The Kidney in Health and Disease

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J. B. Lippincott Company
Philadelphia • Toronto

Distributed in Great Britain by
Blackwell Scientific Publications,
Oxford and Edinburgh

ISBN-0-397-50282-6

Library of Congress Catalog Card Number 75-165976

Printed in the United States of America

1 3 4 2

Preface

This text summarizes and correlates present day knowledge regarding diseases of the kidney by utilizing the findings of clinicians, pathologists and the clinical laboratory. The diagnostic contributions of percutaneous biopsy in differentiating glomerular diseases is emphasized and illustrated. Throughout the text, the aim has been brevity and legibility in order to facilitate comprehension and utility from the standpoint of the nonspecialist. The indicated treatment is mentioned in general terms but is not detailed for therapeutic application.

Several major features of renal disease are emphasized. The vascularity and filtration functions of the kidney cause it to share in cardiovascular diseases arising elsewhere and its filtration membranes are readily damaged by antigen-antibody complexes, whether these be directed against injurious agents elsewhere in the body or against the damaged renal tissue itself. One of the reasons for this is the necessity for antibody complexes to permeate the microcirculation in order to gain access to agents of injury harbored in the interstitium of various organs. This is a common cause of proteinuria. Percutaneous renal biopsy is usually essential to differential diagnosis in this field, and electron microscopy is an indispensable tool.

The highly selective reabsorptive functions of the renal tubular epithelium render it susceptible to a wide variety of endocrine disturbances and also to inborn errors of metabolism, which selectively delete tubular enzymatic or other reabsorptive mechanisms known as epithelial transport.

With the exception of benign and malignant neoplasms and some forms of obstructive uropathy, the end-stage of most renal diseases is uremia, indicating that the two kidneys share and share alike in most forms of renal damage, which is diffuse rather than focal. Only rarely is unilateral nephrectomy curative. This is the reason for present day interest in renal transplantation, which is discussed in the final chapter of the text.

The authors gratefully acknowledge the generosity of their colleagues at Georgetown University Medical School who contributed the clinical material. We also acknowledge with our thanks the excellent Camera Lucida drawings made by Margaret M. Palmer at the Naval Medical School, Bethesda, Maryland. We are indebted to the Editorial staff of the Lippincott Company for their preparation of the index, to Dr. Charles Hollerman, Department of Pediatrics of Georgetown University Medical Center, for reading the original text and to Martha E. Norton for typing and editing the manuscript.

Contents

1

Structure and Physiology of the Kidney

The kidneys regulate the volume and chemical composition of the blood by excreting fluid and waste substances and reabsorbing needed physiologic constituents. This is accomplished within the organ by exposing a glomerular filtrate of blood plasma to the renal tubular epithelium, which then reabsorbs the appropriate solutes and excretes any excess acid plus ammonia. Normal renal plasma flow in the adult approximates 700 ml. per minute, of which 130 ml. emerges as filtrate but only one or two ml. is discarded as urine. These fluid exchanges require an adequate blood supply and access to the exterior by way of the urinary tract for the excreted wastes. Normally, about one fourth of the total blood volume passes through the renal vessels.

STRUCTURE OF THE KIDNEY

Each kidney (adult weight approximately 150 gm.) contains approximately one million nephrons, which comprise the histologic or functional unit (Moore). The nephron consists of a glomerulus, proximal convoluted tubule, loop of Henle, distal convoluted tubule and collecting tubule (Fig. 1-1). The glomerulus is a modified arteriole derived from the tertiary branch of the renal artery, a pair of which spring directly from the aorta. Each of these renal arteries divide into 7 to 9 secondary branches (known as the interlobar or segmental arteries), and these separate into arcuate arteries, which in turn give rise to the interlobular arteries from which the multiple afferent arterioles of the individual glomeruli are derived (Fig. 1-2). Each of these afferent arterioles divides into multiple capillary loops (forming the glomerular tuft), and then reunite to leave the glomerulus through the efferent arteriole, which in turn forms capillaries that intertwine about the tubules of the individual nephrons.

The wall of the glomerular capillaries situated between the afferent and efferent arterioles has a distinctive structure. It contains an endothelial lining, a basement membrane and an outer layer of epithelial cells, which are part of Bowman's capsule. These capillary loops are suspended

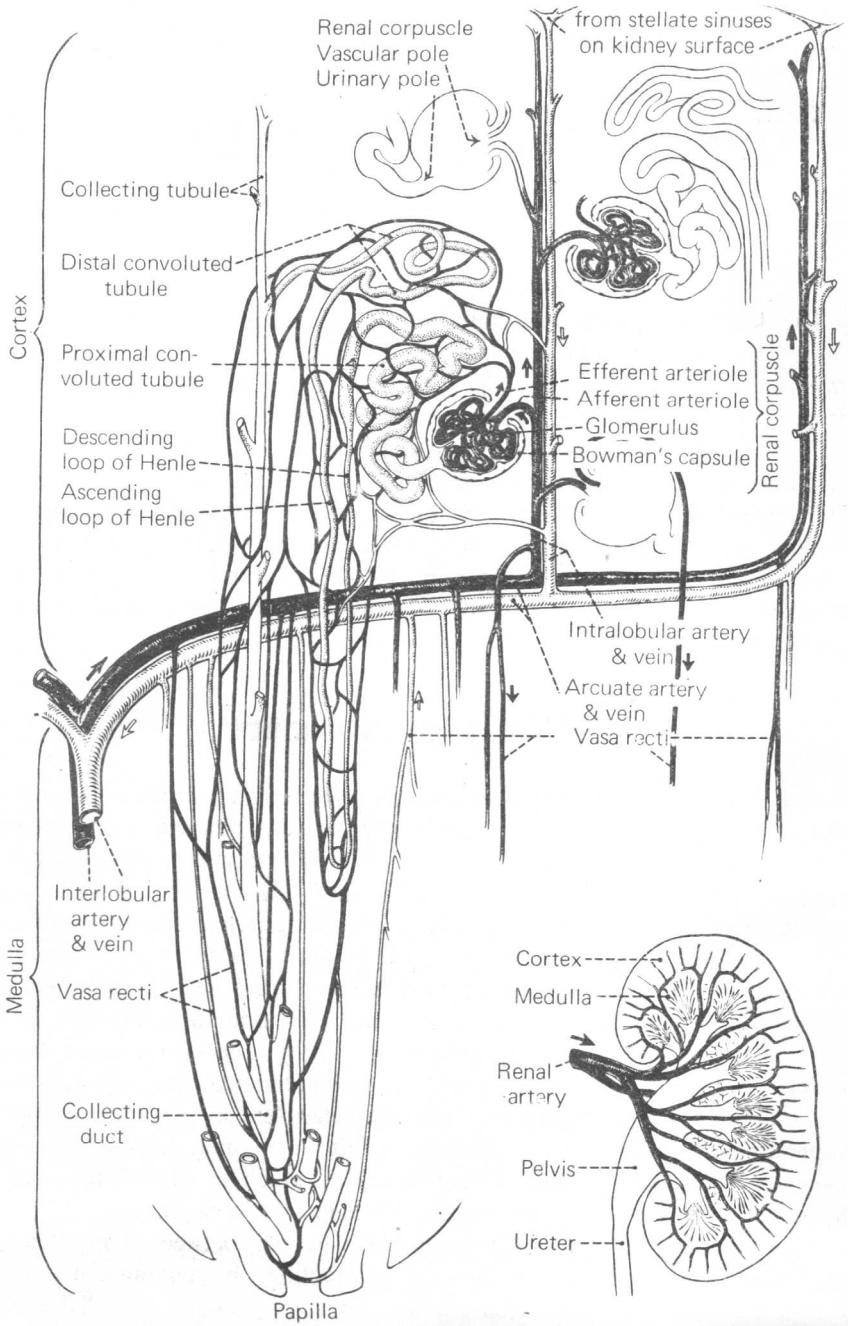

Fig. 1-1. Structure of normal renal functioning unit.

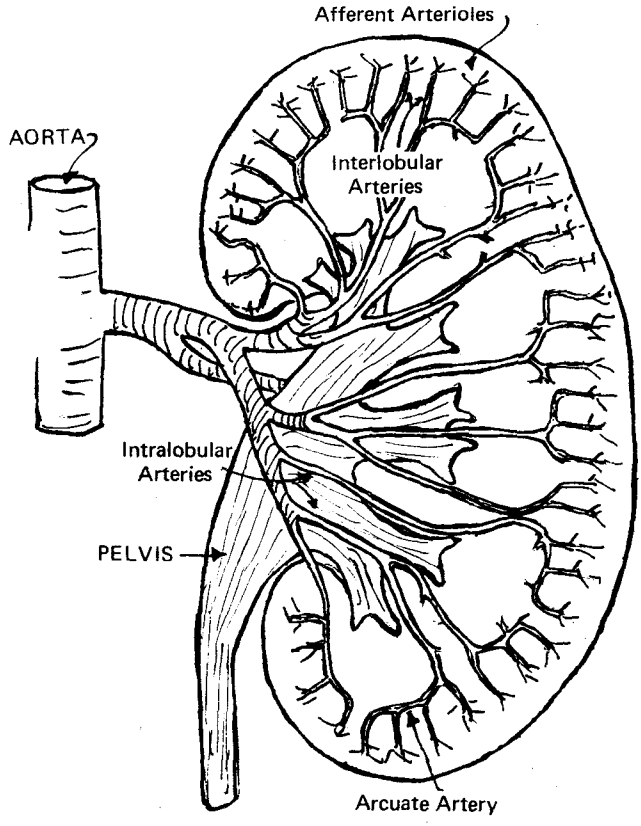

Fig. 1-2. Renal arterial blood supply.

by a stalk of mesangial cells, forming the pole, or axis, of the glomerulus. In this stalk, the endothelial cells adjoin the mesangial cells without an intervening basement membrane. Each capillary loop is lined by a single endothelial cell, the main body of which is located at the axial side, while the circumference of the loop is lined by attenuated fenestrated endothelial cytoplasm. These regularly spaced endothelial pores (varying in diameter from 200 to 900 Å) are sealed by the basement membrane.

This basement membrane between the capillary endothelial cells and the epithelial cells of Bowman's capsule contains 3 layers. The central layer is formed by electro-dense material (the lamina densa). Less dense and electron-light zones are applied to either side (the lamina rara externa and interna, respectively). This basement membrane, which acts as a filter is formed jointly by the capillary endothelium and the epithelium of Bowman's capsule. Through electron microscopy, it has been found that the lamina densa has a fibrillary structure which is formed by its con-

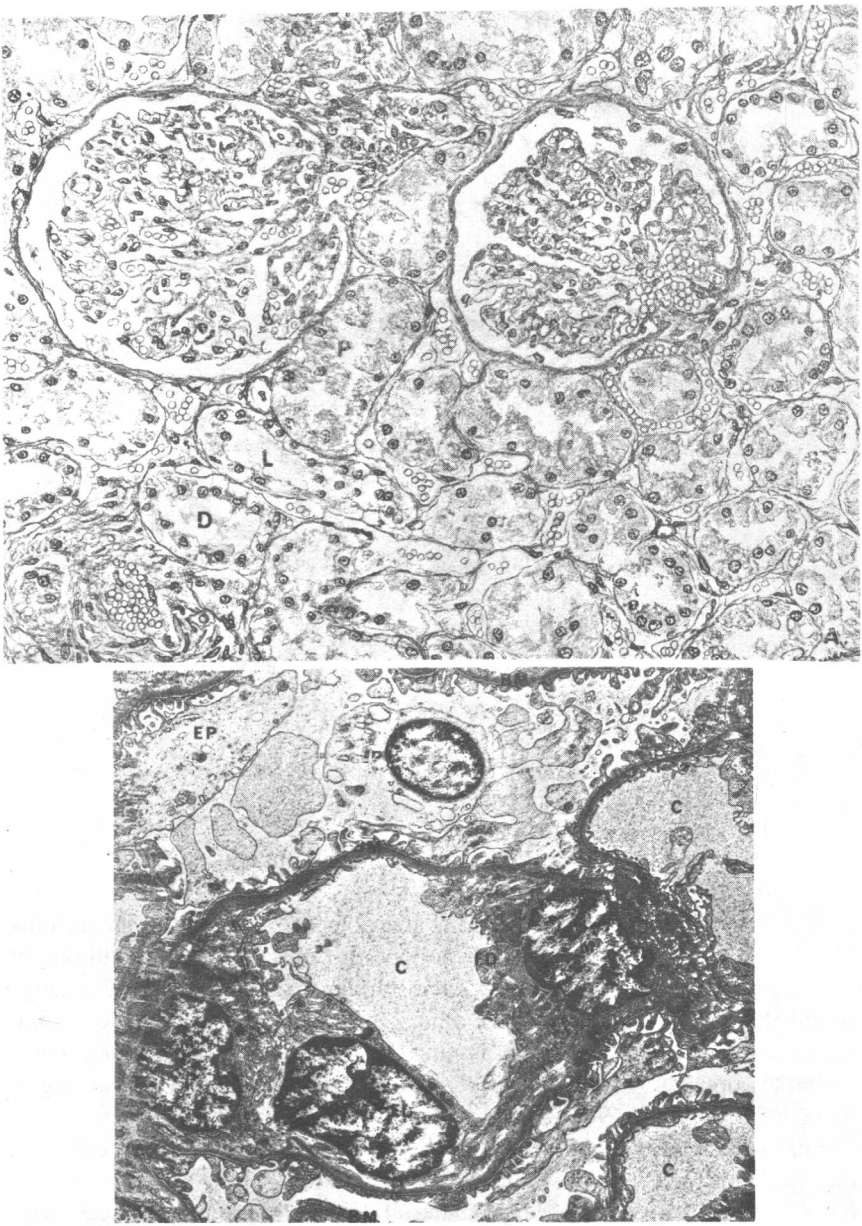

Fig. 1-3. (A) Camera lucida drawing of normal glomerulus. P, proximal tubule; L, loop of Henle; D, distal tubule. (× 220) (B) Electron micrograph of normal glomerulus. C, capillary lumen; ED, endothelial cell; EP, capsular epithelium; M, mesangial cells; BC, Bowman's capsule. (× 3,000)

tinually changing molecular components, the so-called thixotropic gel in which interactions can occur between its protein molecules (Fig. 1-3 (B)).

The epithelial cells covering the basement membrane on its urinary side are attached by interdigitating foot processes with intervening spaces, called the filtration slits. Their large cytoplasmic bodies are rich in endoplasmic organelles, including mitochondria, Golgi material, smooth and rough endoplastic reticulum, and varyingly sized ribosomes or cytosomes, indicative of marked cellular activity. Some investigators believe that these epithelial cells monitor the activity of the basement membrane (Farquhar-Palade).

The mesangial cells (found mainly at the axis of the glomerulus) provide the ground substance for the capillary loops and surround the afferent and efferent arterioles in this region. These "third cells" are suspended in a fibrillary matrix (the mesangial matrix), which supports the capillaries and aids in the regulation of capillary pressure, acting as a pressor receptor. The mesangial cells also are phagocytic, of mesenchymal origin, and undergo proliferation and elaborate additional fibrils to reinforce the basement membrane.

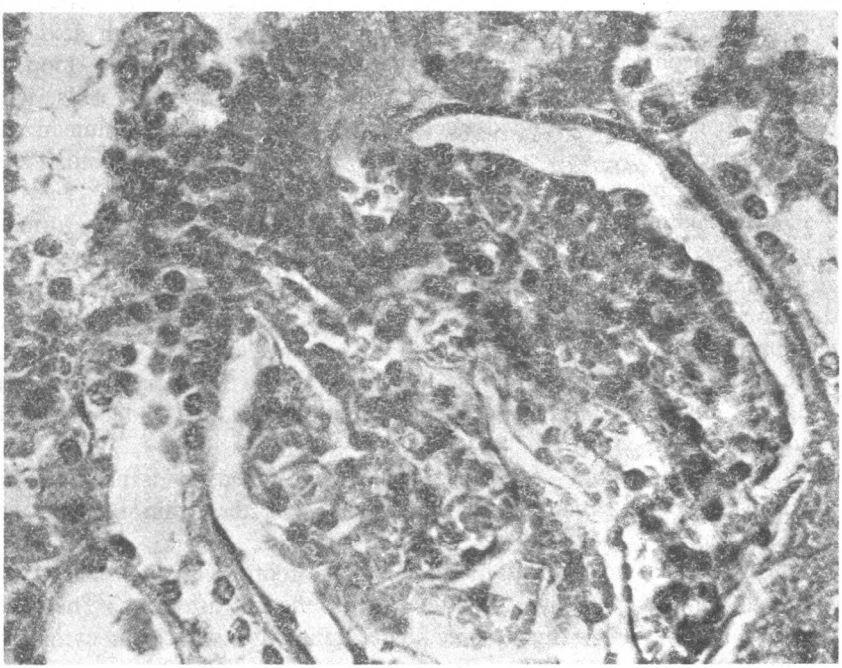

Fig. 1-4. Hyperplasia of the renal juxtaglomerular apparatus of a dog in experimental hypertension. (× 300) (Geschickter, C. F., and O'Malley, W. E.: Production of hypertension by means of injection of N,N'-dimethyl-p-phenylenediamine. Am. J. Clin. Path., *33*:281, 1960)

At the vascular pole of the glomerulus, the afferent arteriole adjacent to the distal convoluted tubules contains a collection of highly granulated cells which form the juxtaglomerular apparatus (Fig. 1-4). These cells are related to the muscular layer of the afferent arteriole and secrete the hormone, renin, which aids in regulating blood pressure.

STRUCTURE OF THE TUBULES

The tubular portion of the nephrons comprises the bulk of the renal parenchyma and has four segments. (1) The proximal convoluted segment (situated in the cortex) is formed by high pyramidal cells with a large spherical nucleus and abundant cytoplasm, which stains deeply with eosin. The luminal surface of these cells has a brush border formed by numerous microvilli (visible with the electron microscope), increasing the surface area 40-fold. Their opposite basal surface contains numerous enfoldings, which increase the surface adjacent to the capillaries. Their cytoplasm has a large number of mitochondria, numerous apical vacuoles, Golgi apparatus and both smooth and rough endoplastic reticulum. Histochemical studies reveal numerous enzymes, including both acid and alkaline phosphatase, lipase, and others. (2) The descending loop of Henle extending into the medulla is lined by low columnar cells, with pale cytoplasm and a rounded nucleus, which bulges into the lumen. By electron microscopy, only a few microvilli are found on their luminal surface and a few basal and lateral cytoplasmic enfoldings.

The ascending loop of Henle is lined by large cuboidal cells forming a thicker wall than the descending portion. The cytoplasm of these cells stains darkly with eosin and, by electron microscopy, contains perpendicular striations. These cells have enfoldings extending from their basal membranes close to the luminal surface with elongated mitochondria close to the enfolded membranes, suggesting active transport. The microvilli on the luminal surface are coarse and numerous. The endoplastic reticulum is sparse.

The descending and ascending tubules are joined by a narrow loop lined by flattened squamous epithelium. This is the "thin segment" of Henle's loop.

(3) The distal convoluted tubules lie close to the vascular pole of the glomerulus in contact with the afferent and efferent arterioles. The main portion of the tubule is lined by cuboidal epithelium with clear cytoplasm and definite cell borders. The lumen is larger than that of the proximal convoluted tubule. The luminal surface shows few villi and the base of the cells is striated by deep enfoldings. The zone of contact of the distal

tubule with the afferent and efferent arterioles contains an eliptical disk of thin, elongated cells (the macula densa), with their basilar portion against a special group of cells in the wall of the afferent arteriole (the juxtaglomerular apparatus) and their luminal surface forming part of the lining of the convoluted tubule. These cells are apparently especially sensitive to the sodium content of the renal filtrate. The terminal portion of the distal convoluted tubule is lined by cells with decreased amounts of cytoplasm with fewer and shorter mitochondria.

(4) In the medulla of the kidney, the straight collecting ducts lead from the distal convoluted tubules to the larger "papillary" ducts found in the renal papillae, known as the ducts of Bellini. The cells of the collecting tubules are cuboidal or low columnar in type, but those in the ducts of Bellini are tall columnar. The cells of the collecting duct prior to their junction with the ducts of Bellini are considered part of the functioning nephron.

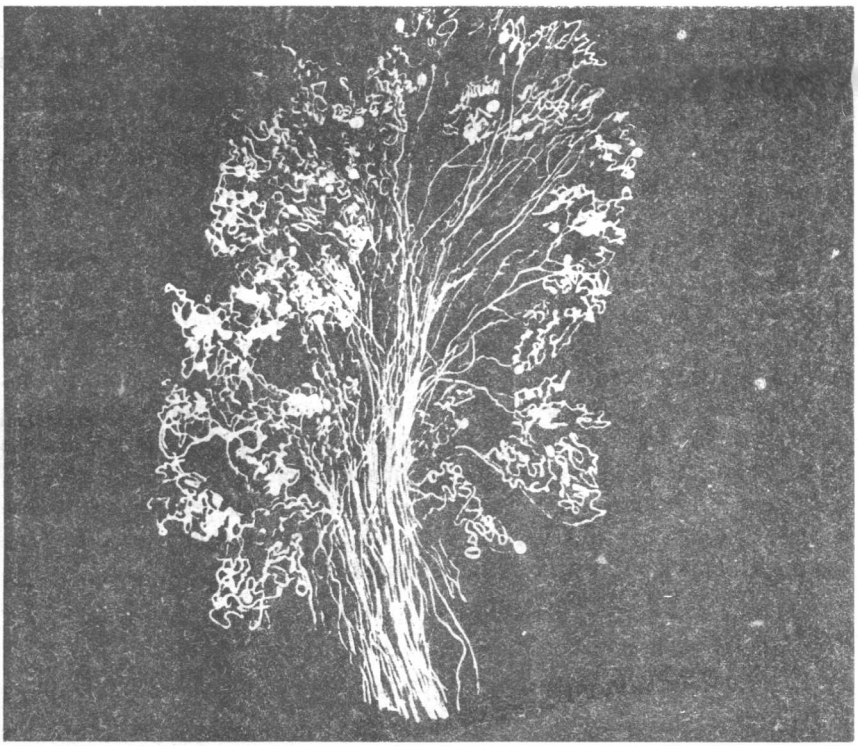

Fig. 1-5. Nephrons freed by microdissection. (Kidney Function in Disease. Lilly Laboratory for Clinical Research, Indianapolis, Indiana)

PHYSIOLOGY OF THE KIDNEY

GLOMERULAR FUNCTIONS

Blood circulates through the glomerular capillaries at a pressure of 50 to 60 mm. Hg, or roughly twice that in other capillaries. This hydrostatic pressure is responsible for the filtration of plasma constituents which pass through the basement membrane into the lumen of the renal tubules. This glomerular filtrate (which resembles blood plasma except for the lack of appreciable protein and lipid constituents) forms at the rate of 110 to 130 ml. per minute and is known as the glomerular filtration rate (GFR). GFR ceases when blood pressure falls to shock levels or when obstruction in the urinary tract raises back-pressure above that in the capillaries, indicating its dependence on hydrostatic pressure. Small protein molecules are filtrable but those with a molecular weight above 40,000 normally are not. The quantity of plasma filtrate per hour (approximately 7500 ml.) exceeds its total circulating volume, but over 70 percent is reabsorbed in the proximal tubules, which act selectively to reclaim all of the glucose and protein and most of the sodium while rejecting much of the urea and all of the creatinine (Table 1-1).

By constriction of the efferent arteriole, the renal glomerulus can maintain filtration near normal levels in spite of moderate declines in blood pressure or renal blood flow when these are lowered by loss of blood volume or by deficient cardiac output. This adjustment is known as *autoregulation.*

Chronic renal failure is usually the result of loss of filtration surface because of a reduction in the number of functioning glomeruli (the total normal filtration area of the glomeruli in both kidneys has been estimated as 1.5 square meters). Such a loss of glomerular units by scarring or thrombonecrosis reducing the filtration surface by two thirds or more is responsible for retention in the plasma of increased amounts of urea, creatinine, uric acid, phosphates and potassium when progressive disease is present. Reduction in GFR can be measured by obtaining the creatinine clearance. This is expressed by the quotient:

$$\frac{\text{amount of excreted creatinine in urine/minute (mg./min.)}}{\text{plasma concentration of creatinine (mg./ml.)}} \text{ or } \frac{UV}{P}$$

(U = concentration in urine (mg./100 ml); V = urine volume (ml./min.))

The GFR also can be measured by the intravenous injection of the polysaccharide, inulin, which is neither secreted nor reabsorbed by the renal tubules, passing directly out of the capillaries into the excreted urine. Since the concentration of inulin is the same in the plasma and the filtrate,

its amount in the urine excreted during one minute equals the amount of plasma water filtered in one minute. If plasma inulin is 1 mg. per milliliter and urine excretion is 130 mg. per minute, then one minute's urine contains the inulin filtered from 130 ml. of plasma and the GFR is 130 ml. per minute.

The function of the glomerular basement membrane as a filter is determined not so much by its microscopic appearance as by its finer structural arrangements at a molecular level. A *pathologically widened membrane is usually a more porous membrane* and such glomerular disease, regardless of its cause, is usually associated with proteinuria. Increased permeability of damaged glomeruli with proteinuria occurring in the presence of nitrogen retention often seems paradoxical to the student, but the proteinuria is dependent upon membrane leakage, whereas the azotemia, retained nitrogen wastes in the blood, is dependent upon the reduced number of functioning glomeruli, which are being progressively eliminated by scarring. Thus, patients with moderate glomerular damage have proteinuria; those with major damage and loss of glomeruli have proteinuria plus azotemia.

With the exception of ammonia, which is formed in the kidney by enzymes acting on glutamine, the capacity of the kidney to increase the rate of excretion of waste substances depends upon the rate at which the arterial blood in the glomeruli delivers the material. Under normal conditions, the amount of filtrate formed is equal to one fifth of the plasma flow through the glomeruli. This ratio, determined by dividing renal plasma flow (RPF) into GFR (which equals about 0.2), is known as the filtration fraction. During moderate decrease in renal blood flow, the GFR tends to be maintained by constriction of the efferent arterioles so that the filtration fraction is adjusted toward normal. Conversely, the filtration fraction tends to be reduced to conserve sodium or potassium in patients in whom these ions are depleted.

When progressive glomerular damage decreases the patency or number of perfused capillary loops available for forming the glomerular filtrate, the renal clearance of waste substances falls proportionately to the diminution of GFR, and azotemia develops. Cholinergic drugs such as acetylcholine tend to increase renal blood flow to the intact kidney but are ineffectual in combating azotemia. Diuretics acting on the renal tubules to diminish the reabsorption of solutes are also ineffective since they do not influence GFR. The only practical influences during azotemia are artificial hemodialysis or the reduction of protein intake in the diet.

Chronic glomerular damage without azotemia or hypertension but with marked proteinuria occurs in the condition known as the nephrotic syndrome, which results from increased porosity of the glomerular basement membrane. The smaller protein molecules (albumin) rather than the

larger ones (globulins) are lost and a corresponding reduction in blood volume occurs through loss of fluid to the extravascular space because of decreased plasma oncotic pressure. This hypovolemia diminishes GFR. An acute fall in GFR promotes tubular reabsorption of salt, the so-called *glomerular-tubular imbalance,* which enhances edema. Diuretics occasionally are helpful but other factors are present which influence sodium retention. The administration of steroids diminishes proteinuria in juvenile lipoid nephrosis but is less effectual in the nephrotic syndromes associated with other forms of glomerular injury such as diabetes mellitus and amyloid disease.

A chronically diminished blood supply to the renal cortex, resulting from narrowing of the renal artery or one of its major branches, or from intrarenal infection and scarring in pyelonephritis, causes an increased secretion of renin from the juxtaglomerular cells and may result in renal hypertension. When the condition is unilateral, the hypertension may be cured by nephrectomy. Progressive renal insufficiency, resulting from glomerular damage, is associated with azotemia and elevated blood pressure with death in uremia. The cause of the hypertension, which may be accelerated to the malignant form, is unknown but is attributed by some to a vasodilator effect of normal renal tissue, which is lost in advanced renal disease.

TUBULAR FUNCTIONS

The proximal convoluted tubules reabsorb water, glucose and salt in proportions similar to that found in Locke's solution. They also absorb amino acids, some protein and a considerable portion of filtered urea. Here, 70 to 80 per cent of the GFR is reabsorbed. The capacity of the renal tubular epithelium to reclaim essential metabolites is similar to the capacity of the intestinal epithelium to absorb nutrients. Thus, hereditary defects in the absorption of certain amino acids affect both the kidney and the intestine. This is also true of genetically determined renal loss of phosphate, which is associated with deficient absorption of phosphate by the intestinal epithelium. The mechanisms whereby constituents of the glomerular filtrate are reclaimed are variable. The reabsorption of sodium and bicarbonate, which takes place in the proximal tubules along with water, requires the active secretion of hydrogen ions derived from carbonic acid in the blood by the action of carbonic anhydrase. A genetic deficiency in this enzyme leads to an alkaline urine and metabolic acidosis, a disease known as *renal tubular acidosis.* The reabsorption of glucose also depends upon enzymatic action and is limited to 300 to 400 mg. per minute, hyperglycemia above this limit leading to glycosuria. This enzymatic

action is blocked experimentally by phlorhizin, which prevents tubular reabsorption of glucose. Approximately 60 per cent of the urea content of the glomerular filtrate undergoes tubular reabsorption by a passive reaction of "back-diffusion." On the other hand, amino acids are reclaimed from the filtrate by a process of cellular transport which involves selective adherence of the substance to the cell membrane and an additional "cellular pump," which moves these molecules into the cell without chemical alteration (Scriver).

Table 1-1. Threshold Substances Reabsorbed by Tubules from Glomerular Filtrate *

Substance	Amount in Filtrate	Amount in Urine	Per Cent Not Reabsorbed
Sodium	600 Gm.	6 Gm.	1%
Potassium	35 Gm.	2 Gm.	6%
Calcium	5 Gm.	0.2 Gm.	2.2%
Glucose	200 Gm.	——	——
Urea	60 Gm.	35 Gm.	65%
Water	180 liters	1.5 liters	0.9%
Amino Acids	10 Gm.	300 Gm.	3%

* Per 24 hours

Urinary Substances Excreted by Tubules

Ammonia
Hydrogen ions
Potassium (also filtered and reabsorbed)
Paraaminohippuric acid
Creatinine (also filtered)
Penicillin
Phosphate (also filtered and reabsorbed)

The glomerular filtrate reaching the distal segments of the nephron is reduced from about 120 ml. per minute to approximately 20 ml. per minute. The changes in the distal segments involve alternate dilution and concentration. Dilution refers to the selective reabsorption of sodium and chloride that occurs in the ascending loop of Henle and the distal convoluted tubules, whereas concentration refers to the selective reabsorption of water, which occurs distally in the distal convoluted tubules and in the collecting ducts. These changes are hormonally accentuated. The secretion of aldosterone by the adrenal cortex increases the reabsorption of sodium in these segments, and the secretion of antidiuretic hormone (ADH) from the posterior pituitary under the influence of the hypothalamus increases the reabsorption of water. In the opposite direction, parathyroid hormone inhibits tubular reabsorption of phosphates. The ascending loop of Henle is impermeable to water, but the cells are capable of