REFLECTIONS
ON
RENAL FUNCTION

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PREFACE

For several years I have given a few lectures upon the physiology of the kidney to a small class reading physiology for Part II of the Natural Sciences Tripos in Cambridge, and have often been urged to have the lectures published. There is no convenient book to bridge the gap between the chapters in general textbooks and larger treatises such as that of Homer Smith; and so I have ventured to publish, not the lectures exactly as they were given, but a small and rather informal book written in the spirit of the lectures from the same notes. This is not intended to be a comprehensive review of the literature of renal physiology, but aims at presenting in moderate compass a picture, sometimes an impressionistic one, of the working of the kidneys and of its adjustment to meet the changing needs of the body.

Renal physiology is controversial, and perhaps ought to be more so. There is a temptation, especially when teaching, to seek clarity by a too well organized presentation which gives the impression of a greater understanding than we really have. I have tried to steer a middle course, and to present a clear picture without concealing its incompleteness and its lack of finality. In so far as fundamentals have been stressed, the approach is elementary; but a certain amount of new interpretation and integration, as well as of emphasis on the unsolved problems of the processes which underly renal function at the cellular level, makes it in some ways advanced at the same time. I cannot claim in so short an account to have been completely fair to all parties in controversy, but I hope that important points at issue have not been ignored, and ask the indulgence of any whose views have been too lightly passed over.

Friends suggested that a book without references would be refreshing, but the reader needs some guidance to sources. A few important secondary sources have therefore been mentioned in an introductory note, and primary sources which they quote have not been included in the text unless they are of especial interest; but references to some more recent work have been included. The references quoted during a lecture cannot be consulted until a later occasion, and it is hoped that the picture outlined in this book can be grasped as a whole without consulting the bibliography for the filling in of detail.

It is a pleasure to acknowledge the constant encouragement of Prof. R. A. McCance, C.B.E., F.R.S., and of other members of the Department of Experimental Medicine. My thinking about the kidneys has grown up in the atmosphere of this Department, and without its stimulus the book would never have been written. I also wish to thank the publishers for the friendly co-operation which made the path to print so smooth.

Cambridge, January 1954.

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I. INTRODUCTION

A NOTE ON SOURCES

The literature of renal physiology is extensive and widely dispersed through a large number of journals primarily devoted to physiology, zoology, anatomy, pathology, clinical medicine and paediatrics. Homer Smith's treatise [85] is an invaluable guide to the contents of more than 2,000 original contributions published up to 1951. The shorter and more closely knit account of renal physiology in the first edition (1937) is still worth reading. [83] Some special aspects are treated more fully and make pleasanter reading in the "Lectures on the Kidney" published in 1943. [84] Cushny's classical monograph [15] reviews some earlier material which is still interesting. Another treatise by Wolf, [112] with over 1,000 references, surveys the field in somewhat different fashion. This is a stimulating book because it is critical, provocative, and iconoclastic; and although the invention of a new and unfamiliar jargon makes it also at times irritating, some parts of the book are extremely illuminating. During 1950 the American Journal of Medicine published a series of "Seminars on Renal Physiology" which provide compact reviews of particular aspects of the subject; some of these will be quoted individually in the text.

FUNCTIONS OF THE KIDNEY

The principal functions of the kidney are conveniently summarised under three headings:

1. *Excretion.* The kidneys excrete, in aqueous solution in the urine, end-products of metabolism such as urea, uric acid and creatinine, as well as soluble foreign substances which have been

introduced into the body, or products of their detoxication. They also excrete the surplus of normal constituents of the body such as sodium chloride and water which have been absorbed in excess of requirements. The urine contains small amounts of other soluble constituents of the body, such as amino acids, especially glycine, serine, threonine, lysine and histidine, but these are thought of as leaking out or escaping rather than as being excreted. In so far as only the surplus of many solutes is excreted, and the rest is retained, the kidneys perform a second major function:

2. *The conservation* of the soluble constituents of the body, such as glucose, inorganic salts, amino acids and other metabolites, and of the water which holds all of these in solution. By striking a balance between the conservation and the excretion of water and of the substances dissolved in it, the kidneys perform a third most important function:

3. *Regulation* of the chemical structure of the body fluids. This includes regulation not only of the *total concentration* or *osmotic pressure* of these fluids, and of their detailed *chemical composition*, including their pH, but also of their *volume*. Provided that intake in the diet is sufficient, the kidneys play a major role in regulating the concentrations of water, sodium, potassium, chloride, phosphate, calcium, glucose and urea in the plasma, and they take a large part in the long-term regulation of acid-base balance. The manner in which they regulate the amount of water in the body and its distribution between the major fluid compartments is less direct, for it depends upon the metabolic activity of all the cells in the body, not merely of those within the kidney. So long as metabolism continues normally in the tissues, the sodium of the body is mostly extracellular, whilst most of the potassium is in the intracellular fluids. This distribution is maintained in defiance of a concentration gradient across every cell membrane by energy derived from metabolic processes in the cells in a manner which still remains to be elucidated. But while

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this unequal distribution of ions persists, the cell membranes behave *as if* they were semipermeable, and the volume of the cells is determined by the osmotic pressure of the fluids outside them, most of which is contributed by sodium salts. Hence if the amount of sodium in the body remains constant, the kidneys can regulate the osmotic pressure of the extracellular fluids by adjusting the excretion of water, and in doing this they can control the volume of the cells. On the other hand, so long as the osmotic pressure of the extracellular fluids is kept constant by controlling the excretion of water, the total volume of the extracellular fluids (plasma, lymph and the interstitial fluids) can be increased or decreased by retaining or excreting sodium. The kidneys can therefore regulate the volume of fluid inside the cells by the controlled excretion of water, and the volume of fluid outside the cells by the controlled excretion of sodium.

The kidneys may be regarded as organs which help to stabilize the internal environment of the body and to keep it chemically distinct from its surroundings. The elimination of waste products is but one aspect of this much larger task. Other functions, such as the long-term regulation of blood pressure, have been postulated, but will not be discussed here. The two main questions to be considered are, first, how the kidneys do what they do, and, secondly, how they know what to do, or more properly, how they are directed to do it. This second question is concerned with the kidney as one part of the body in relation to other parts, and is for that reason more complex. The simpler question of the mechanism of the kidney itself will be taken up first.

STRUCTURE AS A CLUE TO FUNCTION

Certain structural features of the kidney which bear upon its mechanism will now be summarised. Each human kidney consists of about a million more or less similar units, called "nephrons", arranged in parallel. Each nephron commences in a glomerulus, which leads in turn to a proximal convoluted tubule,

a loop of Henle, and a distal convoluted tubule. The loop of Henle includes a thin descending limb which varies in length from one nephron to another, and a thicker ascending limb lined by a columnar epithelium continuous with that of the distal convoluted tubule. The proximal and distal convoluted tubules lie near the corresponding glomerulus in the cortex of the kidney; the descending limb of the loop of Henle runs down radially into the medulla, to turn back upon itself at a hair-pin bend. The distal convoluted tubules end in collecting tubules which descend again into the medulla but do not return; they drain instead into the renal pelvis.

Although they are similar in pattern the nephrons are not all alike. They differ most strikingly in their vascular arrangements, which depend upon the position of their glomeruli within the kidney. Nephrons with glomeruli lying in the outer two-thirds of the cortex — called *cortical nephrons* — are the more numerous. They were developed embryologically later than the nephrons more deeply placed in the kidney, and their loops of Henle do not descend so far into the medulla; the thin segments are short, and may be altogether absent. The blood leaving a cortical glomerulus by its efferent arteriole is collected into an intertubular capillary plexus investing the convoluted tubules of the same and nearby nephrons. Nephrons whose glomeruli are closer to the medulla, in the inner third of the cortex, are called *juxta-medullary nephrons*. These have larger glomeruli than the cortical nephrons, their loops of Henle plunge more deeply into the medulla, and have longer thin segments. The efferent arterioles of juxta-medullary glomeruli differ in two ways from those of the cortical glomeruli. They are wider, instead of narrower, than the afferent arterioles, and they do not lead into intertubular capillaries, but drain instead into wide, straight, thin-walled venous channels called vasa recta which run in bundles parallel to the loops of Henle in the medulla. Like the loops of Henle the vasa recta descend for a variable distance into the medulla

and then turn abruptly back towards the cortex, where they end in veins. Both sets of tubes run radially, the bundles of vasa recta are embedded in the mass of loops of Henle, and individual loops are also interposed between the vasa recta within the bundles. The vasa recta are wider than capillaries, but their walls are made of the same kind of endothelium, so that this whole arrangement appears well suited to promote equilibrium by diffusion between the fluid in the loops and the venous blood in the vasa recta.

The convoluted tubules have a "secretory" type of epithelium. The cells are columnar with basal striations formed by a parallel packing of mitochondria at right angles to the basement membrane. The proximal convoluted tubules show in addition a brush border at the luminal poles of the cells. The cells lining the thick ascending limb of the loop of Henle resemble those of the distal convoluted tubule. Those of the thin limb are not much thicker than a capillary endothelium, but their nuclei may be seen bulging out into the lumen. Sjöstrand & Rhodin (1953) have published illustrations of structural details revealed by the electron microscope in epithelial cells of the kidneys of mice. [82] Histological evidence therefore suggests that the cells lining the tubules might secrete like those of other glands; the glomeruli, on the other hand, look like ultrafilters, and their simpler function will be considered before the more complex processes of tubular secretion.

II. GLOMERULAR FILTRATION AND TUBULAR REABSORPTION

GLOMERULAR FILTRATION

Over a century ago the structure of the glomeruli suggested to Bowman that they might excrete the water and salts of the urine. Bowman's capsule encloses a tuft of capillary loops arranged in parallel between a wider afferent and a narrower efferent arteriole. The afferent vessel arises from an interlobular artery, which has arisen fairly directly from the renal artery. The renal arteries themselves are short and wide and arise from the abdominal aorta. By this arrangement, blood at a pressure of one-half to two-thirds of that in the aorta is exposed in a layer a few microns in thickness over a thin membrane which consists of a single layer of endothelial cells supported on a basement membrane. This thin membrane in man has about the same total area as the external surface of the body. The glomerulus thus presents the appearance of an ultrafilter, and the fact that no urine is formed unless the head of pressure available for ultrafiltration exceeds the colloid osmotic pressure of the plasma proteins suggests that it functions as such. More direct evidence has been obtained in Amphibia, whose glomeruli resemble those of mammals in structure but are nearer to the surface of the kidney; Richards and his colleagues collected the glomerular fluid in tiny quartz pipettes pushed into the capsular space, and analysed it chemically. [75] No more than a trace of protein was present, and although the quantities of fluid obtained were too small to be analysed with great accuracy, the glomerular fluid had the composition of an ultrafiltrate of plasma within the limits of the methods employed.

In particular, it contained glucose when the urine in the bladder did not, and about as much chloride and urea as the plasma when the urine contained less chloride and more urea. The general similarity to plasma suggests filtration of protein-free fluid as a whole, rather than transpiration by diffusion, which might be expected to alter the proportions of the various solutes according to their diffusion coefficients (inversely proportional to the square root of the molecular weight).

The glomeruli of mammalian kidneys are less accessible to puncture than those of Amphibia, but Walker, Bott, Oliver & MacDowell [102] managed to withdraw fluid from different parts of the nephron in rats and guineapigs, and found that the fluid obtained when the proximal convoluted tubule was punctured nearest to the glomerulus resembled an ultra-filtrate of plasma most closely. If the mammalian kidney is chilled or poisoned with cyanide, either of which might be expected to stop the secretory activity of the epithelial cells, the urine comes to resemble an ultrafiltrate of plasma in chemical make-up. It is reasonable to conclude that the glomeruli in mammalian kidneys, like the similar ones in the kidneys of Amphibia, produce an ultrafiltrate of the blood plasma by a physical process which is nonselective for substances of low molecular weight. No work need be done by the glomerular cells in this process. Energy imparted to the blood by the beating heart and stored in the distended elastic walls of the aorta and renal arteries supplies the hydrostatic pressure required to separate the proteins from the other constituents of the plasma. Although this process is strictly one of ultrafiltration, common usage, which will now be followed, refers to it as "glomerular filtration" and to the ultrafiltrate produced as the "glomerular filtrate".

GLOMERULAR FILTRATION IN MAMMALS

Although the capsular fluid of the mammalian kidney cannot be collected and analysed, the rate at which it is formed can be

estimated in intact animals including man without drastic surgical procedures. Apart from its practical value in the assessment of renal function for clinical purposes, a knowledge of the rate at which the glomerular filtrate is formed is important theoretically because it enables the part played by the tubules in the elaboration of the urine to be discovered. If the rate at which a substance appears in the glomerular filtrate exceeds its rate of excretion in the urine, then the cells which line the tubules must be reabsorbing it; on the other hand a substance which appears in the urine more rapidly than it is filtered by the glomeruli must be actively excreted by the tubular epithelium. Most workers are content to assume that the composition of the glomerular filtrate may be determined by analysing plasma or serum. Non-electrolytes are taken to have the same concentration in the filtrate as in arterial plasma, but the concentrations of electrolytes in the plasma are multiplied by the appropriate factors for a Donnan distribution of anions and cations across the glomerular membrane. Suitable factors are 1.02 for chloride and bicarbonate, 0.95 for sodium and 0.90 for potassium, when there are 6 grams of protein in each 100 ml. of plasma. Because an appreciable fraction of the volume of the plasma is occupied by the proteins, the concentrations of solutes in the watery phase of the plasma are about 6% greater than their concentrations in whole plasma. Hence in order to obtain the actual concentrations of solutes in the glomerular filtrate, it would be necessary to multiply all concentrations determined by the analysis of whole plasma by a factor of about 1.06 as well as by any Donnan factor which might be required. This is a correction which is hardly ever made for a reason which will shortly become apparent.

EXCRETION RATES AND CLEARANCES

The rate which a substance X is excreted in the urine is $U_x \cdot V$, where U_x is the concentration of X in the urine, and V is the rate at which urine is formed. V is most commonly expressed in ml.

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