintains constant pressure on a minute by minute basis, reducing the high frequency variation.

3') Extent: Does not return pressure all the way back to normal.

4') Duration: Loses the capability for pressure control after a few hours to a few days. These mechanisms become less effective with the passage of time, adapting to the abnormal pressure.

5') Mechanism: Hormonal, nervous system, or local factors.

b) Long-term mechanisms

1') Speed: Very slow acting, taking hours to days.

2') Frequency of fluctuations controlled: Controls the low frequency fluctuations of pressure that occur over a period of days, weeks, and months.

3') Extent: Has the ability to bring the pressure all the way back to normal.

4') Duration: Becomes more effective with increased time, not adapting to the abnormal pressure.

5') Mechanism: Acts through the kidneys by regulating blood volume (part of this mechanism, however, does involve hormonal factors (renin, angiotensin, aldosterone).)

14. The mechanisms for arterial pressure control are diagramed in Figure 9, showing the time scale of action (x-axis) and the effectiveness of action (y-axis). The mechanisms are classified according to whether they are short-term or long-term. The short-term mechanisms, which will be discussed first, are:

h) Nervous system control via
   1') Baroreceptors
   2') Chemoreceptors
   3') CNS Ischemic Response

b) Hormonal Control
   1') Angiotensin II
   2') Antidiuretic Hormone (ADH) (Vasopressin)
   3') Epinephrine and Norepinephrine

c) Capillary Fluid Shift

d) Stress Relaxation
16. Nervous System Control of Arterial Blood Pressure

The nervous system control of arterial pressure is through the vasomotor center sending signals to the blood vessels, heart and adrenal glands. The vasomotor center is controlled by higher centers in the brain and by signals sent by baroreceptors chemoreceptors. These receptor controls along with a response of the vasomotor center itself to very low arterial pressures, CNS ischemic response are discussed below. It should be noted in Figure 8 that the nervous system response to arterial pressure change is the quickest happening within seconds.

a) Baroreceptors (see Figure 6)

1') Mechanism

These receptors send signals to the vasomotor center causing a change in blood vessel construction and heart activity (rate and strength of constriction) as given below: Thus for an increase in pressure the baroreceptors is stretched sending an increase signal to the vasomotor center, which elicits a response in the vasculative and the heart as outlined below.

Blood vessels response

a') Signals sent to the vasomotor center inhibitory signal to the vasoconstrictor center of the vasomotor center brain also controls baroreceptor. Thus increase of pressure felt by the baroreceptors causes a decrease in signal sent down the vasoconstrictor fibers from the vasomotor center to the blood vessels, resulting in vasodilation of the blood vessels. This vasodilation results in a lowering of the blood pressure.
Signals sent to the vasomotor center from the baroreceptors cause an excitation of the vagus nerve (which is parasympathetic) which causes of this center, which leads to a decreased heart rate and a decreased strength of contraction of the heart. This has the effect of decreasing cardiac output, resulting in a lowering of blood pressure.

The response of baroreceptors to arterial pressure is shown in Figure 10. Comments concerning this response are:

a') Baroreceptors have the greatest sensitivity of response when the pressure is near the normal range.

b') There is no response in the arterial pressure range of 0-60 mm Hg.

c') The response is more sensitive to rapidly changing pressure. That is, the baroreceptors send more signals per second when the pressure is 150 mm Hg and rapidly rising than if it is 150 mm Hg and holding.

d') The primary purpose of the baroreceptors is to reduce daily variation in arterial pressure by 1/2 to 1/3. This is shown in Figure 11.

e') Adaptation of baroreceptors to changes in arterial pressure

Baroreceptors adapt to new pressure changes after one or two days and thus are no use in long term pressure regulation.

Figure 10 (Ref. 1, p. 247)
b) Chemoreceptors

1') Chemoreceptors located in the aortic and carotid arteries. Receptors are a clump of chemosensitive cells that are 1 to 2 mm in diameter.

2') These receptors are stimulated by the change in chemical content of blood when it moves too slowly. The chemoreceptors are sensitive to the oxygen, the carbon dioxide and the hydrogen ion content of the blood. When the blood flow is diminished the oxygen content decreases, the carbon dioxide content increases, and the hydrogen ion content increases, causing the chemoreceptors to fire.

3') An increased signal from the chemoreceptor is transmitted to the vasomotor system, which causes an increase signal sent down vasoconstrictor fibers to fire, which causes the blood vessels to constrict, leading to an increase in arterial pressure. Chemoreceptors are only active when the arterial pressure goes below 80 mm Hg.

c) CNS Ischemia

1') This mechanism is not initiated until the arteriole pressure falls to below 60 mm Hg (with the greatest response seen for pressures 15-20 mm Hg). It is the body’s last ditch effort to restore arterial pressure when the pressure falls to dangerously low levels.

2') The CNS ischemic response is tremendous, it can elevate the pressure to 270 mm Hg. It does this by causing the peripheral vessels to become totally or almost totally occluded. It also causes the kidneys to cease urine production. It is the most powerful activator of all activators of the sympathetic vasoconstrictor system.

3') Mechanism
Neurons of the vasomotor system itself respond to a drastically low blood flow rate, causing the vasoconstrictor fibers to be strongly excited. The possible agent that the vasomotor responds to is increased concentration CO\textsubscript{2}. This mechanism has 3-10 min. to work because neuronal cells will die due to nutritional deficiency brought about by the slow blood flow. Without vasomotor center control, the arterial pressure will fall to 40-50 mm Hg.

**Figure 8 (Ref. 1, p. 238)**

17. Hormonal control of arterial pressure
   
   a.) Angiotensin II

1') Summary Comments
Angiotensin II is the most potent vasoconstrictors known (vasopressin also vies for this distinction). The pathway by which angiotensin II is generated in response to low arterial pressure is shown in Figure 12.
Some comments concerning the pathway for the generation of angiotensin II

The kidney responds to a decrease in arterial pressure by the release of renin from the juxtaglomerular cells of the kidney. This release is mediated through:

1') macula densa cells
2') direct sympathetic stimulation.

Renin persists in the blood for 30 min. to 1 hr.

b') Renin is a proteolytic enzyme which splits off a decapeptide unit (angiotensin I) from renin substrate (also called angiotensinogen) [which is a plasma protein (α-2 globulin fraction)] Angiotensin I has no physiologic role.

c') Angiotensin II is formed by the action of converting enzyme on Angiotensin I, splitting off 2 additional amino acids. This reaction occurs almost exclusively in the lungs, where converting enzyme is present in the small circulating vessels.

d') Angiotensin II causes vasoconstriction (especially of the arterioles and to a lesser extent the veins and venules) which has the effect of increasing the peripheral resistance and increasing the venous return.

e') Angiotensin II persists in blood for about one minute, being rapidly inactivated by different blood and tissue enzymes called angiotensinases.
f’) As seen in Figure 9, the renin-angiotensin system requires 20 minutes to become fully active and thus is slower in response than the nervous reflexes, epinephrine-norepinephrine system, and the vasopressin system. However, the renin-angiotensin system is correspondingly longer in its duration of action in comparison to these systems.

g’) Angiotensin II also causes increased reabsorption of sodium by the tubular system of the nephron. This is discussed later (see Chapter 7).

b.) Antidiuretic Hormone (vasopressin)
1’) The hypothalamus is stimulated to secrete antidiuretic hormone (ADH) either via increase in osmolarity of the ECF, decrease in blood volume, or decrease in arterial pressure (see chapter 8 for details). Pertinent to this discussion is ADH’s release in response to arterial pressure decrease.

2’) ADH has a direct vasoconstrictor effect on blood vessels

3’) Experiments showing the importance of vasopressin in short-term arterial pressure regulation:

a’) Physiological amounts of vasopressin were found to increase the blood pressure 35-50 mm Hg in hemorrhaging animals that had the baroreceptor mechanism disengaged.

b’) ADH by itself was shown to return the blood pressure to 75% of normal in hemorrhaging conditions that had reduced the blood pressure to 50 mm Hg.

4’) ADH has a significant action in the regulation of blood volume through controlling water excretion by the kidneys. This long-term effect is discussed later in chapter 8.

c.) Epinephrine and norepinephrine

1’) Blood Pressure effects
Sympathetic nerves from the vasomotor center cause a release of epinephrine and norepinephrine from the adrenal medulla. Both generally act as vasoconstrictors. However there are differences in interaction depending on the type of adrenergic receptors present on the tissue. The two type of adrenergic receptors are \( \alpha \) - and \( B \), which elicit different responses as given in Table I. \( \alpha \)-receptors interact with both epinephrine and norepinephrine, while \( B \)-receptors interact with epinephrine but are relatively insensitive to norepinephrine (i.e. not as great in response as epinephrine). Thus norepinephrine causes constriction of all blood vessels-through its action on the \( \alpha \) receptors. Ephinephrine causes vasoconstriction or vasodilation depending on which receptors are present. For example epinephrine causes mild vasodilation in both skeletal cardiac muscle. However in other tissues epinephrine causes vasoconstriction through its action on the alpha receptor binding. Of note in Table I is epinephrine’s effect on arterial pressure through its causing increased heart rate. In contrast, no repinephrine does not elicit a significant cardiac response. (It should be pointed out that norepinephrine does cause increased force and rate of contraction in an isolated
heart, but in a total body response it may not be a significant increase (or may even decrease) due to the baroreceptor feedback to the heart causing decrease hear activity responding to the body’s strong vasoconstriction response of norepinephrine causing an increase in arterial pressure.

On summary, norepinephrine increases arterial pressure due to its strong vasocontractor effects on all blood vessels, while epinephrine increases arterial pressure mainly through its stimulating effects on cardiac activity.

Table I (Ref. 4, p. 1741)

Other effects (Ref. 2, pp 326-327)
Norepinephrine and epinephrine cause a variety of metabolic effects. The particular effect elicited depends on the adrenergic receptors present. For example epinephrine and norepinephrin both cause glycogenolysis as via the B-adrenergic receptors. Increased in salin and glucagon synthesis occurs via the B-adrenergic mechanism, while a decrease in the insulin and glucagon is seen through an an adrenergic response. Other effects of these two hormones include mobilization of free fatty acids, increased plasma lactate and stimulation of the metabolic rate. It should be noted that the cardiac and metabolic effects of epinephrine are more physiologically significant than the effects of norepinephrine. This is because the threshold values of these hormones in plasma needed to cause these effects are physiologically attainable for epinephrine but are seldom attained for epinephrine.

18. An overview of the capillary system.

There are 10 billion capillary vessels in the human body. The capillaries form such an extensive network bathing the cells of the body that it is rare that any cell is more than 20-30 microns from the capillary. (Typical size of a cell is 10 to 20 µm)

19. Circulatory vessels going into and out of the capillaries (see pp. 1-2, Figure 1)

a) Arteries branch 6 to 8 times before the arteries are small enough to be considered an arteriole. Arterioles have a diameter of 40 µm.

b) Arterioles branch 2 to 5 times reaching diameters of 9 µm at which point they supply blood to the capillaries. The diameter of a capillary vessel is 4-9 µm, barely enough room for a red blood cell to squeeze through it.

c) Venules are considerably larger than arterioles.
20. Given in Figure 13 is the structure of the capillary wall

![Figure 13](Ref. 1, p. 349)

a) Endothelial cells are cells that line the cavities of the heart, blood vessels, lymph vessels, and serous cavities of the body.

b) The basement membrane consists of proteoglycan fibers.

c) Between the endothelial cells are passages called intercellular clefts. The width of these passages will determine the permeability characteristics of the capillary wall to hydrophilic compounds.

21. Passage of materials through the capillary membrane into the interstitial fluid (ISF) occurs by:

a) Diffusion - movement of the substance due to thermal motion

The distinction between diffusion and net exchange needs to be made. Diffusion is a process that occurs in both directions (in this case, into and out of the capillaries). This process is very rapid, with the exchange of water into and out of the capillaries in the entire body being 240,000 mL/min. However, there is only a net exchange of water of 2 mL/min out of the capillaries in the entire body. The greater the concentration difference of the substance between the plasma and the ISF, the greater the net movement of substance across the membrane. Examples include the large net movement of oxygen from the plasma to the ISF, and the large net movement of CO₂ from the ISF to the plasma.

b) Bulk Flow - movement of the substance due to a pressure difference

22. Diffusion Processes

Depending on the characteristic of the molecule, passage from the capillary into the ISF by diffusion occurs through one of two locations:
a) Through the membrane of the endothelial cells

1') Lipid soluble substances pass directly through the membrane (examples are oxygen, carbon dioxide, and urea; lipid drugs pass through the lipid portion of the membrane by passive diffusion.

2') Water can also go directly through the membrane. A water molecule transfers back and forth 80 times from the time it enters the capillaries, until it leaves.

b) Through the intercellular clefts (between the endothelial cells)

1') Water soluble substances that are lipid insoluble (such as Na\(^+\), Cl\(^-\), glucose) can only diffuse from plasma into the interstitial fluid through the intercellular clefts.

2') The average width of capillary intercellular cleft is 6-7 nm (20 times the size of a water molecule).

3') The permeability characteristics of the intercellular cleft will vary with the size of the molecule. This is shown in Table II.

4') Intercellular clefts of capillaries of different organs have different widths.

a') In the liver capillary sinusoids, proteins pass through the capillary wall as easily as water. This is necessary because the liver synthesizes most plasma proteins and these proteins have to pass into the blood.

b') In the brain the junctions are very tight between the endothelial cells. This is known as the blood-brain barrier, allowing the passage of only small...
molecules. This is necessary to protect the brain from toxic substances. The blood-brain barrier keeps the neurotransmitter substances (such as acetylcholine, norepinephrine, dopamine, and glycine) from exchanging between the blood and the brain, so that neurotransmission is tightly controlled. The barrier also keeps K\(^+\) from rising in the brain with increased K\(^+\) in the plasma.

\[c')\] The permeability of the renal glomerular membrane is 500 times that of muscle.

23. Bulk Flow

The distribution of fluid volume between the plasma and the ISF is governed by two types of pressures (forces):

a) Hydrostatic pressure (filtration force)
b) Colloid osmotic pressure (absorption force)

24. Each of the pressures listed above are present in the plasma and the ISF. These forces are diagramed in Figure 14, with the arrow indicating the direction of water flow due to that particular force (where \(P\) is the hydrostatic pressure, \(\pi\) is the colloid osmotic pressure, and the subscripts \(p\) and \(f\) standing for plasma and interstitial fluid, respectively).

![Figure 14](image)

25. The direction and amount of net fluid movement will depend on the magnitude of each of these four pressures, which are added together to give a net effective pressure. It is the magnitude and direction of this net effective pressure which determines the magnitude and direction of the fluid flow. The equation for the net effective pressure (NOTE: movement of water out of plasma into the ISF is a positive value) is:

\[
\text{net effective pressure} = \sum \text{pressures out of plasma} + \sum \text{pressures into plasma} \quad (4)
\]

\[
\text{net effective pressure} = (P_{p1} + \pi_f) + (P_{f1} + \pi_p) \quad (5)
\]
26. Figure 15 shows that the net effective pressure at the arteriole end of the capillaries causes a net filtration of the water into the ISF and the net effective pressure at the venule end of the capillaries causes a net filtration of the water into the capillaries. Using Equation 5 and the values given below (remember, a positive value indicates a flow out of the capillary) the effective pressure at the arteriole end is calculated to be + 13 mm Hg and at the venule end to be - 7 mm Hg at the arteriole and venule ends respectively.

\[ P_{\text{p1}} \text{ (arterial end of the capillary)} = + 30 \text{ mm Hg} \]
\[ P_{\text{p1}} \text{ (venous end of the capillary)} = + 10 \text{ mm Hg} \]
\[ \pi_{\text{p}} = + 5 \text{ mm Hg} \]
\[ \pi_{\text{f}} = + 6 \text{ mm Hg} \]
\[ \pi_{\text{01}} = - 28 \text{ mm Hg} \]

![Diagram of net filtration pressures](image)

**Figure 15 (Ref. 9, p. 320)**

27. Other comments about water movement into and out of the capillaries

a) The net effective pressure at the arterial end of the capillaries is + 13 mm Hg, which causes a movement of plasma out of the capillaries. The amount that moves into the ISF is 0.5% of the plasma volume.

b) The hydrostatic pressure in the capillaries is lost going from the arteriole end to the venule end, being dissipated along the entire length of the capillary. The reason for this is that there is a release of hydrostatic pressure due to the fact that there is no muscular coat around the
capillaries and to the fact that the venous capillaries are more numerous and permeable than the arterial capillaries.

c) The pressure at the venous end of the capillaries of -7 mm Hg is less than the filtration pressure at the arterial end of the capillary of +13 mm Hg. Not as much pressure is needed to move liquid back into the capillaries at the venous end because of the previously mentioned fact that venous capillaries are more numerous and more permeable than arterial capillaries. Nine-tenths of the water entering the ISF from the capillaries is reabsorbed into the capillaries. The remaining 1/10 is returned into the circulatory system via the lymphatics.

28. Capillary Fluid Shift mechanism for the control of blood pressure
With the background given above, capillary fluid shift control of arterial blood pressure can now be explained. See below.

a) Arterial blood pressure changes cause a similar change in the capillary hydrostatic pressure. Thus if the arterial pressure rises, then the fluid from blood moves across the capillary membrane into the ISF, causing a decrease in blood volume. This will result in a lowering of the arterial blood pressure. The reverse is true with a lowering of the arterial pressure.

b) Within a few minutes to a couple of hours, a new state of equilibrium is reached.

c) Note from Figure 8 that this mechanism is a slower acting mechanism in returning the arterial pressure to normal. It is effective in restoring the blood pressure 3/4 of the way back to normal.

29. Stress-relaxation mechanism for the control of blood pressure

a) There is an accommodation of the diameter of the vessel to the amount of blood in the vessel. The diameter decreases with a decreased amount of blood (a decreased diameter increases the resistance and thus increases the blood pressure), and increases with an increased amount of blood (an increased diameter decreases the resistance and thus decreases the blood pressure).

b) This mechanism has very definite limits: no more than a 30% increase of blood volume, or a 15% decrease in blood volume can be corrected.

30. Long-term blood pressure regulation

The mechanism of long-term control of arterial pressure, blood volume regulation by the kidney. Figure 8 shows an additional long-term regulation to be the renin-angiotensin-aldosterone system. In actuality this letter system of regulation is one of several mechanism by which the kidney controls blood volume and thus should not be considered a separate mechanism.

31. The kidneys control blood volume by regulating the urine output. ECF volume is regulated by the kidney’s urine output. Thus a decrease in urine output will result in an increase in ECF volume. This will increase the arterial pressure according to the mechanism indicated by Figure 16. The sequence
of this mechanism is shown in Figure 16 for an increase in arterial pressure (opposite effects are seen for a decrease in arterial pressure).

Figure 16 (Ref. 1, p. 261)

Figure 17
References


Chapter 4
Glomerular Filtration Rate and Autoregulation

1. The idea has been introduced that the kidney plays a central role in long-term blood pressure regulation, through the regulation of blood volume (Ref. 1, p. 259). How the kidney regulates blood volume (or, more generally, ECF volume) is a subject covered in the next chapter. Before discussing this, it is necessary to understand the process of autoregulation, the process by which the kidney maintains a constant blood flow and filtration rate. This subject is covered in this chapter.

2. Glomerular Filtration

![Diagram of glomerular filtration](image)

**Figure 1**

The force driving filtration of plasma from the glomerular capillary into Bowman's space is the hydrostatic pressure of the glomerular capillary $P_{GC}$ (Ref. 1, p. 408).

3. The forces opposing this filtration pressure are (Ref. 1, p. 408):
   a) Hydrostatic pressure in Bowman's capsule ($P_{BC}$)
b) Colloid osmotic pressure in the glomerular capillaries ($\pi_{GC}$)

The colloid osmotic pressure in the glomerular capillaries, which arises from the presence of proteins in the plasma, "pulls" the water back into the capillaries.

4. The net filtration pressure (NFP) can be expressed as the algebraic sum of the hydrostatic and osmotic pressures in the glomerular capillaries and the Bowman's capsule, as given by Equations 1 and 2 (Ref. 2, p. 15), where $P$ and $\pi$ are the hydrostatic and colloid osmotic pressures, respectively, and the subscripts GC and BC represent the glomerular capillaries and Bowman's capsule, respectively.

\[
\text{NFP} = \sum \text{Pressures inducing filtration} - \sum \text{Pressures opposing filtration} \quad (1)
\]

\[
\text{NFP} = (P_{GC} + \pi_{BC}) - (P_{BC} + \pi_{GC}) \quad (2)
\]

where $P_{GC}$, $P_{BC}$, and $\pi_{GC}$ has been defined above and $\pi_{BC}$ is the colloid osmotic pressure in Bowman's Capsule.

**NOTE:** For Equation 2, a positive value for $P_{GC}$ and $\pi_{BC}$ indicate a force out of the glomerular capillaries and a positive value for $P_{BC}$ and $\pi_{GC}$ indicate a force into the glomerular capillaries. Equation 2 is a special case of the Starling's hypothesis, which applies to any capillary (see Chapter 2) (Ref. 2, p. 15).

5. $\pi_{BC}$ is essentially zero because there is very little protein in the filtrate. Thus, equation 2 reduces to:

\[
\text{NFP} = P_{GC} - (P_{BC} + \pi_{GC}) \quad (3)
\]

Ref. 4, pp. 22-23

6. Figure 2 shows the various pressures affecting glomerular filtration. Some comments concerning these pressures are given below.

a) In the beginning of the glomerular capillaries, the hydrostatic pressure in the glomerular capillaries (produced by the pumping of blood by the heart) (50 mm Hg), is opposed by the hydrostatic pressure in the Bowman's capsule (15 mm Hg) and the colloid osmotic pressure in the glomerular capillaries (20 mm Hg). Thus the net filtration pressure at the beginning of the glomerulus is 15 mm Hg. Thus fluid crosses the glomerular membrane.

b) As fluid crosses the membrane, the concentration of protein in the plasma increases (as proteins cannot pass through the glomerular membrane). Consequently, the colloid osmotic pressure of the glomerular capillary increases, leading to less filtration.

c) The colloid osmotic pressure in the glomerular capillaries increases as the blood proceeds toward the efferent arteriole. At some point, the pressure inducing filtration will be equal to the pressure opposing filtration. This point occurs, in fact, shortly after the blood enters the
glomerular capillary bed. So there is no net filtration pressure over much of the glomerular capillary bed, leaving a large reserve for filtration should it be needed.

Figure 2 (Ref. 3, p. 51)

Ref. 2, p. 16

7A. Table I gives the pressures in the glomerulous at the afferent and efferent ends. Note that the pressures listed in this table are only estimates, as measurements have only been made in one mammal, the rat ($P_{oc}$ has been measured at 45 mm Hg in the rat (Ref. 5, p. 398)). The mean net filtration pressure (the average pressure over the entire length of the glomerulous) is 5-6 mm Hg.
7B. Definitions

Renal blood flow (RBF) - the rate of blood flow through both of the kidneys (1100 mL/min) (Ref. 5, p. 395; Ref. 2, p. 36).

Renal plasma flow (RPF) - the rate of flow of the aqueous portion of blood through both of the kidneys. Since the fraction of hematocrit (which is the cellular portion of the blood) is 0.45, the renal plasma flow is (Ref. 2, p. 37):

\[
RPF = (\text{Fraction of blood that is plasma}) \times (\text{RBF})
\]

\[
RPF = 0.55 \times 1100 \text{ mL/min} = 605 \text{ mL/min}
\]

Glomerular Filtration Rate (GFR) (Ref. 5, p. 398) - the rate of filtrate formed in all the glomeruli in both kidneys. For a normal person the GFR is 125 mL/min.

Filtration Fraction (FF) (Ref. 2, p. 37) - the fraction of renal plasma flow that becomes glomerular filtrate. The filtration fraction equals:

\[
\frac{125 \text{ ml/min}}{605 \text{ ml/min}} \approx 0.20
\]
8. Now let’s discuss the question of how the kidney regulates arterial pressure. One might think that the pressure is regulated by the following scenario: an increased arterial pressure leads to an increased hydrostatic pressure in the glomerular capillaries ($P_{GC}$), which causes an increase in the net filtration pressure as seen by Equation 3, which leads to more filtrate being formed, which leads to a decreased blood volume, which leads to a decreased venous return to the heart, which leads to a decreased cardiac output, which leads to a decreased arterial pressure. This scenario, though **DOES NOT** describe how the kidney regulates arterial pressure.

9. Surprisingly, the response to increased arterial pressure is not an increase in GFR. This is clearly shown in Figure 3.

![Figure 3 (Ref. 5, p. 411)](image)

A constant GFR and RBF is shown in Figure 3 for the mean arterial ranges between 80 to 180 mm Hg (Ref. 4, p. 38). (Remember that an average young man has a mean arterial pressure of 96 mm Hg (Ref. 5, p. 244)). Constancy in GFR and RBF is a process called autoregulation.

10. Autoregulation is surprising. As mentioned in point 8, it is expected that GFR would go up with increased arterial pressure. It is also expected that RBF would increase with increased arterial pressure in light of the relationship derived in chapter 2 (Equation 2) which is rewritten below:

$$\text{Blood flow} \propto \frac{\text{arterial pressure} - \text{venous pressure}}{\text{resistance}} \quad (4)$$
So let's discuss how the kidney maintains constant RBF and constant GFR in the face of changing arterial pressure.

Ref. 2, p. 38

11. But first let's talk about why autoregulation is necessary.

Autoregulation is necessary, otherwise there would be large changes in the amounts of water and solutes in the body with a change in the arterial pressure (Ref. 2, p. 16). Recall that the mean net filtration pressure is 5-6 mm Hg, which causes a GFR of 125 mL/min, which eventually leads to the production of 1-2 liters of urine a day (Ref. 2, p. 16). It is thus apparent that even a slight change in pressure, if transmitted to the glomerulus, would lead to tremendous change in urine output. Since the arterial pressure depends on activity (with a reduction of pressure during sleep or recumbency and an elevation during exercise or acute episodes of stress (Ref. 6, p. 85)), autoregulation is greatly needed to maintain a constant urine output.

12. There are three aspects of autoregulation that need to be explained:

a) How is the GFR maintained constant?
b) How is the RBF maintained constant?
c) How is the fraction filtered maintained constant?

The answer to the third question is straightforward. If the GFR and RBF are constant then the fraction filtered would be constant (since the filtration fraction equals the ratio of GFR to RBF). The task at hand is thus to show how the GFR and RBF are maintained constant.

Ref. 2, p. 18; Ref. 4, p. 22

13. The GFR is maintained constant by maintaining the glomerular hydrostatic pressure (i.e., the hydrostatic pressure in the glomerular capillaries) constant. Even though there are three forces that effect GFR ($P_{GC}$, $P_{BC}$, $\pi_{GC}$) (see Equation 3) only $P_{GC}$ is subject to change ($P_{BC}$ and $\pi_{GC}$ are fairly constant entities).

Ref. 4, p. 22

14. As shown in Figure 4, the glomerular hydrostatic pressure is controlled by two resistances to flow: resistance at the efferent arteriole and resistance at the afferent arteriole.
The afferent arterial resistance determines how much of the arterial blood pressure is transmitted to the glomerulous - the higher this resistance, the less hydrostatic pressure is transmitted. Resistance in the efferent arteriole maintains the hydrostatic pressure in the glomerulous, an increased in this resistance will cause an increase in the glomerular hydrostatic pressure. Since resistance is inversely related to the diameter of the arteriole, the glomerular hydrostatic pressure increases with:

a) Vasodilation of the afferent arteriole
b) Vasoconstriction of the efferent arteriole

15A. The exact mathematical relationship giving the relationship between the resistances in the efferent and afferent arterioles, the GFR, and the hydrostatic pressure in the glomerulous is derived below. This is done by making the analogy of the circulation of blood through the glomerulous to the flow of electrons through an electronic circuit, with the pressure being analogous to the voltage, the flowrate being analogous to the current, and the resistance in the blood vessels being analogous to the resistance in the electronic circuit. With this analogy, the electronics equation

\[ V = IR \]  \hspace{1cm} (5)

becomes

\[ P = k \times \text{(Flowrate)} \times R \] \hspace{1cm} (6)

15B. Shown in Figure 5 is the pathway of circulation of blood through the renal corpuscle with \( P \) standing for the hydrostatic pressure, \( R \) standing for the resistance, \( PF \) standing for the blood flow rate entering the glomerulous, \( GFR \) standing for the glomerular filtration rate, and the subscripts \( \text{Aff} \), \( \text{Eff} \), \( \text{GC} \)
standing for afferent, efferent, and glomerular capillaries, respectively. Note that the $P_{\text{Eff}}$ is taken to be negligible.

**Figure 5**

15C. Derivation of equation:

a) The following relationships are apparent from Figure 5:

$$P_{\text{aff}} - P_{\text{GC}} = K \cdot P_{\text{F}} \cdot R_{\text{AFF}}$$  \hspace{1cm} (7)$$

$$P_{\text{GC}} - O = K \cdot (P_{\text{F}} - \text{GFR}) \cdot R_{\text{Eff}}$$  \hspace{1cm} (8)$$

$$k \cdot P_{\text{F}} = \frac{P_{\text{GC}}}{R_{\text{Eff}}} + k \cdot \text{GFR}$$  \hspace{1cm} (9)$$

b) Rearranging Equation 8:

$$P_{\text{aff}} - P_{\text{GC}} = \left(\frac{P_{\text{GC}}}{R_{\text{Eff}}} + k \cdot \text{GFR}\right) R_{\text{Eff}}$$  \hspace{1cm} (10)$$

c) Substituting Equation 9 into Equation 7:

d) Rearranging Equation 10:
Chapter 4
Autorregulation

16. Equation 12 shows that $P_{GC}$ can be increased by:

a) Decreasing $R_{Aff}$

b) Increasing $R_{Eff}$

17. Figure 6 shows the pressure changes that occur in various points of the renal circulation. A decrease in pressure occurs whenever the blood flow experiences a resistance (due to a loss of energy of the flow as it goes through the resistance). Thus the following points are apparent from the examination of Figure 6:

$$P_{Aff} - k \cdot (GFR) \cdot R_{Aff} = P_{GC} \left(1 + \frac{R_{Aff}}{R_{Eff}}\right)$$

$$= P_{GC} \left(\frac{R_{Eff} + R_{Aff}}{R_{Eff}}\right) \quad \text{(11)}$$

$$\left[P_{Aff} - k \cdot (GFR) \cdot R_{Aff}\right] \left(\frac{R_{Eff}}{R_{Aff} + R_{Eff}}\right) = P_{GC} \quad \text{(12)}$$

e) Rearranging Equation 11:
Fig. 4-2. Pressure profile of the renal circulation. 
Ra, renal artery; Aa, afferent arteriole; Glom, glomerular capillaries; Ea, efferent arteriole; Pc, peritubular capillaries; V, venule; Rv, renal vein. Experimental data from the rat. (Data from Brenner BM, Troy JL, Daugherty TM: J Clin Invest 50:1776-1780, 1971)

Figure 6 (Ref. 3, p. 45)
a) The afferent arteriole provides the major resistance to blood flow, dropping the pressure from 95 mm Hg to 40-53 mm Hg in the glomerular capillaries (Ref. 4, p. 37).

b) The second major resistance in the renal circulation is the efferent arteriole, with a drop in the pressure to 15-20 mm Hg at the peritubular capillaries (Ref. 4, p. 37).

c) Note, there is no resistance in the glomerular or the peritubular capillaries.

18. Let’s summarize what we have learned to this point.

Question: How does the body maintain a constant GFR?

Answer: By maintaining a constant glomerular hydrostatic pressure.

Question: How is a constant glomerular hydrostatic pressure maintained?

Answer: By adjusting the resistances (by dilation or constriction) in the efferent and afferent arterioles (Ref. 4, p. 22).

10. The exact detailed mechanism of how vasoconstriction/vasodilation of the afferent and efferent arterioles occurs with arterial pressure changes is complex and not well understood. Figure 7 shows again how the control of the diameter of afferent and afferent/efferent arteriole effect RBF and GFR. The first response to an increase in arterial pressure is met by constriction of the afferent arteriole. This prevents the arterial pressure change from being transmitted to the glomerulus, maintaining GFR. In addition, RPF, which would increase with increased pressure (see Equation 4), does not change due to increased resistance in the afferent arteriole. The bottom part of Figure 7 showing constriction of both afferent and efferent arterioles is a case in which there is a dissociation of the autoregulation of RPF and GFR [i.e., RPF is greatly decreased and while GFR is slightly decreased (or even increased)]. Control of afferent and efferent arterioles is controlled through different mechanisms as mentioned below. Prior to discussing these autoregulation aspects with respect to the kidneys, a short discussion on mechanisms of autoregulation of blood flow through tissues in general is given next.
In talking about the control of blood flow through the kidneys, let's talk about it in the context of the control of blood flow through any tissue. In any tissue there is an autoregulation mechanism. An acute increase or decrease in arterial pressure in the tissue causes an immediate increase or decrease in the blood flow rate. However, the blood flow rate returns to normal in usually less than a minute in response to pressure changes.

Two theories given below are advanced to explain this:

i) **Metabolic Theory:** (Ref. 5, pp. 234-5)

In this theory, an increased arterial pressure resulting in an increased blood flow rate causes an increase of nutrients delivered into, and a flushing out of vasodilator substances out of the blood vessel. Both of these effects cause a constriction of the blood vessel, which lowers the blood flow rate.
b) **Myogenic Theory:** (Ref. 5, pp. 234-5; Ref. 8, p. 59)

In this theory, an increase in arterial pressure causes an increase in blood flow rate, which causes a stretching in the small blood vessel wall, which causes a contraction of the vessel, resulting in a lowering of the blood flow rate. The principle governing this contraction of the vessel wall is the principle of maintaining a constant vessel wall tension. According to La Place's Law for vessels (Equation 13)

\[
T = (\Delta P)(r)
\]  

(13)

(where \(T\) is the wall tension and \(\Delta P\) is the difference in pressure across the wall, and \(r\) is the radius of the vessel) an increase in pressure will cause a decrease in \(r\) (i.e., constriction of the vessel) in order to maintain wall tension.

Note: the metabolic theory does not apply to the autoregulation of blood flow through the kidney. There is ample blood flow for the metabolic needs of the kidney (remember that approximately 20% of the cardiac output is directed through the kidneys) (Ref. 3, pp. 43,45).

Ref. 5, p. 411-412

12. **Anatomical consideration pertinent for kidney autoregulation are give below.** See Figure 8.
Feedback occurs at the point where the tubule of the nephron makes contact with the afferent and efferent arterioles. The distal tubule cells that come in contact with the arterioles (collectively called the macula densa) are more dense and the golgi apparatus (an intracellular secretory organelle) within these cells is directed towards the arterioles. This is in contrast to all other tubular epithelial cells in which golgi apparatus is directed towards the lumen. This indicates that something is being secreted from the macula densa toward the arterioles (perhaps a signal whenever the GFR changes). The smooth muscle cells of the afferent and efferent arterioles are swollen and contain dark granules containing renin. These cells are called juxtaglomerular cells (Juxta is Latin for near or close by.) The juxtaglomerular apparatus is a term referring to the macula densa together with the juxtaglomerular cells.

Several mechanisms have been hypothesized to explain constriction of the afferent arteriole in the face of increased arterial pressure. One is a myogenic mechanism in which increased arterial pressure is met by vasoconstriction of the afferent arteriole. The other is a tubuloglomerular feedback. In this mechanism an increased ISF chloride concentration ([resulting from greater C1 delivery to the macula densa cells resulting from increased GFR] (i.e. less C1 is reabsorbed in tubular segments prior to this due to the increased tubular fluid flow)) in the region surrounding the early distal tubule (the ISF is poorly perfused in this region (i.e. solutes slowly removed) compared to all other regions vasoconstriction of the afferent arteriole.

It should be noted that afferent dilation maintains GFR and RPF with the initial decrease in arterial pressure. However there is maximum dilation at 70 to 80 mm Hg in healthy individuals and thus autoregulation ceases at pressures below 70 mm Hg leading to the decline in GFR and RPF with decreasing pressure as shown in Figure 3.

The mechanism of the modulation of efferent diameter is through the action of angiotensin II as described below. This effect is most prominent when the pressure is substantially reduced (the initial decrease in arterial pressure is primarily mediated by afferent dilation). Also angiotensin II is unlikely to play an important role in autoregulation response to increased arterial pressure - since a decrease from basal levels of angiotensin II would have minimal effect. Described in point 24 are the details of how angiotensin II is generated in response to decreased arterial pressure.

Detailed mechanism of angiotensin II causing efferent arteriole constriction (Ref. 5, pp. 411-412). The GFR is regulated by the macula densa cells monitoring the flow rate in the tubular system and sending a signal to the efferent arterioles to constrict with decreased GFR. What the macula densa cells are sensitive to is the concentration of sodium in the tubular fluid, which is related to the flow rate of the tubular fluid as described below.

a) The tubular flow rate is related to the sodium concentration as follows:

a low GFR - lowers the sodium concentration in the tubular fluid because of the increased reabsorption of sodium in the ascending limb of the loop of Henle.
b) The mechanism of GFR autoregulation is thus as follows. With decreased GFR resulting from decreased arterial pressure, the tubular concentration of sodium decreases. This decrease in sodium concentration cause the macula densa cells to send signals to the efferent arteriole to constrict. This causes the glomerular capillary pressure to rise, causing an increase in GFR back to normal.

The mechanism of the efferent arteriole constriction in response to the macula densa sensing a decrease in tubular Na⁺ concentration is that the juxtaglomerular cells release renin. Renin causes the formation of angiotensin II according to the sequence of reactions given in Figure 12 in Chapter 3. Angiotensin II causes vasoconstriction of the afferent arteriole. This causes an increase in GFR. [It should be noted that although there is converting enzyme in the kidneys, it is thought that the formation of angiotensin II in response to macula densa stimulation still occurs in the lung (Ref. 9, p. 239).]

16. Autoregulation of RBF (Ref. 12, p.55)
   RBF is principally autoregulated through afferent vasodilation as discussed in point 22. Angiotensin II does not appear to play a role.

26. There is another control which overrides autoregulation, the sympathetic nervous system (Ref. 2, p. 38). During sympathetic stimulation afferent arterioles are constricted (Ref. 5, p. 400). There are no sympathetic fibers to the efferent arterioles and thus no sympathetic nerve constriction of the efferent arterioles (Ref. 4, p. 38).

27. General Sympathetic Nervous System Effect on RBF
   a) When at person is at rest there is very little activity in the renal nerve (Ref. 4, p. 40). Thus the nerves do not have a tonic effect on renal hemodynamics (Ref. 7, p. 99).

   Ref. 4, p. 40

   b) With mild sympathetic stimulation (such as sitting or standing), there is a general increase in the nerve activity, including the renal nerve (Ref. 4, p. 40).

   Ref. 4, p. 38

   The result is a reduced blood flow through the cortex and an increased blood flow through the medulla (i.e., there is a shift in blood flow through the kidneys) (Ref. 4, p. 38). Note the normal distribution of blood flow in the kidneys is 90% through the cortex and 10% through the medulla (Ref. 3, p. 46). The consequence of this increased blood flow through the medulla is that the rate of sodium excretion will decrease (because there is a higher rate of reabsorption of Na⁺ by the tubules that extend deep in the medulla) (Ref. 7, p. 104). The overall evidence for this mechanism, however, is not conclusive (Ref. 7, p. 104).

   Ref. 4, pp. 38, 40
c) A more intense sympathetic stimulation causes vasoconstriction throughout the cortex, which drops the renal blood flow. The GFR may not fall, however, until the RBF is severely reduced.

d) Stretch receptor effects on sympathetic nervous system control of RBF and GFR (Ref. 1, pp. 250, 426-427).

Stretch receptors affect RBF and GFR through stimulation of sympathetic nerves. Recapping information presented previously (Chapter 3), stretch receptors are located in the atria of the heart and the pulmonary arteries and are sensitive to blood volume. With increased blood volume, stretch receptors cause an inhibition of sympathetic nerves attached to the afferent arterioles, causing a dilation of the afferent arteriole, a subsequent rise in the glomerular hydrostatic pressure, an increase in RBF and GFR, and an increase in urine rate. The other effect of a stimulated stretch receptor is an inhibition of antidiuretic hormone release.

28. Other comments about autoregulation of GFR and RBF

a) Autoregulation is virtually absent at a mean arterial pressure lower than 70 mm Hg (see Figure 3).

b) To reiterate, the sympathetic nervous system overrides autoregulation.

29. GFR in disease and other conditions (Ref. 11, p. 1262)

j) GFR provides the most useful general index in the assessment of the severity and progress of renal damage. It is used for diagnosis of renal impairment and for following the course of progressive, chronic renal disease. As a wide note, nearly all types of impaired function renal diseases are due to a diminished number of functioning nephrons rather than a diminished function of individual nephrons.

b) The force that is regulated to control GFR is the glomerular hydrostatic pressure. There are disease conditions, however, that affect the forces $\pi_{bc}, P_{bc}$ and $\pi_{gc}$.

1') Obstruction of ureter causes an increase in $P_{bc}$, which causes a decrease in GFR (Ref. 4, pp. 22-23).

2') Conditions that result in a loss of ECF water volume (such as diarrhea, excessive sweating) cause an increase in $\pi_{gc}$, which results in a decrease in GFR (Ref. 2, p. 17).

3') A massive intake of salt and water may dilute plasma protein concentration causing a decrease in $\pi_{gc}$, resulting in an increased GFR (Ref. 4, p. 23).

Ref. 4, p. 23
4') Disease states that are characterized by protein loss in urine cause a decrease in $\pi_{GC}$ and an increase in $\pi_{BC}$, leading to an increased GFR. Note that this effect is mitigated by a decrease in blood volume and a decrease in arterial pressure, which will cause a drop in the glomerular hydrostatic pressure.

5') GFR increases by 50% during pregnancy (Ref. 10, p. 119).

6') GFR increases in diabetes mellitus (increase of 25%) due to increased glomerular size. GFR returns to normal with adequate control with insulin (Ref. 10, p. 119).

7') GFR increases in major burn patients due to hypoproteinemia and increased renal blood flow (secondary to volume replacement) (Ref. 10, p. 119).

8') GFR is lower in neonates (until age 3-5 months) and progressively decrease in adults past middle age, due to immature glomeruli and a reduction in the number of glomeruli, respectively (Ref. 10, p. 119).

c) One might think that an altered structure of the glomerular membrane caused by disease would affect GFR.

There are diseases that alter the structure of filtering surface to make the glomerular membrane less permeable to water (Ref. 4, p. 23). However, the GFR is usually not affected, because of the large reserve of surface area available for filtration in the glomerulous (Ref. 4, p. 23).

30. Conditions leading to a reduction in RBF

a) Hemorrhage or heart disease which is marked by severe hypotension (Ref. 4, p. 40)

Ref. 3, p. 45 (point b through e)

b) Hypoxia

c) Anxiety, exercise or sudden posture change

d) Pharmacological stimuli such as barbiturates, anesthetics, hormones (vasopressin, serotonin or angiotensin).

e) Epinephrine and norepinephrine administration (which causes severe vasoconstriction).

31. Conditions leading to an increase in RBF

a) Presence of pyrogens produced by bacteria. Pyrogens (which are fever producing substances) have a direct effect on arterioles (Ref. 4, p. 40).

b) High protein diet (Ref. 3, p. 45)
c) Administration of the central sympatholytic drug, hydralazine (sympatholytic opposes sympathetic nervous activity).
References


Chapter 5

Measurement of GFR and RBF

Measurement of glomerular filtration rate (GFR) and renal blood flow (RBF) is done by continuous infusion of various substances into the patient [or sometimes endogenous substances are measured, which do not need to be infused] and then the concentration of the substance in the plasma, the concentration of the substance in the urine, and the rate of urine production is determined. Different substances (see below) are required in order to determine GFR in comparison to RBF. Given below is a discussion of the principles necessary to understand how GFR and RBF is measured.


One needs to measure the plasma clearance of an appropriate substance (as described below) in order to measure GFR and RBF. Plasma clearance is the measure of the kidneys' ability to clean or clear the plasma of various substances. It is given in terms of (mL plasma)/min. So, for example, a clearance of urea of 70 mL/min means that 70 mL of plasma are completely cleared of urea per minute. The equation for plasma clearance is developed below. The first step is to write an equation giving the amount of substance X excreted in the urine per time (Equation 1):

$$ER = (UFR) \times [X]\text{ urine}$$

where $ER$ is the excretion rate of the substance in moles/min, $UFR$ is the urine formation rate in mL/min, and $[X]\text{ urine}$ is the concentration of the substance X in the urine in moles/mL. $UFR$ and $[X]\text{ urine}$ are usually done by collecting the urine over a 24 hour period, and subsequently measuring the volume collected and the concentration of $X$ in the collected urine. $UFR$ (in mL/min) equals the volume of urine divided by 1440 (the number of minutes in 24 hours).

Plasma clearance of substance X ($C_x$) is equal to $ER$ divided by $[X]\text{ plasma}$, the concentration of substance X in the plasma yielding Equation 2.

$$C_x = \frac{ER}{[X]\text{ plasma}} = \frac{UFR \times [X]\text{ urine}}{[X]\text{ plasma}}$$

Dividing $ER$ by $[X]\text{ plasma}$ gives the amount of plasma that is “cleared” of the substance per unit time by the kidneys. Of course this concept is an artificial one since in most cases, the blood is not completely of the substance with one pass through the kidneys are 90% cleared. (remembering that only 20% of the plasma is filtered leaving 80% of
the plasma not being filtered which has roughly the same concentration of small molecular weight components).

2. Corrected plasma clearance (Ref 2 p. 119).

To determine a normalized clearance, it is necessary to correct the value of clearance calculated by Equation 2 for the size of the individual. The total kidney mass is proportional to the surface area of the entire body. The bigger the kidney mass, the larger the size and number of glomeruli in the kidney. The larger the size the and the number of the glomeruli, the greater the clearance. Thus the corrected plasma clearance \((C_x)_{cor}\) is calculated from Equation 3:

\[
(C_x)_{cor} = \frac{(UFR) \times [X]_{urine} \times 1.73}{[X]_{plasma} \times A}
\]

where \(A\) is the surface area of the individual in \(\text{m}^2\) (the average-sized person is 1.73 \(\text{m}^2\)).


a) The corrected plasma clearance is determined (using Equation 3) for a substance that passes freely through the glomerular membrane and is not secreted or reabsorbed. Since the entire amount of substance that is filtered is equal to the amount of substance that is excreted in the urine, it is clear that the corrected plasma clearance equals the corrected GFR.

b) Substances used in the measurement of GFR. (Ref. 1, p. 407)

1') An ideal substance is a substance that is: a) freely filtered; i.e must be small enough to pass through the glomerular membrane, including having the property of not being bound to proteins [Ref. 2, p. 119] b) not secreted c) iothalamate reabsorbed.

2') Infused substances (these substances are close to ideal and are continually infused).

a’) Inulin

b’) Mannitol

c’) Radioactive iothalamate
Endogenous substance creatinine (Ref. 3, p. 46)

a) Creatinine is often used for the determination of GFR because it is being produced by the muscle cells at a constant rate, which is independent of diet and physical activity (thus it is being “internally infused” into the body).

b) The advantage of using creatinine in the determination of GFR is that it is endogenous and does not require external infusion.

c) The problem with using creatinine in the determination GFR is that creatinine is secreted into the proximal tubule and thus the amount excreted will be greater than the amount that is filtered. The GFR determined by measuring creatinine clearance is 7% higher than the true GFR.

d) The value determined for GFR using creatinine clearance depends on the method used to determine creatinine.

1".) Methods that determine creatinine alone (i.e., an assay that has high specificity) determines a GFR that overestimates the true GFR by 7%.

2".) (Ref. 4, p. 1015). The usual method for determination of creatinine is the coloretric the Folin picrate method (Jaffe’ Method). The basis of this assay (see Figure 1) is the reaction of creatinine (I) with an alkaline solution of sodium picrate (II) to form a red Janovski complex (III), which is monitored spectrophotometrically between 510-520 nm (Ref. 4, p. 1015) (see Figure 1).
Plasma contains interfering compounds that form chromagens by the Jaffe' reaction. Glucose, uric acid and ascorbic acid reduce picrate to picramate, which absorbs at 482 nm (Ref 4, p. 1017). Other interferences include: acetone, acetoacetic acid, fructose, hippuric acid, urea, indole, histidine, asparagine, resorcinol, glycocyamidine hydantoin, and cephalosporin antibiotics (Ref. 5, p. 4). Without modification of this assay to minimize these interferences, creatinine clearance determined by this method will (ref 3, p. 46):

a") Approximate the true GFR at normal levels of GFR (due to assay overestimating creatinine in plasma).

b") Overestimate the true GFR at low levels of GFR (overestimates GFR by 50% when GFR is 20 mL/min). The reason for this is:

1") The creatinine represents a larger fraction of the total Jaffe' chromagens in the plasma at low GFR levels.
The fraction of creatinine secreted into the tubules increases at low GFR levels.

4. Measurement of renal plasma flow (RPF) and RBF (Ref. 1, p. 408; Ref. 2, p. 120)

a) The corrected plasma clearance is determined (using Equation 3 for substance that is totally cleared in one passage through the kidney). The ideal substance would pass totally from the blood into the tubular system through a combination of filtration and secretion. If this is the case, it is clear that the corrected renal plasma flow (RPF$_{cor}$) equals the corrected plasma clearance.

b) Infusion of para-aminohippurate (PAH).

No substance has been found that is completely cleared on one pass through the kidneys. PAH infused at low levels has a 90% clearance. Thus the value of RPF$_{cor}$ is calculated from the corrected clearance of PAH as given Equation 4.

\[
RPF = \frac{(C_{PAH})_{cor}}{0.90} \quad (4)
\]

The fraction of blood that is plasma is 0.55, so the RBF is given by Equation 5.

\[
RBF = \frac{C_{PAH}}{(0.91)(0.55)} \quad (5)
\]

20. The filtration fraction (FF) is given by Equation 6.

\[
FF = \frac{GFR}{RPF} \quad (6)
\]
21. Problems

a) Calculate the uncorrected GFR knowing the following data: [ answer: 110 mL/min]

\[
\begin{align*}
[\text{Inulin}]_{\text{plasma}} &= 5.65 \text{ mg/mL} \\
[\text{Inulin}]_{\text{urine}} &= 260 \text{ mg/mL} \\
24 \text{ hour urine volume} &= 3456 \text{ mL}
\end{align*}
\]

b) Calculate the uncorrected renal plasma flow knowing the following data: [answer: 779 mL/min]

\[
\begin{align*}
[\text{para-aminohippuric acid}]_{\text{plasma}} &= 0.050 \text{ mg/mL} \\
[\text{para-aminohippuric acid}]_{\text{urine}} &= 14.6 \text{ mg/mL} \\
24 \text{ hour urine volume} &= 3456 \text{ mL} \\
\text{Hemarocrit} &= 55\% \\
\text{Extraction ratio for para-aminohippuric acid} &= 0.9
\end{align*}
\]
References


Chapter 6
Mechanisms of Sodium and Water Reabsorption by the Kidneys

1. The long-term control of blood pressure through regulation of the ECF volume. This is accomplished through:
   a) controlling the **OUTPUT** of water from the body, by the kidney controlling the volume of urine.
   b) controlling the **INTAKE** of water into the body, mediated through thirst sensations.

2. Intimately associated with the issue of ECF volume is the sodium content of the ECF. In fact, it is the amount of sodium in the ECF that is the major determinant of the ECF volume (Ref. 1, p. 94). **As sodium goes, so goes water.** Thus, an increase in the amount of sodium in the ECF leads to an increase in water in the ECF and vice versa.

3. It is important to note that it is the amount of sodium in the ECF that is important to water regulation and **NOT** the concentration.

Ref. 1, p. 94, 95

Thus there are various conditions which lead to an expansion of ECF volume and depending on the condition, the Na\(^+\) concentration in the ECF can be increased, normal, or decreased. Similarly, there are various conditions which lead to a decrease in ECF volume and depending on the condition, the Na\(^+\) concentration in the ECF can be increased, normal, or decreased. Thus, the serum sodium concentration does not provide unequivocal information on total Na status.

4. ECF volume is regulated by the kidneys controlling the sodium excretion (ref. 3, p. 106).

5. Let’s look at how the kidney excretes sodium. In a general way the amount excreted is given by Equations 1 and 2 (ref. 1, p. 97).

\[
E_{Na} = F_{Na} - R_{Na} \tag{1}
\]

where \(E_{Na}\) is the amount of sodium excreted per unit time, \(F_{Na}\) is the amount of sodium filtered per unit time, and \(R_{Na}\) is the amount of sodium reabsorbed per unit time.

\(F_{Na}\) can be written in terms of the glomerular filtration rate (GFR) and the concentration of sodium in the filtrate [Na\(^+\)] filtrate giving Equation 2.

\[
E_{Na} = GFR \cdot [Na^+]_{filtrate} - R_{Na^+} \tag{2}
\]
6. We will explain the totality of Equation 2 later chapters. The rest of this chapter deals with the \( R(\text{Na}) \) term in this expression, by explaining the mechanisms by which the kidney reabsorbs \( \text{Na}^+ \).

7. Overview of fluid osmolarity in the various tubules of the kidney.

   a) **Proximal Tubule** - isoosmotic with plasma (i.e., tubular fluid has the same osmolarity as the plasma).

   b) **Thin Descending Limb of the Loop of Henle** - hyperosmotic

   c) **Thin and Thick Ascending Limb of the Loop of Henle** - osmolarity decreases progressively to the point that the fluid is hypoosmotic at the start of the distal tubule.

   d) **Distal Convoluted Tubule** - osmolarity decreases further

   e) **Cortical Collecting Tubule and Medullary Collecting Duct** - osmolarity depends on the presence of ADH (hyperosmotic with ADH present, further decrease in osmolarity with ADH absent).

8. Sodium Reabsorption in the Proximal Tubule is discussed below. The percentages of sodium reabsorbed in the tubule system is depicted in Figure 1A.

---

Refer to Figure 1A (Ref. 16, p. 46)

Ref. 14, p. 34; Ref. 6, p. 67; Ref. 9, p. 46; Ref. 15, pp. 100, 105

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Chapter 6
Mechanisms of Sodium and Water Reabsorption by the Kidneys

96
9. A summary of the substances reabsorbed in the proximal tubule under normal circumstances is given below, along with the percentages reabsorbed.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>60%-65%</td>
</tr>
<tr>
<td>Sodium</td>
<td>60%-65%</td>
</tr>
<tr>
<td>Potassium</td>
<td>80%</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>80%-90%</td>
</tr>
<tr>
<td>Glucose</td>
<td>100%</td>
</tr>
<tr>
<td>Amino Acids</td>
<td>100%</td>
</tr>
<tr>
<td>Phosphate</td>
<td>80-95%</td>
</tr>
<tr>
<td>Proteins</td>
<td>100%</td>
</tr>
</tbody>
</table>

10. Shown in Figure 1B is the change in solute concentration (graphed as % of concentration of that which is present in the initial filtrate) with respect to location in the proximal tubule (except for water, which is graphed as the percentage of water remaining in the tubule compared to the initial filtrate).

![Figure 1B (Ref. 15, p. 87)](image)

11. We will now discuss the mechanism of sodium reabsorption in the proximal tubule. This is a very important process, as the reabsorption of most of the substances listed in point 9 depend on sodium reabsorption. Conversely the reabsorption of sodium depends on the presence of some of these substances, as will be discussed below.

   a) Electrochemical gradient via transport proteins
The main mechanism is shown in Figure 2: passive entry of Na\(^+\) through the luminal membrane of the epithelial cell and then active transport of Na\(^+\) across the basolateral membrane into the interstitial fluid (ref. 15, p. 90). Sodium moves into the tubule cell via 1) Na\(^+\) concentration difference force between the lumen and the cell (Na\(^+\) concentration being greater in the lumen than within the epithelial cell) and 2) an electrostatic force between the proximal tubular cell and lumen (with the epithelial having a negative potential with respect to the lumen) (ref. 15, p. 91; ref. 2, p. 401). This effect is known collectively as an electrochemical gradient. As discussed below, the diffusion of Na\(^+\) into the tubular cell occurs via carrier proteins, since ions are not able to pass through membranes (which have a lipid composition) (ref. 15, p. 90). Sodium is transported against an electrochemical gradient across the basolateral membrane through a transport protein present exclusively on the basolateral membrane, Na-K ATPase (ref. 7, p. 146).

![Figure 2 (Ref. 15, p. 91)](image)

1') The key to the above mentioned Na\(^+\) reabsorption mechanism is the Na-K ATPase, which maintains a low sodium concentration within the proximal tubule cell. This mechanism is referred to as a secondary active transport mechanism (the primary mechanism being passive movement of Na\(^+\) into the cell down its electrochemical gradient) (ref. 15, p. 90). The Na,
K ATPase also serves the function of pumping out reabsorbed Na\(^+\) (ref. 6, p. 67). The Na-K ATPase pumps Na\(^+\) out of the cell and K\(^+\) into the cell at a ratio of 3 to 2 (ref. 6, p. 67).

2') Transport Proteins

a') Overview

Shown in Figure 2 are the co-transport and counter-transport proteins on the luminal membrane which are necessary for Na\(^+\) to diffuse through the membrane. Thus these other constituents (glucose, amino acids, bicarbonate) are needed for sodium reabsorption (ref. 15, p. 90) (removal of glucose, amino acids and/or bicarbonate from the tubular fluid completely abolishes fluid reabsorption in the proximal convoluted tubule (ref. 7, p. 155). Conversely, sodium is responsible for the reabsorption of glucose, amino acids (ref. 6, p. 67) and bicarbonate (ref. 7, p. 153), providing the necessary energy (from the electrochemical gradient) to move these solutes against the unfavorable concentration gradients that exist between the lumen and the epithelial cell (ref. 6, pp. 68-69).

b') Na/H\(^+\) counter-transport

One of the Na\(^+\) transport proteins on the luminal membrane is the Na\(^+\)/H\(^+\) counter-transport protein which exchanges one H\(^+\) into the lumen (from the cell) for each Na\(^+\) into the cell (from the lumen) (ref. 15, p. 90).

1") This protein is responsible for most (if not all) of the secretion of H\(^+\) in the proximal tubule (ref. 7, p. 153). The transporting property of this protein is increased with increased H\(^+\) concentration within the proximal tubular cell and thus accounts for the increased H\(^+\) secretion into the proximal tubule in response to intracellular acidosis (ref. 7, p. 154).

Ref. 14, pp. 48-9

2") This secretion of H\(^+\) leads to the reabsorption of bicarbonate as depicted in Figure 3 and described below. Referring to Figure 3, HCO\(_3^-\) is taken from the lumen into the tubular cell in the form of CO\(_2\) and water. This is accomplished by the reaction of HCO\(_3^-\) with H\(^+\) (which has been secreted into the lumen from the tubule cell) to form H\(_2\)CO\(_3\), which is broken down to CO\(_2\) and H\(_2\)O, a reaction catalyzed by carbonic anhydrase (which is present on the brush border). Within the tubular cell, carbonic anhydrase catalyzes the formation of H\(_2\)CO\(_3\) from CO\(_2\) and H\(_2\)O, which dissociates into HCO\(_3^-\) and H\(^+\). While H\(^+\) is secreted into the tubule, HCO\(_3^-\) follows Na\(^+\) through the basolateral membrane. [NOTE: The transfer of HCO\(_3^-\) through the basolateral membrane is a carrier mediated process, with the carrier co-transporting 3HCO\(_3^-\) and 1 Na\(^+\). This transport process depends on the negative potential of the cell to drive out the negatively charged HCO\(_3^-\) (thus, it is a form of secondary active transport, since Na,K ATPase causes K\(^+\) concentration differences inside and outside of the cell) (ref. 15, p. 92.)]
Mechanisms of Sodium and Water Reabsorption by the Kidneys

Figure 3 (Ref. 14, p. 49)

**c') Sodium/Glucose Co-Transporter**

This mechanism of transport is much more prevalent in the early proximal tubule than in the late proximal segment (this is due to the decreased affinity that the transport protein has for glucose in the later segments) (ref. 7, p.154). In normal circumstances, 100% of the glucose is reabsorbed in the early proximal tubule (ref. 1, pp. 49-50).

**d') Sodium/Amino Acid Co-Transporter**

There appears to be multiple transporter proteins present on the luminal membrane. For example, neutral amino acids have at least 3 different separate systems (ref. 7, p. 154). In normal circumstances, 100% of the amino acids are reabsorbed in the early proximal tubule (ref. 1, pp. 49-50).

**b) Generation of Lumen potential**

The lumen potential along with the concentration gradient difference drives sodium into the proximal tubule cell. Generation of the lumen potential in the proximal tubule is discussed.
below. The lumen potential is important to not only the electrochemical gradient mechanism of sodium reabsorption but to the electrogeneric mechanism of sodium reabsorption discussed in point 12.b.

1') The potential profile in the proximal tubule lumen is given in Figure 4. This potential is with respect to the interstitial fluid outside the tubule cells.

![Figure 4 (Ref. 7, p. 151)](image)

2') Negative lumen potential in the beginning of the proximal tubule

The negative potential in the beginning of the proximal tubule is due to the co-transport of Na\(^+\) into the tubule cell with neutral species (i.e., glucose and amino acids) which leaves a negative charge behind in the lumen) (ref. 7, pp. 151-152). It should be noted that deletion of glucose and amino acids from the proximal tubule fluid results in an initial lumen potential of 0 mV (ref. 7, p. 152).

3') Positive lumen potential in the remaining proximal tubule.

The positive potential is due to the diffusion potential arising from the chloride concentration difference between the lumen and the interstitial fluid (ref. 7, p.152). See Figure 5.

![Figure 5](image)
**Figure 5 (Ref. 1, p. 51)**

a') Comparing the lumen with the ISF (peritubular space), the concentration of all ionic species is the same **EXCEPT** for Cl\(^{-}\) and HCO\(_3\)\(^{-}\). Thus the potential established between these locations will depend on the permeability of the membrane (junction membrane) to these ions. The junction membrane is more permeable to Cl\(^{-}\) and HCO\(_3\)\(^{-}\), thus Cl\(^{-}\) has a greater influence on the potential, causing a positive lumen potential (ref. 1, p. 51).

Ref. 6, p. 69; ref. 14, p. 34

b') The origination of the concentration difference between the lumen and the peritubular ISF is the preferential absorption of HCO\(_3\)\(^{-}\) over Cl\(^{-}\) in the early segments of the proximal tubule (due to the Na\(^{+}\)/H\(^{+}\) counter-transporter) and the isoosmotic reabsorption of water in the proximal tubule, which results in an increased Cl\(^{-}\) concentration in the tubular fluid compared to the pericapillary ISF.

c') Electrogenic mechanism for Na\(^{+}\) reabsorption (ref. 7, p. 155).

When all other mechanisms of Na\(^{+}\) reabsorption are blocked, there is a -1.0 mV lumen potential, which suggests that the luminal membrane has a permeability to Na\(^{+}\) (i.e., that there are sodium channels in the membrane). If this is the case, then Na\(^{+}\) entry into the tubule cell driven by a positive lumen potential is a mechanism of Na\(^{+}\) reabsorption. This mechanism is limited to the straight segment of the proximal tubule.

c) Passive NaCl Absorption as a mechanism for Na\(^{+}\) reabsorption (Ref. 7, p. 155; ref. 15, p. 93)

Chloride is driven through the junction from the lumen to the peritubular ISF by a concentration gradient. Na\(^{+}\) follows the negatively charged Cl\(^{-}\) to maintain electronegativity (ref. 6, p. 69). This mechanism accounts for 1/3 of the net sodium reabsorption in the straight segment.

d) Solvent drag as a mechanism for Na\(^{+}\) reabsorption (ref 1, p. 50).

Another mechanism for Na\(^{+}\) reabsorption is solvent drag of permeable solutes through the junction as water is pulled from the lumen to the ISF of the peritubular capillaries. Since the junction is highly permeable to NaCl, NaCl is dragged by the water flux.

Ref. 9, p. 44

13. We have discussed the reabsorption of Na\(^{+}\) from the glomerular filtrate in the proximal tubule. The reabsorption of water in the proximal tubule is directly linked to reabsorption of solutes through the osmotic pressure generated as shown in Figure 7 and discussed below.
The water flows through the intercellular spaces from the lumen to the ISF by the following means:

a) $\text{Na}^+$ enters the cell and the intercellular spaces by the mechanisms discussed.

b) $\text{Na}^+$ is actively pumped into the intercellular spaces by Na,K ATPase.

c) The increased presence of solutes in the intercellular spaces generates a local hyperosmolarity which osmotically attracts water across the membrane or through the junction.

d) Fluid accumulates in the intercellular space, increasing the hydrostatic pressure. This forces water across the basement membrane (tight junctions are presumed to be impermeable to water, raising hydrostatic pressure (ref. 7, p. 135)).

e) Water enters the peritubular capillaries through a favorable net force resulting from the algebraic sum of the hydrostatic and colloid osmotic pressures (see next chapter).

There are problems with the above theory. One problem is that the junctions are leaky, and thus the proposed increase in hydrostatic pressure in the intercellular space to force water through the basement membrane is suspect (ref. 7, p. 135). Other explanations have been offered (ref. 7, p. 135).

Ref. 15, pp. 93-94

14. Other absorbed solutes play an important role in the absorption of water. Although there is no difference in osmolarity between the proximal tubular fluid and the ISF of the peritubular
capillaries, there is a difference in the effective osmolarity, since the ISF contains more bicarbonate, glucose, and amino acids than the tubular fluid. Since these species are much less permeable at the junction than chloride (which is the solute that is in greater concentration in the tubular fluid), there is an osmotic pull of water into the intercellular space (see Figure 8).

![Figure 8](Ref. 15, p. 94)

The water in the intercellular space can go in one of two directions depending on the magnitude of the Starling's forces in the various compartments: into the peritubular capillaries or back into the lumen.

Ref. 6, p. 71

In cases where a nonreabsorbable solute is present (a solute that stays in the lumen) there is an osmotic force present in the lumen which diminishes the reabsorption of water. This occurs in diabetes, where the nonreabsorbable solute is glucose (the concentration of glucose is so high that it exceeds the ability of the tubules to reabsorb all of it). Osmotic diuresis causes an increase of urine volume, resulting in weight loss and dehydration.

Ref. 7, pp. 156-158

15. Other factors are listed below that affect salt (water) reabsorption in the **proximal tubule**. These are discussed in more detail in the next chapter.

   a) A n increase in GFR leads to an increase in sodium and water reabsorption (called glomerulotubular balance).
b) An increase in the capillary oncotic pressure leads to an increase in reabsorption of sodium and water.

c) Renal nerve stimulation increases the reabsorption of sodium and water.

d) A low concentration of angiotensin II causes an increase in fluid reabsorption (shown to stimulate the Na\(^+\)/H\(^+\) counter-transport mechanism), while high concentrations of angiotensin II depress fluid reabsorption.

e) Atrial natriuretic factor inhibits fluid retention. This effect is largely through hemodynamic effects, however, a direct effect on tubular transport has not been ruled out.

f) Others factors include parathyroid hormone, thyroid hormones, and corticosteroids.

16. The isoosmotic character of the tubular fluid in the proximal tubule is due to the permeability of the proximal tubule to water (i.e., leaky junctions). Thus any absorption of solute is immediately followed by water reabsorption.

17. Some comments about glomerulotubular balance

a) This mechanism is operative not only in the proximal tubule, but in all tubular segments (ref. 9, p. 68).

b) Glomerulotubular balance is the process by which changes in GFR are balanced by a concomitant change in fluid and sodium reabsorption (ref. 1, p. 52).

c) It blunts the effect of change of GFR on the amount of sodium (and water) excreted, by adjusting the rate of fluid absorption (ref. 9, pp. 68-9). Thus, if the GFR decreases 25\%, the rate of proximal fluid reabsorption will decrease by 20\% (ref. 9, p. 68).

d) Glomerular tubular balance is the second line in defense preventing spontaneous changes in GFR, with the first line of defense being GFR autoregulation. Autoregulation prevents GFR from changing too much in response to blood pressure changes and glomerulotubular balance blunts the sodium-excretion response to whatever GFR change does occur (ref. 9, p. 69).

Ref. 6, p. 74; Ref. 1, p. 53

e) The mechanism of this effect in the proximal tubule remains unknown despite much research (ref. 1, p. 52). Two proposed mechanisms are given below:

1') Starling Forces

a') An increase in glomerular capillary pressure leads to an increase in the fraction filtered, which leads to an increase in GFR.

b') This increases the protein concentration in peritubular fluid.
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This increases the colloid osmotic pressure in the peritubular fluid, which leads to increased reabsorption of fluid.

Ref. 14, p. 39

2') Stimulation of Na\(^+\)/H\(^+\) Counter-Transport Protein

a') The increased filtration rate leads to less reabsorption of bicarbonate.

b') The higher concentration of bicarbonate in the tubular fluid stimulates the Na\(^+\)/H\(^+\) counter-transport protein.

c') There is an increased reabsorption of Na\(^+\) by the proximal tubule cell.

18. Overview

Sodium Reabsorption in the Loop of Henle is discussed below.

a) The Loop of Henle reabsorbs 15-20% of the original glomerular filtrate volume and passes the remaining 20 to 30% of the original filtrate volume on to the distal tubule (ref. 10, p. 58). The Loop of Henle absorbs about 25 to 40% of the filtered sodium load (ref. 7, p. 159).

b) While salt and water reabsorption are coupled in the proximal tubule, they are dissociated in the Loop of Henle, as seen below (ref. 7, p. 159).

c) In the thin segments of the Loop of Henle, the water and solute movement through the epithelial cells is passive (ref. 1, p. 54). There is no evidence that the solute transfer is active (ref. 7, p. 159). This lack of active transport is consistent with cell morphology and the relative lack of Na,K ATPase (ref. 7, p. 159-160). However, there are marked differences in the permeability characteristics of the descending versus the ascending thin limb (ref. 7, p. 159).

19. Reabsorption in the descending thin limb of the Loop of Henle

a) Has a high permeability to water but a low permeability to solutes (ref. 1, p. 54).

Ref. 10, p. 56

b) Water is absorbed into the interstitium because of this permeability and the high osmolarity of the medullary ISF. Shown in Figure 9 is a diagram of a kidney lobe showing the osmolarity values of the ISF at different levels. The osmolarity of the ISF increases from 300 mOsm/L in the cortex [the same value as it is for the ECF in almost all parts of the body (and in plasma) (ref. 2, p. 415)] to 1200-1400 mOsm/L in the papillary tip (ref. 2, p. 415). The tubular fluid becomes progressively more concentrated as it approaches the tip (because the water is reabsorbed and the solute is not).

c) Addition of urea and NaCl from the medulla interstitium to the tubular fluid also contributes to the rise of osmolarity in the tubular fluid (ref. 7, p. 160).
20. Reabsorption in the ascending thin limb of the Loop of Henle

   a) Dilute urine begins to form in the ascending thin limb (ref. 7, p. 160). The tubular fluid is more dilute than the thin descending limb in all parts of the thin ascending limb at the same height (ref. 7, p. 160).

   b) This decrease in osmolarity in the ascending thin limb is accounted for primarily by a fall in the NaCl content in the tubular fluid (ref. 7, p. 137).

   c) This drop in NaCl content happens because the ascending thin limb has a high sodium chloride permeability and a low water permeability.

   Ref. 1, p. 54

   d) See Figure 10. NaCl is reabsorbed by the ascending thin limb of the Loop of Henle because of the concentration difference in NaCl between the tubular fluid and the interstitium. Even though the osmolarity for the tubular and interstitial fluid is the same at the tip of the Loop of Henle, there is a higher concentration of NaCl, and a lower concentration of urea, in the tubular fluid than in the interstitium. Thus NaCl diffuses out of the lumen and urea diffuses into the lumen. The ascending thin limb of the Loop of Henle has a greater permeability to NaCl than urea (represented in Figure 10 by a difference in thickness in the arrows) resulting in a decreased osmolarity in the tubular fluid.

Figure 9 (Ref. 11, p. 27)
fluid in the ascending thin limb of the Loop of Henle and an increased osmolarity in the interstitium of the medulla.

**Figure 10 (Ref. 1, p. 55)**

Ref. 15, p. 132

e) There are problems with the above mechanism for Na\(^{+}\) reabsorption as explained in Ref. 15, p. 132. The problem is summarized as follows: there is a significant diffusion of urea into the descending thin limb lumen causing the NaCl gradient between the lumen and ISF to not be as great as needed to support the passive NaCl reabsorption in the thin ascending limb.

21. The Reabsorption in thick ascending limb of the Loop of Henle (TALH)
Ref. 1, pp. 54-55

a) This segment is impermeable to water. Salt is reabsorbed through an secondary active process. The luminal fluid becomes hypoosmotic (in comparison to plasma) by the time it leaves the TALH.

Ref. 15, pp. 117-119

b) The process by which Na\(^{+}\) is reabsorbed through the TALH epithelial cell is shown in Figure 11 and is described below.
The Na,K ATPase serves to:

a') Actively transport Na\(^+\) out of the TALH tubule cell, such that Na\(^+\) enters from the lumen into the tubule cell down its concentration gradient.

b') Actively pump reabsorbed Na\(^+\) out of the TALH tubule cell against its concentration gradient into the ISF, and ultimately into the peritubular capillaries.

2') The Na\(^+\) diffusion into the TALH cell occurs via a Na\(^+\), K\(^+\), 2Cl\(^-\) carrier on the luminal membrane (all sites on transport protein must be bound for there to be transport).

3') Cl\(^-\) is the rate limiting species for this transport process. NaCl transport in the TALH has been shown to be directly related to Cl\(^-\) concentration (K\(^+\) is not limiting, because K\(^+\) diffuses back into the lumen via a K\(^+\) channel).

4') The K\(^+\) diffusion into the lumen leaves the lumen at a positive potential, which drives passive paracellular reabsorption of cations (such as Na\(^+\), Ca\(^{2+}\), Mg\(^{2+}\)).
(See Figure 12). Fifty percent of the sodium reabsorption in the TALH is by the paracellular pathway driven by the lumen-positive voltage (ref. 7, p. 161).

5') The Cl\(^-\) enters the peritubular capillary ISF by a Cl\(^-\) channel.

Ref. 15, p. 121

c) In the TALH that is in the cortex (i.e., for outer cortical nephrons) there is another mechanism of Na\(^+\) transport, in addition to the Na\(^+\), K\(^+\), 2Cl\(^-\) carrier. This mechanism is parallel Na\(^+\)/H\(^+\) and Cl\(^-\)/HCO\(_3^\-) counter-transporters.

1') Water and CO\(_2\) combine in the tubule cell to form H\(_2\)CO\(_3\) which dissociates into H\(^+\) and HCO\(_3^\-\).

2') H\(^+\) is secreted into the lumen, and exchanged for Na\(^+\) entering the tubule cell.

3') HCO\(_3^\-\) enters the lumen exchanging for Cl\(^-\) entering the tubule cell.

4') H\(^+\) combines with HCO\(_3^\-) in the lumen to form H\(_2\)CO\(_3\), which recycles back into the tubule cell.

5') The Na\(^+\)/H\(^+\) counter-transporter reabsorbs some of the filtered HCO\(_3^\-\) that escapes the proximal tubule.

Ref. 7, pp. 163-164.

d) Other factors that control NaCl absorption in the TALH are:

1') ADH (which increases salt reabsorption in the medullary TALH)

2') Prostaglandin E\(_2\) (which inhibits salt reabsorption in the medullary TALH)

3') Increased peritubular osmolarity (which inhibits the ADH-stimulated rate of NaCl reabsorption by the medullary TALH).

4') Renal nerve activity. (Nerve endings have been found attached to the basement membrane of the TALH. Increased renal nerve activity increases the rate of NaCl reabsorption.)
22. Glomerulo tubular balance in Loop of Henle
Glomerotubular balance is operative in the Loop of Henle as a whole, which means there is an increased reabsorbance of sodium and water when the rate of filtrate delivered to it is increased (ref. 15, p. 120).

23. Overview of hormones affecting reabsorption acting on the distal convoluted tubule, connecting segment, and collecting tubules
There are four segments after this in the tubules which have different functions, different histology and different responses to hormones as seen in Table 1 (ref. 15, p. 139).
24. Characteristics of tubular system distal to the TALH

a) Can generate and maintain a large Na\(^+\) concentration difference between the lumen and the tubule cell. It is able to maintain this concentration difference because of the impermeability of the junctions to water and salt.

b) The total reabsorptive capacity for Na\(^+\) is limited. Has less Na,K ATPase than other nephron segments (except for the thin segments of the Loop of Henle).

c) The reabsorptive capability of the distal nephron for Na\(^+\) greatly depends on the rate of delivery of Na\(^+\) to the distal nephron. There is a great need to keep the Na\(^+\) and fluid flowrate constant to the distal nephron. Without this control of delivery of fluid to the distal nephron, there would be serious loss of Na\(^+\) and water. This is accomplished through autoregulation and glomerulotubular balance (discussed in previous sections).

Ref. 15, p. 141

25. Function of each segment depends on the responsiveness to hormones (see Table 1).

a) Sodium reabsorption and potassium secretion occurs in segments that are responsive to aldosterone (connecting segment, cortical collecting tubule, medullary collecting tubule). Note the distal tubule also reabsorbs Na\(^+\), but via a different mechanism.
b) Water reabsorption occurs only when ADH (Antidiuretic hormone) is present and in only those segments that are ADH responsive (cortical collecting tubule, medullary collecting tubule).

c) Calcium reabsorption occurs only in those segments responsive to parathyroid hormone (distal convoluted tubule, connecting segment).

d) H⁺ secretion occurs in the intercalated cells, which are present in the cortical collecting tubule and the outer medullary collecting tubule.

Ref. 15, pp. 141-143

26. Reabsorption of sodium and water in the distal convoluted tubule

a) The mechanism is depicted in Figure 13.

b) Mechanism

![Figure 13](Ref. 15, p. 142)

There is diffusion of Na⁺ down the concentration gradient that exists between the lumen and the cell. Entry requires a Na⁺/Cl⁻ co-transporter protein. The low concentration of Na⁺ in the tubular cell is maintained by Na⁺, K ATPase.
c) Glomerulotubular balance is operative in this segment, as Na\(^+\) reabsorption varies directly with Na\(^+\) delivery. (The mechanism is as follows: the higher the fluid delivery rate, the higher the concentration of Na\(^+\) in the lumen, the greater the diffusion force into the cell.)

d) The segment is impermeable to water (a very minimal amount of water is reabsorbed). It is not responsive to ADH.

e) This is a diluting segment because Na\(^+\) is reabsorbed and water is not.

Ref. 7, p. 166

f) The distal tubule is the site of the action of the diuretic thiazide. Thiazide inhibits the Na\(^+\)/Cl\(^-\) co-transporter.

g) The distal tubule normally plays little role in the secretion of H\(^+\) and K\(^+\) (ref. 15, p. 143).

Ref. 15, p. 143

27. Reabsorption of sodium and water in the connecting segment

a) Shares characteristics common to both the distal tubule and cortical collecting tubule.

b) Impermeable to water even in the presence of ADH.

c) Reabsorption of Na\(^+\)

1') Via Na\(^+\)/Cl\(^-\) co-transporter

2') Reabsors Na\(^+\) (via Na\(^+\) channels) and secretes K\(^+\) in response to aldosterone.

d) The distal tubule and the connecting segment absorbs roughly 10% of the filtered sodium load (ref. 7, p. 165).
28. Reabsorption of sodium and water in the cortical collecting tubule

a) There are two types of tubular cells in this segment: the principal cells and the intercalated cells. Only the principal cells reabsorb Na\(^+\). The intercalated cells are involved in H\(^+\) secretion and K\(^+\) reabsorption.

b) The mechanism of Na\(^+\) reabsorption in the principal cells is shown in Figure 14 and described below.

1') Na\(^+\) enters the tubule cell through ion specific Na\(^+\) channels on the luminal wall, being driven by a concentration gradient force (these channels are blocked by the diuretic amiloride).

2') Electronegativity is maintained either by reabsorption of Cl\(^-\) via a paracellular route or secretion of K\(^+\) into the lumen.

3') Reabsorbed Na\(^+\) is pumped out of the tubule cell by the Na, K ATPase.
4’) This is one of the sites of aldosterone’s action. Aldosterone plays an important role in the reabsorption of Na\(^+\), primarily by increasing the number of open Na\(^+\) channels in the luminal membrane (See Figure 15). (Increased aldosterone leads to increased Na\(^+\) reabsorption.) Aldosterone also causes an increased Na, K ATPase activity and an increased K\(^+\) secretion into the lumen (through the K\(^+\) channels). These latter effects are due primarily to Na\(^+\) influx into the tubule cells, rather than a direct effect of aldosterone.

Figure 15 (Ref. 15, p. 144)

- The permeability of the cells in the cortical collecting tubule to water is dependent on the presence of ADH. In the presence of ADH the osmolarity of the tubular fluid can equilibrate with the cortical interstitium. [With no ADH present the luminal fluid osmolarity can drop further (ref. 1, p. 59).]

- Urea concentration increases with ADH present (since ADH leads to increased water permeability, but not urea permeability, of the epithelial cells).
29. Sodium and water reabsorption in the medullary collecting tubule.

a) The medullary collecting tubule consists of an outer and inner tubule (the dividing point being at the level where the TALH begins).

b) The outer medullary collecting tubule does not participate in Na\(^+\) reabsorption to any extent because the majority of cells are comparable to the cortical intercalated cells. These cells are principally involved with H\(^+\) secretion and K\(^+\) reabsorption. Water permeability depends on the presence of ADH (no permeability without ADH being present). [The lumen potential is negative (ref. 7, p. 167).] There is no permeability to urea even with ADH present.

c) Na\(^+\) reabsorption occurs in the inner medullary collecting tubule.

1') The lumen potential is positive (ref. 7, p. 167).

2') The mechanism is depicted in Figure 16. Whether Na\(^+\) reabsorption occurs depends on whether the condition of volume depletion or volume expansion is present.
Figure 17 (Ref. 15, p. 149)

3') Volume depletion

a') Aldosterone release leads to Na\(^+\) reabsorption by opening more Na\(^+\) channels. Na\(^+\) enters the tubule cell through Na\(^+\) channels (blocked by the diuretic amiloride) driven by an electrical gradient (not principally driven by a concentration difference because there are situations in which the lumen concentration is less than the tubule cell concentration and Na\(^+\) is still reabsorbed). The electrical gradient driving the Na\(^+\) reabsorption is from two sources: a positive lumen potential (ref. 7, p. 167), and a negative cell potential (K\(^+\) channels on the basolateral membrane leads to the negative cell potential).

b') Reabsorption of Na\(^+\) into the peritubular ISF is via Na, K ATPase active transport.

c') The temporary lumen-negative potential condition created by the transfer of Na\(^+\) into the cell drives Cl\(^-\) reabsorption via a paracellular route.

4') Volume expansion

a') There is a fall of Na\(^+\) reabsorption due to both a reduction in aldosterone secretion and increased atrial natriuretic peptide (ANP) release.
b') ANP leads to the production of cyclic GMP, which causes a reduction in Na\(^+\) reabsorption by decreasing the number of open Na\(^+\) channels.

5') Water reabsorption depends on the presence of ADH. With ADH present, water is absorbed and the osmolarity of the tubular fluid equilibrates to the osmolarity of the medullary interstitium (leading to a concentrated urine).

6') There is a higher basal permeability of the inner medullary collecting tubule to urea that is increased four-fold with the presence of ADH. This is different than the cortical and outer medullary collecting tubule.

7') This segment reabsors K\(^+\) (particularly in states of K\(^+\) depletion). It can secrete K\(^+\) in states of dietary load. The mechanisms by which these occur are unknown.

30. The total amount of the filtered Na\(^+\) load that is reabsorbed in the cortical and medullary collecting tubule (taken together) is 2% (ref. 7, p. 144).

31. Figure 18 shows the concentration of various species at different parts of the tubular system. Urine osmolarity can vary between 50-1500 mOsm/L (ref. 1, p. 59).

**Figure 18 (Ref. 12, p. 22)**
### Table I. Summary of Transport Properties of the Renal Tubule

<table>
<thead>
<tr>
<th>Region</th>
<th>Solute reabsorbed</th>
<th>Solute secreted</th>
<th>Permeability</th>
<th>Sodium transport rate (% of filtered)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal tubule</td>
<td>Na⁺, Cl⁻, HCO₃⁻, K⁺, organic</td>
<td>H⁺</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>solutes, etc.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convoluted H₂O</td>
<td>Na⁺, Cl⁻, HCO₃⁻, K⁺</td>
<td>H⁺, organic acids</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Straight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop of Henle</td>
<td>NaCl</td>
<td>—</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Thin descending</td>
<td>NaCl</td>
<td>—</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Thick ascending</td>
<td>NaCl, K⁺, Ca²⁺</td>
<td>—</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Distal nephron</td>
<td>Na⁺, Cl⁻, HCO₃⁻, K⁺</td>
<td>H⁺, K⁺</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Distal convoluted tube</td>
<td>Same</td>
<td>Same</td>
<td>Low; ADH: high</td>
<td>Low</td>
</tr>
<tr>
<td>Cortical collecting tube</td>
<td>Same</td>
<td>Same</td>
<td>Low; ADH: high</td>
<td>Low</td>
</tr>
<tr>
<td>Medullary collecting duct</td>
<td>Same, urea</td>
<td></td>
<td>Low; ADH: high</td>
<td>Low</td>
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### References


Chapter 7
Renal Regulation of Extracellular Fluid Volume Through Sodium Excretion

27. Extracellular fluid (ECF) volume varies little during the lifetime of the individual because renal regulation is so effective (Ref. 1, p. 106).

28. Why is ECF volume important? The regulation of plasma volume is through the regulation of ECF fluid volume (Ref. 1, p. 106) since the plasma subcompartment is part of the ECF compartment. Any change in the ECF volume will thus change the plasma volume similarly (i.e., if the ECF volume increases the plasma volume will increase). The plasma volume is significant to health status as diagramed in Figure 1. Maintaining ECF volume is crucial to maintaining blood pressure. The two scenarios outlined in Figure 1 are summarized below:

(Ref. 1, p. 106; Ref. 3, p. 96)

a) If the blood volume is inadequate, the blood pressure falls no matter how vigorous the pumping action or how constricted the resistance. In addition, a very important consequence is shown in Figure 1 (right flow chart). Significantly decreased ECF volume leads to decreased cardiac output, causing decreased peripheral blood flow (which is augmented by a reflex vasoconstriction response). This results in insufficiency in delivery of nutrients and carrying out of metabolic waste products from the tissues, meaning that the function and viability of the tissue is compromised.

(Ref. 1, P. 106; Ref. 3, p. 96)

b) Conversely, if fluid volume increases, the vascular system is tense no matter how dilated the resistance, causing the pressure to rise. The left flow chart of Figure 1 shows that this leads to conditions of edema and/or an increase in plasma and blood volume, which can precipitate or accentuate congestive heart failure.

Figure 1 (Ref. 3, p. 95)
3. ECF volume is directly dependent on the quantity of ECF total sodium content, because of the primacy of sodium in determining the ECF osmolarity. Sodium can thus be thought of as the “body’s sponge” because of its ability to retain water.

(Ref. 3, pp. 93-94)

4. The distribution of sodium in the body is summarized in Figure 2. There is an exchangeable sodium fraction (consisting of sodium in the ICF, ECF, and exchangeable portion of the bone) and a non-exchangeable fraction in the bone. The ECF volume is dependent on the amount of exchangeable sodium in the body, because the ECF sodium is in dynamic equilibrium with the body’s total exchangeable sodium. Facts about sodium in the body are given below.

a) The total sodium amount in a 70 kg individual is 4200 mEq.

b) The distribution of sodium in the body is as follows:
   1') Exchangeable sodium (70%)
      • ICF (7%)
      • ECF (50%)
      • Bone (13%)
   2') Non-exchangeable sodium (30%)
      • Bone (adsorbed to hydroxyapatite)
29. To summarize, the kidney controls ECF volume (and thus total body water volume, since gains and losses of water affect the volume of all fluid compartments proportionally (Ref. 8, p. 33)) in the following way:
   Water will follow wherever sodium is due to sodium’s osmolarity attraction. If sodium is retained by the body, water will be retained by the body. If sodium is excreted, then water will be excreted.

30. The other point of regulation of body water volume is the amount of intake. Thus the total control of body water volume is a regulation of:
   
   a) Intake - through the thirst mechanism
   
   b) Output - through renal excretion of water (via a sodium excretion mechanism)

To keep the body water volume constant, regulation occurs such that volume\_output equals volume\_intake.

31. Control of water intake is through the thirst mechanism, which will be discussed in the next chapter. The renal output of water can vary between 0.5 liters to 15 liters of urine per day, depending on the water balance requirements (Ref. 4, p. 119). The normal daily urine output is 1 to 2 liters per day.

32. Before discussing the renal excretion mechanisms of sodium (and thus water), there are other output pathways for body water, which are designated as extrarenal losses of water. However, these pathways are not regulated to maintain water balance. These pathways are summarized below in point 9.

33. Extrarenal body losses of water

   a) Respiration (Ref. 9, p. 26)
      This is the loss of water through the lungs or skin. It is also called insensible perspiration, to differentiate from the water loss that occurs from the sweat glands.
      - Amount lost is 900-1100 mL/day
      - It consists of pure water containing no electrolytes (thus produces a hyperosmotic ECF)
      - Normally a constant rate of loss, but it can be changed by the rate and depth of the respiration (e.g., in fever the loss of water through the lungs is considerable)

   b) Sweat (Ref. 9, p. 26)
      - Sweating is the mechanism by which the body temperature is
maintained in conditions of heat generation through the process of evaporation.

- Electrolyte loss does occur in this process. However, the loss of water is in excess of electrolyte loss, thus producing a hyperosmotic ECF. The concentration of sodium in sweat depends on the training status of the individual (60 mOsm/kg in a trained individual compared to 150 mOsm/kg in an untrained individual). The concentration of sodium and potassium in sweat depends on the aldosterone concentration in blood (increased [aldosterone] leads to decreased [Na⁺] and increased [K⁺] in sweat).
- Extreme cases happen with professional athletes. A loss of 8 L in insensible perspiration and sweat can occur during a professional basketball game.

34. Only the kidney responds to body water volume for maintaining water homeostasis (Ref. 4, p. 119), doing this through the control of sodium excretion. The equation describing sodium excretion by the kidney is given by Equation 1 (Ref. 3, p. 97):

\[
E_{\text{Na}} = \text{GFR} \times [\text{Na}]_{\text{plasma}} - R_{\text{Na}}
\]  

(1)

where \(E_{\text{Na}}\) is the urinary excretion rate of sodium, GFR is the glomerular filtration rate, \([\text{Na}]_{\text{plasma}}\) is the concentration of sodium in plasma, and \(R_{\text{Na}}\) is the rate of sodium reabsorption in the tubular system. The main mechanism of control of sodium excretion by the kidney is through the second term in Equation 1 (\(R_{\text{Na}}\)). The first term does come into play (in pathologic conditions), but not as a control mechanism in health. In normal circumstances, GFR and \([\text{Na}]_{\text{plasma}}\) are tightly regulated and thus do not serve as control points for the kidney’s regulation of the body’s sodium status. Also, if GFR does change, glomerulotubular balance comes into play to mitigate its effect on sodium excretion [increased GFR results in increased tubular sodium reabsorption and decreased GFR is accompanied by a decrease in sodium reabsorption (Ref. 7, p. 239)]. However GFR changes do affect sodium excretion status proportionally, showing greater effects with greater changes in GFR.

The diminished importance that the change of GFR has on the sodium excretion is
supported by two lines of evidence (Ref. 3, p.100):

a) An increased GFR which is not accompanied by an increase in ECF volume does not lead to natriuresis (increased excretion of sodium in the urine)

b) A natriuretic response to increased ECF volume occurs even if GFR is maintained constant or even decreased

35. The remainder of the chapter is devoted to the mechanisms by which the second term ($R_{Na}$) is modulated in the kidney. These mechanisms are separated into various categories, as given below.

a) Hormonal Factors
   - Aldosterone
   - Renin - Angiotensin
   - Atrial Natriuretic Peptide
   - Prostaglandins
   - Kallikrein-Kinin system

b) Physical and Hemodynamic Facts
   - Pressure Natriuresis
   - Renal Interstitial Pressure
   - Medullary Blood Flow

c) Renal Nerve Activity

36. Hormonal Factors

a) Aldosterone
   1') Significance to sodium homeostasis
   Many textbooks take a simplistic approach by attributing the kidney’s sole control mechanism of the body’s sodium status to the action of aldosterone. Although important, it is far from being the only factor involved in the control of sodium reabsorption and secretion.

   a') Facts supporting a diminished importance of aldosterone to sodium regulation
   1") Only a very small fraction of the filtered sodium is under aldosterone’s control, about 2% of the filtered sodium load

   (Ref. 11, p. 144).
Figure 3 (Ref. 10, p. 433)

3") Patients with primary hyperaldosteronism (who produce large amounts of aldosterone) have a sodium concentration in the plasma that rises only 2 to 3 mEq/L above the normal concentration (Ref. 10, p.433).

4") Other experiments (Ref. 2, p. 1143)
- A acute volume expansion leads to an immediate natriuresis, while an aldosterone effect takes 30-60 min
- A large increment of urinary sodium excretion accompanies volume expansion even in the presence of simultaneous administration of aldosterone

b’) Facts supporting a significant role of aldosterone to sodium regulation (Ref. 2, p. 1143).

1") Salt excretion occurs in adrenal insufficiency (conditions leading to decreased adrenal gland function)

2") There is an inverse relationship between dietary sodium intake and aldosterone concentration.

3") There is an inverse relationship between ECF volume and plasma aldosterone concentration.
c’) It is hypothesized that aldosterone participates significantly in the control of sodium excretion in health, but other factors grow in importance when there are excessive volume loads or deficits (Ref. 2, p. 1144).

2’) Mechanism of action
Aldosterone increases the permeability of the cellular membrane to sodium in the connecting segment and the collecting tubule cells, thus increasing the reabsorption of sodium (see Chapter 6).

3’) Aldosterone is released from the adrenal cortex (Ref. 5, p. 88).

4’) Factors causing release of aldosterone (Ref. 5, p. 98)
a’) Angiotensin II (major factor)
b’) Other factors
   • Low [Na⁺] plasma
   • High [K⁺] plasma
c’) ACTH released from the anterior pituitary gland has a permissive effect; its presence is necessary for aldosterone secretion to increase in response to other stimuli.

b) Renin - Angiotensin
1’) Mechanisms of renin release
a’) A decrease in ECF volume leads to a reduction in renal artery pressure which leads to an increased rate of renin release. This response is most important when there is an acute blood pressure fall, as in a hemorrhage (Ref. 1, p. 112). The cells of the afferent arteriole (presumably juxtaglomerular cells) sense a change in the renal perfusion pressure, causing a change in the output of renin (Ref. 3, p. 79).

b’) Response mechanism via the macula densa cells
A decrease in ECF volume decreases the sodium load at the macula densa cells (via a decrease in GFR as shown in Figure 4) which increases renin release from the juxtaglomerular cells (Ref. 7, p. 239).
c’) Response mechanism via renal nerve activity (Ref. 7, p. 78; Ref. 14, p. 48; Ref. 15, p. 70, 72; Ref. 1, p. 112).

Increased renal nerve stimulation causes increased renin release. This sympathetic nerve activity is first and foremostly modulated through stretch receptors in the low-pressure vessels close to the heart. These vessels are expandable and are capable of holding up to 80% of the total normal blood volume. These vessels thus act as a buffer in maintaining cardiac output and arterial pressure by maintaining the delivery of appropriate levels of blood to the heart (either storing blood in water excess conditions or delivering more blood in water deficient conditions). The volume state of these vessels are monitored by these stretch receptors, with these receptors subsequently modulating the renal nerve activity. Thus an increase in renal nerve activity occurs with a decrease in volume sensed by the stretch receptors, causing renin release and subsequent reabsorption of sodium. Conversely, increased plasma volume leads to inhibition of renin release through stretch receptor modulation of the renal nerve activity. Note that with an extreme volume deficiency (such as would arise with a hemorrhage) there is a compromise in the filling of the heart with blood. In this case, the arterial baroreceptors are affected, which will lead to the baroreceptors (in addition to the stretch receptors) modulating a renin release via increased renal nerve activity.

2’) Summary of the effects of increased angiotensin II in blood on sodium
reabsorption by the kidney (see Figure 5)

a') Affects renal hemodynamics (described below) (Ref. 7, p. 239)
b') Causes aldosterone release (Ref. 7, p. 239)
c') Directly acts on the proximal tubule to promote sodium reabsorption (not shown in Figure 5) (Ref. 12, p. 1152)

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**Figure 5 (Ref. 7, p. 239)**

(Note (+) indicates an increase in the response indicated in the box, while (-) indicates a decrease in the response indicated in the box)

3') Details of how angiotensin II affects sodium reabsorption by the kidney

a') Control of hemodynamics

1") Proximal tubule (Ref. 1, p. 115; Ref. 5, p. 90, Ref. 7, p. 240)

A decreased ECF volume leads to an increase in angiotensin II in the blood, causing an increase in efferent arteriole resistance in the kidney. This causes a decrease in the RBF and an increase in GFR. This results in an increase in the filtration fraction, which leads to an increase in the peritubular capillary colloid osmotic pressure. This leads to an increased movement of water from the interstitial fluid (ISF) adjacent to the peritubular capillaries, which leads to
more water (along with sodium) entering the ISF from the proximal tubule. In addition, the reduced renal blood flow (RBF) leads to a decrease in peritubular capillary hydrostatic pressure, which leads to water (and sodium) reabsorption into the peritubular capillaries from the proximal tubule by the same reasoning.

2") Effect on medullary blood flow
(Ref. 7, p. 240) Angiotensin II has been shown to produce a marked reduction in medullary blood flow. This leads to an increase in osmolarity in the medullary ISF, which leads to enhanced sodium reabsorption, as discussed in section 13.c.2' below.

b') Angiotensin II causes a release of aldosterone from the adrenal cortex, which causes an increase in sodium reabsorption, as described previously (see point 12.a.2').

c') Angiotensin II in low doses has been shown to enhance reabsorption of sodium in the proximal tubule; while at higher doses it inhibits reabsorptive rates of sodium (Ref. 12, p. 1152). This is controversial role of angiotensin II (Ref 12, p.1145).

c) Atrial Natriuretic Peptide (ANP) (Ref. 7, p. 241)
ANP is a peptide hormone synthesized and stored in the atria of the heart. The hormone causes increased sodium excretion in the outer medullary collecting tubule by closing sodium channels (see Chapter 6). ANP is released from the atria by a mechanism by which increased plasma volume causes atrial distension and subsequent release of ANP.

d) Prostaglandins
PGE₂ is the most important prostaglandin that affects sodium excretion, with increased PGE₂ leading to increased sodium excretion (Ref. 7, p. 240). In addition, renal prostaglandins cause vasodilation (Ref. 3, p. 104).

e) Kallikrein - kinin system (Ref. 3, pp. 83-84, 104)
The general pathway of the kallikrein system generating kinins is similar to the renin system generating angiotensin II, although the physiological effects of the generated peptides are different. Referring to Figure 6, kallikrein is a proteolytic enzyme which acts on a plasma protein (kininogen, an α-2 globulin in plasma) splitting off active peptides called kinins. There are three biologically active peptides:
- methionyl-glycyl-bradykinin (11 aa)
- lysil-bradykinin (kallidin) (10 aa)
- bradykinin (9 aa)
Kininases in plasma and tissues rapidly degrade active kinins. Kinins are potent vasodilators and act to increase sodium excretion.

Figure 6 (Ref. 3, p. 84)

13. Physical and Hemodynamic Factors

a) Pressure Natriuresis (Ref. 7, p. 243)

1') Changes in renal perfusion pressure produces changes in sodium excretion. This effect is seen even with no change in GFR or RBF (i.e., without a change in filtered load).

2') This mechanism is thought to play an important role in sodium excretion but it has been hard to quantitate. The mechanisms by which increased renal vascular pressure causes increased sodium excretion are through several pathways, as shown in Figure 7. The mechanisms of renal interstitial pressure and medullary blood flow referred to in Figure 7 are discussed below in sections 13.b and 13.c, respectively.
(Note (+) indicates an increase in the response indicated in the box, while (-) indicates a decrease in the response indicated in the box)

b) Renal Interstitial Hydrostatic Pressure (RIHP)

1') Causes of increased RIHP
   a') Increased renal perfusion pressure causes increased movement of water from the renal vasculature to the renal interstitial spaces due to an increase in hydrostatic pressure. This increases RIHP by virtue of there being more water in the ISF compartment (Ref. 16).
   b') An increase in ECF volume in general will lead to an increase in water volume throughout all ECF compartments, including the ISF of the kidneys. This increases RIHP by virtue of there being more water in the renal ISF compartment (Ref. 16).

2') Effect of RIHP on sodium excretion
   An increase in RIHP increase sodium excretion. A 2 to 3 mm Hg increase in RIHP can result in a five-fold increase in sodium excretion (Ref. 7, p. 243).
3') A possible mechanism for the RIHP effect is that the increase in RIHP leads to a leak of sodium and water back into the proximal tubule (i.e., consider the change in Starling forces). However, the mechanism is not fully understood. (Ref. 7, p. 243)

c) Medullary Blood Flow
1') Summary of effect
Increased medullary blood flow reduces interstitial osmolarity in the medulla due to a medullary washout mechanism. This leads to increased sodium excretion.
2') Details of mechanism (Ref. 7, pp. 243-244, Ref. 16)
Figure 8 gives the detailed outline of the medullary blood flow control of sodium excretion.

![Figure 8 (Ref. 7, p. 244)](Note (+) indicates an increase in the response indicated in the box, while (-) indicates a decrease in the response indicated in the box)

a') With an increased ECF volume there is an increase in blood flow in general, which includes an increase in the blood flow in the vasa recta capillaries which flow through the renal medulla.
b') With an increased blood flow through the vasa recta there is an
increase in the solute content which the vasa recta carries out of the renal medulla (called medullary washout). This causes a decrease in the medulla osmolarity. The mechanism of why increased vasa recta flow increases solute carried out is explained with the help of Figure 9. Figure 9 shows that the osmolarity of the vasa recta capillary system attempts to equilibrate with the osmolarity of the tissue that it traverses through, the medulla. A flow system is inherently a kinetic process, thus the extent that the vasa recta at each level of the medulla reaches the osmolarity of the medulla depends on the flow rate. At extremely slow flow rates, equilibrium osmolarity (or near equilibrium osmolarity) will be reached at each level of the vasa recta [i.e., the osmolarity of the vasa recta will be equal (or nearly equal) to that of the medulla at each level]. Thus the osmolarity of blood leaving the medulla will be 285 mOsm/L (i.e., the same osmolarity at which it entered the medulla and thus no additional osmolarity is added to the blood leaving the medulla). Conversely with a fast vasa recta flow rate, the osmolarity of the vasa recta at each level is “behind” the equilibrium value [i.e., there is not enough time for the solutes to completely diffuse from the medulla into the descending limb of the vasa recta (and thus the descending limb of the vasa recta is at a lower osmolarity than the corresponding level of the medulla) and there is not enough time for solutes in the ascending limb of the vasa recta to completely diffuse into the medulla at each level (and thus the ascending limb of the vasa recta is at a higher osmolarity than each corresponding level of the medulla)]. Thus the osmolarity of the blood exiting the medulla increased from the value of the osmolarity of the blood entering the medulla via the vasa recta (in Figure 9 the blood enters the medulla at an osmolarity of 285 mOsm/L and leaves at an osmolarity of 315 mOsm/L), which means that solutes are being carried out of the medulla. In this case, the osmolarity of the medulla will decrease.
Figure 9 (Ref. 17, p. 55)

c’) With the decreased osmolarity of the medulla there is less water leaving the thin descending limb of loop of Henle (TDLH) (see Chapter 6).
d’) With more water present in the TDLH there is more dilute fluid entering the ascending limbs (both thin and thick) of loop of Henle (i.e., [Na⁺] is decreased). Since absorption of sodium in these segments is through concentration gradient mechanisms (see Chapter 6) there is decreased reabsorption of sodium.
e’) There is thus an increased delivery of sodium to the distal tubules, exceeding the capability of these and other later tubular segments for absorbing sodium.
f’) Thus sodium excretion is increased.

14. Renal Nerve Activity

Stimulation of the renal nerve results in the following effects:

a) renin release (see section 12.b.1’.c’)

b) vasoconstriction of the afferent arteriole causing decreased GFR and RBF (see Chapter 4)

c) a shift of the blood flow from the cortical nephron to the juxtamedullary nephron (with mild nerve stimulation) (Ref. 5, p. 38, see Chapter 4)

d) direct stimulation of various tubular segments to increase reabsorption of
sodium (see below)

These four effects are expanded upon below.
· The release of renin increases sodium reabsorption as discussed previously.

· Renal nerve stimulation decreases GFR and RBF (Ref. 7 p. 244) through constriction of the afferent arteriole (Ref. 16), which decreases the filtered sodium load, leading to sodium retention (Ref. 16).

· A shift of blood flow through the juxtamedullary nephrons means that a greater portion of the filtrate passes through the long loop of Henle of the juxtamedullary nephrons that extend deep into the interior of the medulla. Sodium reabsorption is hypothesized to be greater in these deep extending nephrons than the cortical nephrons (Ref. 3, p. 104).

· The following tubular segments have been found to be innervated: the proximal convoluted tubule, the thick ascending limb of loop of Henle, the distal convoluted tubule, and the collecting tubules (Ref. 7, p. 244). Studies have found that a low level of renal nerve stimulation increases sodium reabsorption in the proximal convoluted tubule and loop of Henle (Ref. 7, p. 244). However, the role of renal nerves in sodium excretion remains controversial because of studies in dog which showed no difference in the response of innervated and denervated kidneys to conditions of increased body water volume (Ref. 7, p. 244). However, another study showed acute (as opposed to chronic) denervation leads to natriuresis and diuresis (Ref. 3, p. 104).

References


49. Electrolyte Imbalances, Tape # 7831, Health Sciences Communications Center, Case Western Reserve University: Cleveland, OH, 1976.


52. Explanation by Dr. David Anderson.
