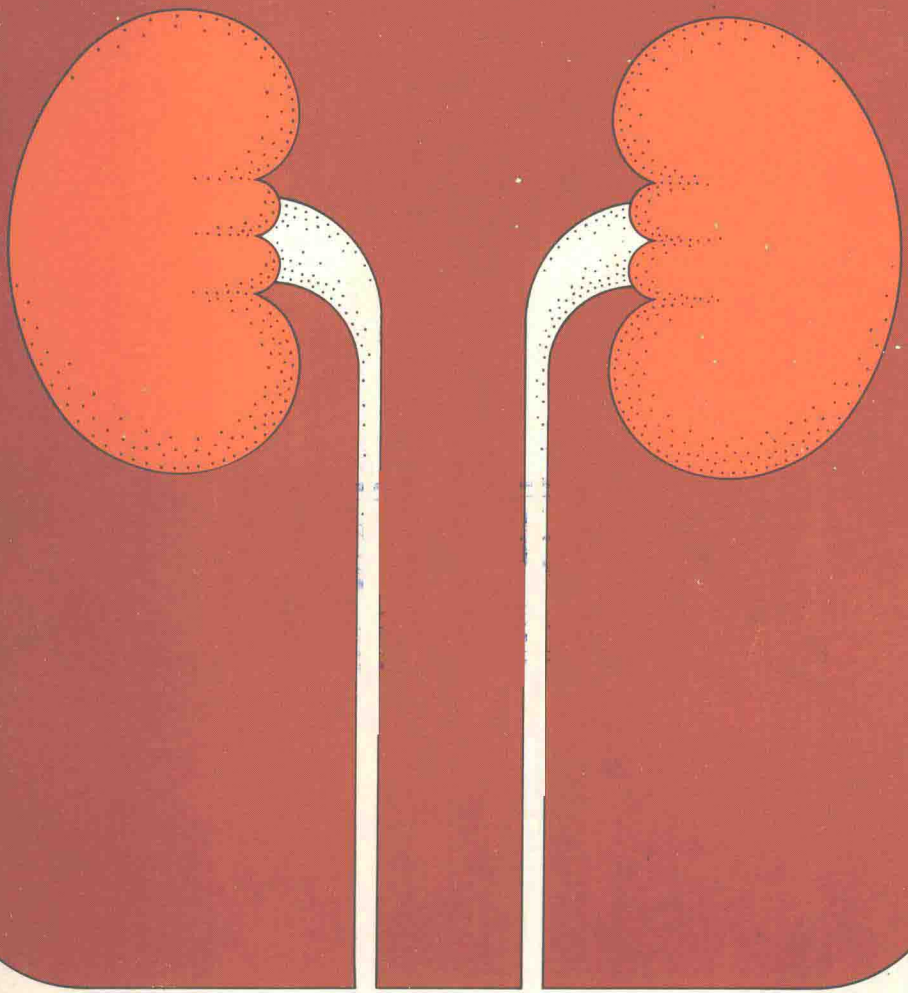
# RENAL PHYSIOLOGY

SECOND EDITION

ARTHUR J. VANDER



# Renal Physiology

## Second Edition

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**McGraw-Hill Book Company**

New York St. Louis San Francisco Auckland Bogotá Hamburg
Johannesburg London Madrid Mexico Montreal New Delhi
Panama Paris São Paulo Singapore Sydney Tokyo Toronto

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1 2 3 4 5 6 7 8 9 0 *FGRFGR* 8 9 8 7 6 5 4 3 2 1 0

This book was set in Times Roman by The Clarinda Company.
The editors were Richard W. Mixter and Abe Krieger;
the production supervisor was Robert A. Pirrung.
The drawings were done by J & R Services, Inc.
The cover was designed by Antonia Goldmark.
Fairfield Graphics was printer and binder.

**Library of Congress Cataloging in Publication Data**

Vander, Arthur J date
Renal physiology.

Bibliography: p.
Includes index.
1. Kidneys. I. Title. [DNLM: 1. Kidney—Physiology. WJ300.3 V228r]
QP249.V36 1980 612'.463 79-18428
ISBN 0-07-066958-9

# Preface

This book is my attempt to identify the essential core content of renal physiology appropriate for medical students and to present it in a way which permits the student to master the material independently, i.e., with no (or very few) accompanying lectures by the instructor. I have been gratified by the wide use the first edition has achieved and the many letters I have received from medical students (and clinicians) who found they were, indeed, able to master its contents by independent study.

Accordingly, my major goals in preparing this edition have been to update the material thoroughly and to strive for greater clarity of exposition (to this latter end, a large number of new flow diagrams has been added) but not to alter the level of coverage. There is one major exception to this last guideline; I have added a systematic description (in Chap. 2) of the general categories of transport processes and their interactions in achieving transepithelial transport and have then applied these concepts to specific solutes in later chapters. I have also expanded the sections on the transport of urea and organic acids and bases. The task of sticking to my intent of presenting only core material was even more painful this time because of the explosion of information in renal physiology over the past 4 years. I can only plead once again with my fellow teachers to share with me their views concerning my choice.

My selection of this core material is made explicit in a comprehensive list of behavioral objectives, which tell students specifically what I believe they should know and be able to do by the book's completion. Obviously, no two instructors would come up with exactly the same core material, but it is a simple matter for instructors to give students a supplementary list of goals to be added or deleted. The information required to achieve any additional goals not covered in the book would, of course, have to be provided by other reading assignments or lectures. However, my belief, based on consultations with other physiologists and clinicians, is that these discrepancies are likely to be few. Of much greater importance is the fact that the behavioral goals (in essence, the content of the book) are explicitly defined so that any such differences are easily determined. This also makes the book quite usable for students in other health sciences, whose required core of information might differ from that of medical students.

In addition to the comprehensive objectives, I have included a large number of study questions with annotated answers. Unlike the lists of objectives, the study questions are neither systematic nor comprehensive in their coverage. Rather, they generally deal with areas I have found usually difficult for students and give them practice and additional feedback.

I advise the student to go through the book one chapter at a time. Some students profit by using the objectives to guide their readings as they proceed through a chapter. In any case, at the end of each chapter go over the objectives in detail and the study questions (at the back of the book) relevant to that chapter. They provide you with the means for determining whether you have mastered the material and for identifying those specific areas which require more work.

I should like to point out several characteristics of the book common to most texts but particularly common in this type of book. I have rarely included the original research upon which this core of knowledge rests, nor have I been able to explore the fascinating controversies in virtually every area. Therefore, the Suggested Readings at the back of the book are of considerable importance for the student who wishes to pursue any subject in greater depth. They are almost all review articles, and their bibliographies provide an entry into the original research literature. The question of how to handle controversy in such a book is a particularly perplexing one. I have tried to present various views (frequently in footnotes) in areas where the evidence is closely balanced, but I have often simply had to ignore an opposing view. Obviously, such decisions are always arbitrary, to a large degree, and I can only apologize, in advance, to those of my colleagues who feel I have slighted their work.

Finally, I should like to thank Peggy Rogers for her splendid typing of the manuscript.

*Arthur J. Vander*

# Contents

Chapter 1

# Function and Structure of the Kidneys

**OBJECTIVES**

The student states the balance concept.

The student knows the functions of the kidneys.

1 Lists seven functions
2 States the components of the renin-angiotensin system and their biochemical interrelations
3 States the role of renal erythropoietic factor

The student defines important gross structures and knows their interrelationships: renal pelvis, calyxes, renal pyramids, medulla, cortex, papilla

The student understands the interrelationships between the components of a nephron.

1 Defines glomerulus and tubule
2 Draws the relationship between glomerular capillaries, Bowman's capsule, and the proximal tubule
3 States the three layers separating the lumen of the glomerular capillaries and Bowman's space; defines podocytes, foot processes, slits, and slit diaphragms

4 Lists in order all the tubular segments; defines proximal tubule, loop of Henle, distal tubule, and collecting duct in physiologists' convention
5 Describes the differences between outer cortical and inner cortical (juxtamedullary) nephrons
6 Defines interstitial cells
7 Defines juxtaglomerular apparatus and states the relationship between its components

The student understands the blood supply to the nephron.
1 Lists, in order, the vessels through which blood flows from renal artery to renal vein
2 Defines vasa recta

## FUNCTIONS

### Regulation of Water and Electrolyte Balance

A cell's function depends not only upon receiving a continuous supply of nutrients and eliminating its metabolic end products but also upon the existence of stable physicochemical conditions in the extracellular fluid bathing it, Claude Bernard's "internal environment." Maintenance of this stability is the primary function of the kidneys.

Since the extracellular fluid occupies an intermediate position between the external environment and the cells, the concentration of any substance within it can be altered by exchange in either direction. Exchanges with cells are called *internal exchanges*. For example, a decrease in extracellular potassium concentration is followed by a counteracting movement of potassium out of cells into the extracellular fluid. Each type of ion is stored in cells or in bone in significant amounts, which can be partially depleted or expanded without damage to the storage site. But these stores are limited, and in the long run any deficit or excess of total body water or total body electrolyte must be compensated by exchanges with the external environment, i.e., by changes in intake or output.

A substance appears in the body either as a result of ingestion or as a product of metabolism. Conversely, a substance can be excreted from the body or consumed in a metabolic reaction. Therefore, if the quantity of any substance in the body is to be maintained at a constant level over a period of time, the total amounts ingested and produced must equal the total amounts excreted and consumed. This is a general statement of the *balance concept*. For water and hydrogen ion all four possible pathways apply. However, balance is simpler for the mineral electrolytes. Since they are neither synthesized nor consumed by cells, their total body balance reflects only ingestion versus excretion.

As an example, let us describe the balance for total body water (Table 1). It should be recognized that these are average values, which are sub-

**Table 1 Normal Routes of Water Gain and Loss in Adults**

| Route | mL/day |
|---|---|
| Intake | |
| Drunk | 1200 |
| In food | 1000 |
| Metabolically produced | 350 |
| Total | 2550 |
| Output | |
| Insensible loss (skin and lungs) | 900 |
| Sweat | 50 |
| In feces | 100 |
| Urine | 1500 |
| Total | 2550 |

ject to considerable variation. The two sources of body water are metabolically produced water, resulting largely from the oxidation of carbohydrates, and ingested water, obtained from liquids and so-called solid food (a rare steak is approximately 70 percent water).

There are four sites from which water is lost to the external environment: skin, lungs, gastrointestinal tract, and kidneys. The loss of water by evaporation from the cells of the skin and the lining of respiratory passageways is a continuous process, often referred to as *insensible loss* because the person is unaware of its occurrence. Additional water can be made available for evaporation from the skin by the production of sweat.

Under normal conditions, as can be seen from the table, water loss exactly equals water gain, and no net change of body water occurs. This is obviously no accident but the result of precise regulatory mechanisms. The question then is: Which processes involved in water balance are controlled to make the gains and losses balance? The answer, as we shall see, is voluntary intake *(thirst)* and urinary loss. This does not mean that none of the other processes is controlled, but it does mean their control is not primarily oriented toward water balance. Carbohydrate catabolism, the major source of water from oxidation, is controlled by mechanisms directed toward regulation of energy balance. Sweat production is controlled by mechanisms directed toward temperature regulation. Insensible loss in humans is truly uncontrolled. Fecal water loss is generally unchanging and is normally quite small (but can be severe in vomiting or diarrhea).

The mechanism of thirst is certainly of great importance, since body deficits of water, regardless of cause, must be made up by ingestion of water. But it is also true that our fluid intake is often influenced more by habit and by sociological factors than by the need to regulate body water. The

control of urinary water loss is the major automatic mechanism by which body water is regulated.

By similar analyses, we find that the body balances of many of the ions determining the properties of the extracellular fluid are regulated primarily by the kidneys. To appreciate the importance of these kidney regulations one need only make a partial list of the more important simple inorganic substances which constitute the internal environment and which are regulated in large part by the kidneys: water, sodium, potassium, chloride, calcium, magnesium, sulfate, phosphate, and hydrogen ion. Indeed, the extraordinary number of substances which the kidney regulates and the precision with which these processes normally occur accounted for the kidneys being the last stronghold of the nineteenth century vitalists, who simply would not believe that the laws of physics and chemistry could fully explain renal function. By what mechanism does urine flow rapidly increase when a person ingests several glasses of liquid? How is it that the patient on an extremely low salt intake and the person who eats a great deal of salt both urinate precisely the amounts of salt required to maintain their sodium balance? What mechanisms decrease the urinary calcium excretion of children deprived of milk?

### Excretion of Metabolic Waste Products

The regulatory role just described is obviously quite different from the popular conception of the kidneys as glorified garbage disposal units which rid the body of assorted wastes and poisons. It is true that some of the chemical reactions which occur within cells result ultimately in end products that must be eliminated. These end products are called waste products because they serve no known biological function in humans. For example, the catabolism of protein produces approximately 30 g of urea per day. Other end products produced in relatively large quantities are uric acid (from nucleic acids), creatinine (from muscle creatine), bilirubin and other end products of hemoglobin breakdown, and the metabolites of various hormones. There are many others, not all of which have been completely identified. Most of these substances are eliminated from the body as rapidly as they are produced, primarily by way of the kidneys. Some of them, e.g., urea, are relatively harmless, but the accumulation of others within the body during periods of renal malfunction accounts for some of the disordered body functions in the patient suffering from severe kidney disease. We still are not sure as to the identity of these "toxins" or which of the problems occurring in renal disease are due to them, as opposed to disordered water-and-electrolyte metabolism.

### Excretion of Foreign Chemicals

The kidneys have another excretory function, which is presently assuming increasing importance, namely, the elimination from the body of

foreign chemicals, such as drugs, pesticides, food additives, and their metabolites.

### Regulation of Arterial Blood Pressure

The kidneys are intimately involved in the regulation of arterial blood pressure by several mechanisms.

First, sodium balance is a critical determinant of cardiac output (and, possibly, arteriolar resistance, over any long time period), and the kidneys, as stated above, regulate this balance.

Second, the kidneys function as endocrine glands in the *renin-angiotensin system,* a hormonal complex of enzymes, proteins, and peptides which are importantly involved in the regulation of arterial pressure. *Renin* is a proteolytic enzyme secreted into the blood by the kidneys, specifically by the granular cells of the juxtaglomerular apparatuses (see below). Once in the bloodstream, renin catalyzes the splitting of a decapeptide, *angiotensin I,* from a plasma protein known as *angiotensinogen,* which is secreted by the liver and is always present in the plasma in high concentration. Under the influence of another enzyme, *converting enzyme,* the terminal two amino acids are then split from the relatively inactive angiotensin I to yield the octapeptide *angiotensin II.* Converting enzyme is present in plasma and in many organs but is most concentrated in the endothelial cells lining the pulmonary capillaries; accordingly, the conversion of angiotensin I to angiotensin II occurs mainly as blood flows through lung capillaries. Until recently it was assumed that angiotensin II is the only physiologically active peptide in the system. However, as Fig. 1 illustrates, angiotensin II can be split to yield the heptapeptide known as

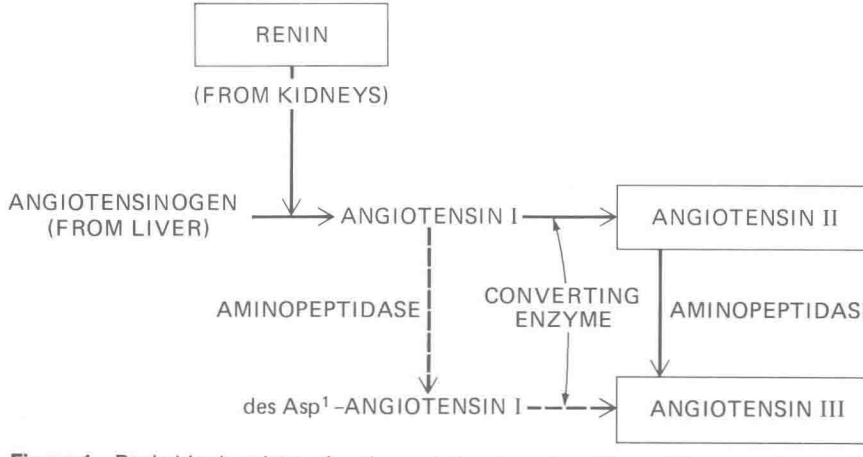


**Figure 1** Basic biochemistry of renin-angiotensin system. The solid arrows denote the major pathway, the dashed arrows a possible alternate pathway for the generation of angiotensin III.

angiotensin III, and it is almost certain that this latter peptide is also quite active biologically. (The enzymes which mediate its generation seem to be located mainly in the target tissues for this peptide.) An evaluation of the relative contributions of antiotensin II or III (and, in a few cases, possibly even angiotensin I) to the effects of the overall system is beyond the scope of this book, and we shall simply refer to these peptides collectively as angiotensin.[1] As we shall see in subsequent chapters, angiotensin exerts an immense number of effects on diverse tissues, but the end results of most of them are to increase arterial blood pressure. A crucial generalization to be gained from the biochemistry of this system is that because angiotensinogen and the enzymes beyond renin are usually present in relatively unchanging concentration,[2] the primary determinant of the rate of angiotensin formation is the plasma concentration of renin, which is physiologically regulated via the control of renin secretion.

In addition to their regulation of salt balance and secretion of renin, the kidneys may exert a third important influence over arterial blood pressure. It is very likely that they either secrete into the blood or remove from it vasoactive substances other than renin. Certainly the kidneys are capable of synthesizing a number of prostaglandins, both vasodilator and vasoconstrictor in action, and the possibility that one or more of these prostaglandins may reach the systemic arterial blood in amounts adequate to dilate or constrict arterioles is the subject of considerable investigation. Lipids other than prostaglandins have also been implicated in the renal regulation of arterial blood pressure.

### Regulation of Erythrocyte Production

The kidneys secrete a second hormone, *renal erythropoietic factor* (REF), which is involved in the control of erythrocyte production by the bone marrow. Just which renal cells secrete REF is not yet clear, but the stimulus for its secretion is a decrease in oxygen delivery to the kidneys (as, for example, in anemia, hypoxia, or hypotension with inadequate renal blood flow). Once secreted, REF acts enzymatically in the plasma on a globulin (secreted by the liver) to split off a polypeptide known as erythropoietin, which then stimulates the bone marrow to increase its production of erythrocytes. (Note the analogies between the biochemistry of this system and that of the renin-angiotensin system.) The REF-

[1]The renin-angiotensin system is among the most intensively studied fields in the medical sciences, and its biochemistry grows more bewildering every day as "prorenins," "pseudorenins," "brain renins," alternate pathways, etc. accumulate. The reader interested in going beyond the extremely basic descriptions given in this book should consult the Suggested Readings.

[2]There are clinically important situations in which changes in angiotensinogen or converting enzyme may significantly influence the generation of angiotensin. For example, oral contraceptives may cause a large increase in plasma angiotensinogen.

erythropoietin system will not be described further in this book; suffice it to say that renal disease may result in diminished REF secretion, and the ensuing decrease in bone marrow activity is one important causal factor in the anemia of chronic renal disease.

### Regulation of Vitamin D Activity

The kidneys produce the active form of vitamin D (1,25-dihydroxyvitamin $D_3$). This makes the third hormone secreted by the kidneys; its synthesis and role in calcium metabolism will be described in Chap. 10.

### Gluconeogenesis

During prolonged fasting, the kidneys synthesize glucose from amino acids and other precursors and release it into the blood. Thus, like the liver, they are gluconeogenic organs.

## STRUCTURE OF THE KIDNEYS AND URINARY SYSTEM

The kidneys are paired organs which lie outside the peritoneal cavity in the posterior abdominal wall, one on each side of the vertebral column. The medial border of the kidney is indented by a deep fissure (called the hilum) through which passes the renal vessels and nerves and in which lies the funnel-shaped continuation of the upper end of the ureter, the *renal pelvis* (Fig. 2). The outer convex border of the renal pelvis is divided into major *calyxes,* each of which subdivides into several minor calyxes. Each of the latter is cupped around the projecting apex of a cone-shaped mass of tissue *(a renal pyramid).*

When the kidney is bisected from top to bottom it can be seen to be divided into two major regions: an inner *renal medulla* and an outer *renal cortex.* The medulla is made up of a number of renal pyramids, the apexes of which, as stated above, project into the minor calyxes. Each pyramid of the medulla, topped by a region of renal cortex, forms a single lobe.

Upon closer gross examination, additional features can be discerned: (1) The cortex has a highly granular appearance missing from the medulla; (2) each medullary pyramid is divisible into an outer zone (adjacent to the cortex) and an inner zone, including the apical tip, called the *papilla.* All these distinctions reflect the arrangement of the various components of the microscopic subunits of the kidneys, to which we now turn.

### The Nephron

In humans, each kidney is composed of approximately 1 million tiny units, *nephrons,* one of which is shown diagrammatically in Fig. 3. Each nephron consists of a "filtering component," called the *glomerulus,* and a

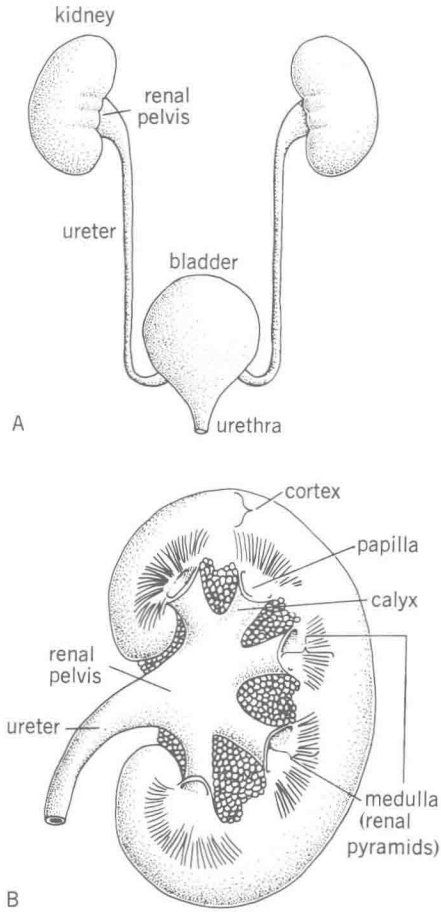


**Figure 2** A. The urinary system. The urine, formed by the kidney, collects in the renal pelvis and then flows through the ureter into the bladder, from which it is eliminated via the urethra. B. Section of a human kidney. Half the kidney has been sliced away. Note that the structure shows regional differences. The outer portion (cortex), which has a granular appearance, contains all the glomeruli. The collecting ducts form a large portion of the inner kidney (medulla), giving it a striped, pyramidlike appearance, and drain into the renal pelvis. The papilla is the inner portion of the medulla. *(From A. J. Vander et al., Human Physiology, © 1970 by McGraw-Hill, Inc. Used with permission of McGraw-Hill Book Company.)*

*tubule* extending out from the glomerulus. Let us begin with the glomerulus, which is responsible for the initial step in urine formation, the separation of a protein-free filtrate from plasma.

**The Glomerulus** The glomerulus consists of a compact tuft of interconnected capillary loops (the *glomerular capillaries*) and a balloonlike hollow capsule *(Bowman's capsule)* into which the capillary tuft protrudes (Fig. 4).[1] One way of visualizing the relationship between the glomerular capillaries and Bowman's capsule is to imagine a loosely clenched fist (the capillaries) punched into a balloon (Bowman's capsule).

[1]There is no complete agreement as to whether the glomerulus should refer only to the capillary tuft or to the tuft plus Bowman's capsule; the latter is presently the more common usage.