WHITE

CLINICAL DISTURBANCES OF RENAL FUNCTION

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W. B. SAUNDERS COMPANY

PHILADELPHIA 1961 LONDON

MADE IN THE U.S.A.

Press of W. B. Saunders Company

Library of Congress Catalog Card Number: 61–6812

Preface

THIS BOOK is meant for the practicing physician confronted with a patient whose kidneys are not functioning normally, either because of intrinsic renal disease or because of one of the many physiological disturbances that may impinge upon the kidneys. I have in mind the doctor facing the patient across the desk of the consulting room, or at the bedside. Three problems are paramount at such a moment: is the patient suffering from renal dysfunction, what is it, and what should be done? Perhaps no elaborate laboratory facilities are available, or perhaps, as happens not infrequently, there is no time to wait for the performance of complex investigations before some decision must be made. This book is meant to help the doctor attain insight into what the patient is suffering from, and what to do for him.

Although this is a clinical work, it is physiologically oriented as a result of the author's years in the laboratory; while the voice is that of the clinician, some of the physiologist's hand will be apparent. The questions presented by physicians in the course of consultations, talks, and seminars have helped to focus this work more sharply on the patient. In particular, I have tried to emphasize the totality of the patient, that the kidneys are but one organ system among many, albeit a very important one.

The major portion of the book consists of sixteen chapters dealing with the clinical disturbances of renal function. In order to maintain continuity of thought and presentation, more detailed discussions of selected topics of a basic physiological, biochemical, and pharmacological nature have been deferred to a series of appendices.

The original literature encompassing all the topics discussed in this book is enormous, and the number of references actually read

during the preparation of this book is retrospectively exhausting. The practicing physician simply does not have the time to explore hundreds or thousands of articles. Accordingly, each chapter has a *selected* list of bibliographic references. For the most part, these consist of monographs, reviews, and key articles. From them the reader may easily gain bibliographic access to such information as he may require or desire on any topic.

I wish to thank the American Heart Association and the National Heart Institute of the National Institutes of Health for supporting my research activities which have provided the stimulus and background for this book.

To those of my friends, professional and personal, without whom I could not have progressed this far, I extend my deep thanks and appreciation. In particular, I should like to acknowledge my debt to Dr. Louis Leiter, Chief of Medicine, Montefiore Hospital, New York, for providing my earliest opportunity and orientation in the study of the kidney. I thank Mr. John L. Dusseau, of the W. B. Saunders Company, for his wholehearted and enthusiastic encouragement during the entire preparation of this book.

Finally, but not least, I want to acknowledge "What Every Woman Knows." Among other things, I refer here to my wife's long hours of patient listening to and reading of what was to her essentially unintelligible material, as well as to her more concrete aid in the preparation of the manuscript.

"Heard melodies are sweet, but those unheard are sweeter." Can any composer know the joy of full realization of his dream melody?

ABRAHAM G. WHITE

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Chapter 1

Introduction: The Nature of Renal Dysfunction; The Kidney as the "Final Common Pathway"

I. DEFINITION OF RENAL DYSFUNCTION

Just as the lower motor neuron is the "final common pathway" for impulses originating in diverse nerve centers, so the kidney is the end organ for the various physiological and biochemical mechanisms designed to maintain the integrity of the volume and composition of the body fluids.

Some thematic definitions may be offered here. When, as a result of either extrarenal physiological disturbances or intrinsic renal disorders, the function of the kidney is altered beyond the normal range of its activities, a state of *renal dysfunction* exists. If, consequently, the volumes and composition of the body fluids are not significantly disturbed, the renal dysfunction may be considered *compensated.* On the other hand, *decompensated* renal dysfunction may be defined as that stage of malfunction of the kidney which is associated with serious distortions of the body fluids leading, sooner or later, to death unless the process remits or is corrected.

II. CLASSIFICATION OF AND ETIOLOGICAL MECHANISMS UNDERLYING RENAL DYSFUNCTION

Like that of the heart, renal dysfunction may be *acute* in onset, or it may develop insidiously and linger on in *chronic* form for months

or years. To emphasize the interrelationship of all the homeostatic physiological mechanisms underlying the regulation of the volume and composition of the body fluids, we shall consider renal dysfunction in one comprehensive category with two major subgroupings: *primary* and *secondary*.

By *primary renal dysfunction* is meant a disturbance of renal function originating in intrinsic renal disease or metabolic aberration. In contrast, *secondary renal dysfunction* denotes a state in which physiological and pathological disturbances of organ systems outside the kidney initiate the alteration of renal function.

Following is the etiological classification of renal dysfunction that will be used in this book:

A. Primary Renal Dysfunction
    1. Acute
        a. Glomerulonephritis
        b. Renal vasculitis
        c. Pyelonephritis
    2. Subacute and chronic
        a. Nephrotic syndrome
    3. Chronic
        a. Glomerulonephritis
        b. Nephrosclerosis and vasculitis
        c. Pyelonephritis
        d. Inborn errors of renal metabolism

B. Secondary Renal Dysfunction
    1. Acute
        a. Tubular necrosis
            (1) Ischemic
            (2) Other (transfusion, chemical)
    2. Chronic
        a. Congestive heart failure
        b. Hepatic cirrhosis
        c. Hormonal and metabolic
            (1) Pituitary
                (a) Anterior
                (b) Posterior
            (2) Thyroid
            (3) Parathyroid
            (4) Adrenal
            (5) Pancreas (diabetes mellitus)
            (6) Gonads
            (7) Miscellaneous (inborn errors of extrarenal metabolism and function)

Although this is a general outline and nosological details of the various subgroups are discussed in appropriate chapters, several points of interest may be mentioned now:

1. An etiological diagnosis, if one can be made, fulfills two important clinical functions by indicating: (1) the therapy to be employed, and (2) the probable course, or prognosis, of a given case.

2. Although the various etiological processes are "neatly" catalogued in the table, in practice they may, at times, be difficult or impossible to diagnose ante mortem. This is particularly true for patients suffering from chronic renal disease who do not give a clear history of antecedent acute involvement. A not infrequent instance of this (diagnostic) kind of difficulty is afforded by the completely asymptomatic patient who, on a routine pre-employment or insurance examination, shows significant albuminuria with or without abnormal urinary sediment on microscopic study.

Another diagnostic problem is exemplified by the patient whose chief complaint is one of lethargy and weakness, perhaps associated with nausea, vomiting and, possibly, some vague changes in personality. He has not been examined by a physician in years. Often, the work-up begins with an x-ray examination of the stomach and upper gastrointestinal tract which probably will show no abnormalities. If the patient is in the hospital, a "routine" blood urea nitrogen will be drawn and returned with a value ranging from 60 to 120 mg. per 100 ml. The urine may show 1 to 4 plus albuminuria and the sediment a few white blood cells, an occasional red blood cell and scattered hyaline or granular casts. The hemoglobin may be 8 grams per cent or even less. Because of the azotemia, intravenous pyelography will not be attempted, thus making the diagnosis dependent, in great part, upon clinical evaluation, unless the patient's condition and the available facilities (personnel) permit renal biopsy. Although the abdominal "flat film" may suggest decreased size of the kidneys in such a case, a finding which can be confirmed by retrograde pyelography, the physician still is confronted with the differential diagnosis of the "contracted kidney."

3. More than one etiological process may be operative simultaneously; for example, congestive heart failure may supervene upon an underlying glomerulonephritis or diabetic glomerulosclerosis. Also, acute tubular necrosis may occur postoperatively in a patient suffering from renal stones and chronic pyelonephritis who undergoes a nephrolithotomy. Such coexistence of different kinds of renal dysfunction may occasionally present therapeutic dilemmas to the extent that treatment for the improvement of one may aggravate the other; in such a case, a decision must be made as to which condition is more threatening to the survival of the patient.

4. As the various entities are discussed in detail, it will be apparent that similar physiological disturbances of renal function can

occur in either primary or secondary renal dysfunction, although the pathogenesis and treatment may differ in the respective cases.

III. CLINICOPHYSIOLOGICAL CORRELATION (PATHOPHYSIOLOGICAL DISTURBANCES)

A. General Considerations

How do the disorders previously catalogued produce physiological disturbances of the body fluids and renal function? How do these physiological disturbances affect the well-being or survival of the patient? What signs and symptoms are produced? As a general proposition, the answers to such questions comprise what we call "clinicophysiological correlation."

This section presents briefly some of the more important features of normal renal function and normal maintenance of the volume and composition of the body fluids. Emphasis is placed on those general features which have a fairly solid experimental basis.

The kidney consists of anatomical and functional units, the "nephrons." There has been a tendency in discussions of renal function to assume that all the nephrons act uniformly. However, they may differ markedly anatomically, with respect to size and configuration, for example. Thus, one of the important tasks in the investigation of renal function has been that of determining whether this anatomical variability of nephrons is associated with concomitant functional heterogeneity.

Renal disease presents a similar problem. Since disease may affect nephrons in a non-uniform manner, does net kidney function represent the sum of variable, individual nephron behavior under these circumstances? Or, as has recently been proposed, does urine from the diseased kidney come only from uniformly functioning nephrons, while sufficiently diseased nephrons do not yield any urine? These are some of the broad physiological questions presented by both the normal and diseased kidney.

B. Excretion as the Main Renal Function; Clearance Concept

Although the physiological functions of the kidney have been described, especially from the investigative point of view, in the relatively complex terms of the clearance concept and the topographical localization of tubular reabsorption and secretion, there is but one primary renal function—*excretion*. But the kidney does not excrete simply for the sake of excretion. Rather, this organ functions to maintain the constancy of the body fluids to the extent that extrarenal processes cannot do so.

Essentially, hypoexcretion and hyperexcretion are the two chief disturbances of renal function with which we are concerned clinically. Normally, water, electrolytes and non-electrolytes are carried by the blood into the glomerular and tubular vasculature of the kidney.

Figure 1 is a schematic representation of the blood flow to the nephron (glomerulus and tubule). One hundred twenty-five cubic centimeters of plasma are filtered through the glomerulus (as estimated by the "clearance" of inulin, cf. p. 12). The blood which is not filtered leaves the glomerulus via the efferent arteriole. In the diagram this blood is represented as supplying the tubule cells of the same nephron of which the glomerulus is a part. This apparently is not always true, since the blood in the efferent arteriole may supply the tubules of adjacent nephrons. Whether the blood in the efferent arteriole supplies the tubule cells of the selfsame or adjacent nephrons

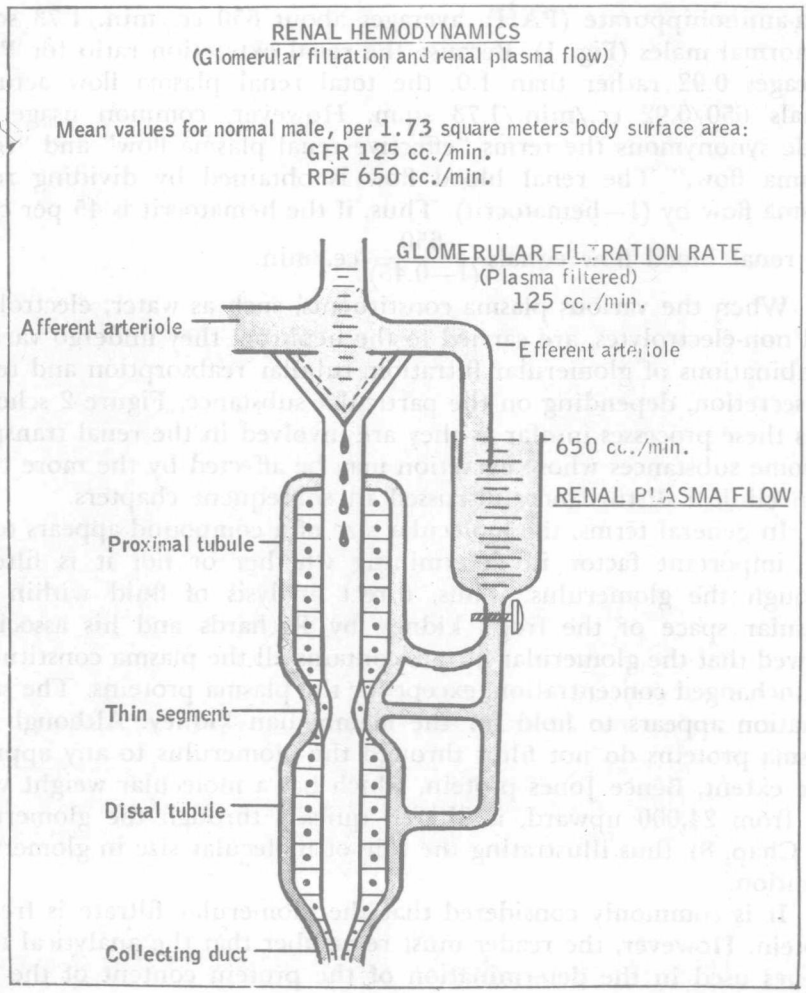

Fig. 1

appears to bear a general relationship to the location of the nephrons. Thus, in those nephrons located in the outer two-thirds of the cortex (the "cortical" nephrons) the efferent arteriole supplies blood to a significant portion of the tubule belonging to the same glomerulus. On the other hand, in those nephrons lying in the inner third of the cortex (the "juxtamedullary" nephrons) the efferent arteriole tends more than that of the "cortical" nephron to supply blood to contiguous nephrons through the arteriolae rectae. Even in the case of the "cortical" nephrons the capillaries from one efferent arteriole anastomose with those from another so that there may be a fairly widespread distribution of postglomerular blood. (For more details on renal vasculature, see Appendix 1.) These generalizations are somewhat tentative for the human kidney and are not yet based on conclusive proof.

The "effective renal plasma flow," measured by the clearance of para-aminohippurate (PAH), averages about 650 cc./min./1.73 sq.m. in normal males (Fig. 1). Because the renal extraction ratio for PAH averages 0.92 rather than 1.0, the total renal plasma flow actually equals 650/0.92 cc./min./1.73 sq.m. However, common usage has made synonymous the terms "effective renal plasma flow" and "renal plasma flow." The renal blood flow is obtained by dividing renal plasma flow by (1—hematocrit). Thus, if the hematocrit is 45 per cent, the renal blood flow equals $\frac{650}{(1-0.45)}$ cc./min.

When the various plasma constituents, such as water, electrolytes and non-electrolytes, are carried to the nephron, they undergo various combinations of glomerular filtration, tubular reabsorption and tubular secretion, depending on the particular substance. Figure 2 schematizes these processes insofar as they are involved in the renal transport of some substances whose excretion may be affected by the more common clinical disturbances discussed in subsequent chapters.

In general terms, the molecular size of a compound appears to be one important factor in determining whether or not it is filtered through the glomerulus. Thus, direct analysis of fluid within the capsular space of the frog's kidney by Richards and his associates showed that the glomerular filtrate contains all the plasma constituents in unchanged concentration, except for the plasma proteins. The same situation appears to hold for the mammalian kidney. Although the plasma proteins do not filter through the glomerulus to any appreciable extent, Bence Jones protein, which has a molecular weight varying from 24,000 upward, is filtered quickly through the glomerulus (cf. Chap. 8), thus illustrating the role of molecular size in glomerular filtration.

It is commonly considered that the glomerular filtrate is free of protein. However, the reader must remember that the analytical techniques used in the determination of the protein content of the glo-

merular filtrate were sensitive only to a minimum concentration of 30 mg. per 100 ml. From the clinical point of view this is very important to keep in mind, especially with regard to the pathophysiology of the proteinurias. If the glomerular filtrate contained 30 mg. per cent protein (a small amount, indeed, compared with the original plasma concentration), 54.0 Gm. of protein would be filtered each 24 hours (assuming a glomerular filtration rate of 125 cc./min.). Since the urine normally contains only trace amounts of protein, a considerable degree of tubular reabsorption of protein must occur if the glomerular filtrate does indeed contain up to 30 mg. per cent protein. The present-day consensus is that the proteinurias result chiefly from the abnormal glomerular leakage of protein, but a contributing role of impaired tubular reabsorption has not been conclusively excluded.

Tubular reabsorption occurs in both the proximal and distal convoluted tubules. Among the substances reabsorbed in the *proximal tubule* are: water, sodium, chloride, bicarbonate, glucose, phosphate, uric acid, amino acids and vitamins. The sodium transport, from the

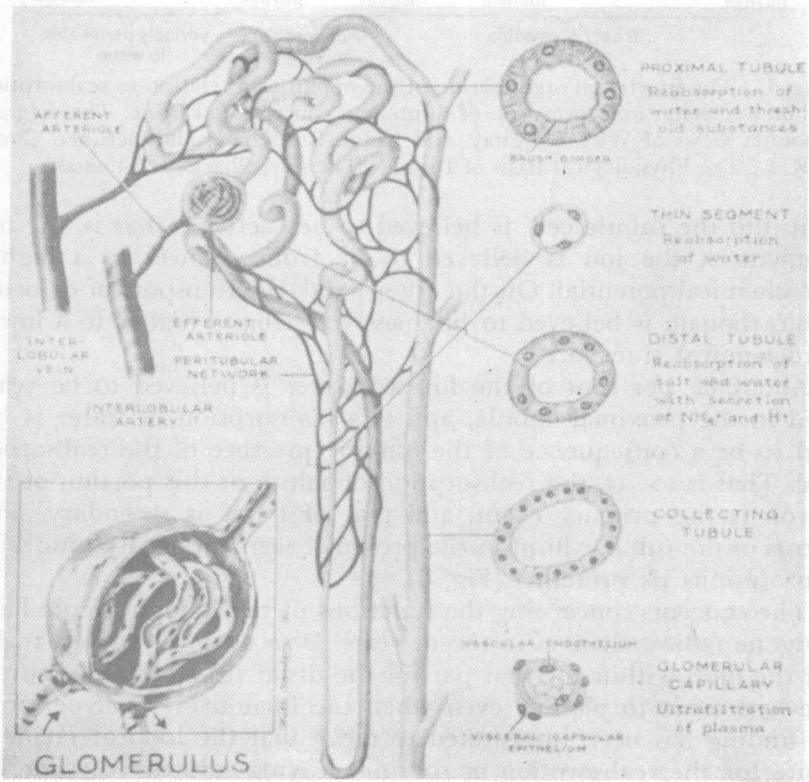

Fig. 2. As indicated in the text, recent investigations suggest that many of the secretory and reabsorptive processes formerly localized to the distal tubule apparently also take place in the collecting tubule. The thin segment probably absorbs solute to a larger extent than it does water (cf. Fig. 3). (From Grollman, Pharmacology and Therapeutics, 2nd Ed., Lea & Febiger.)

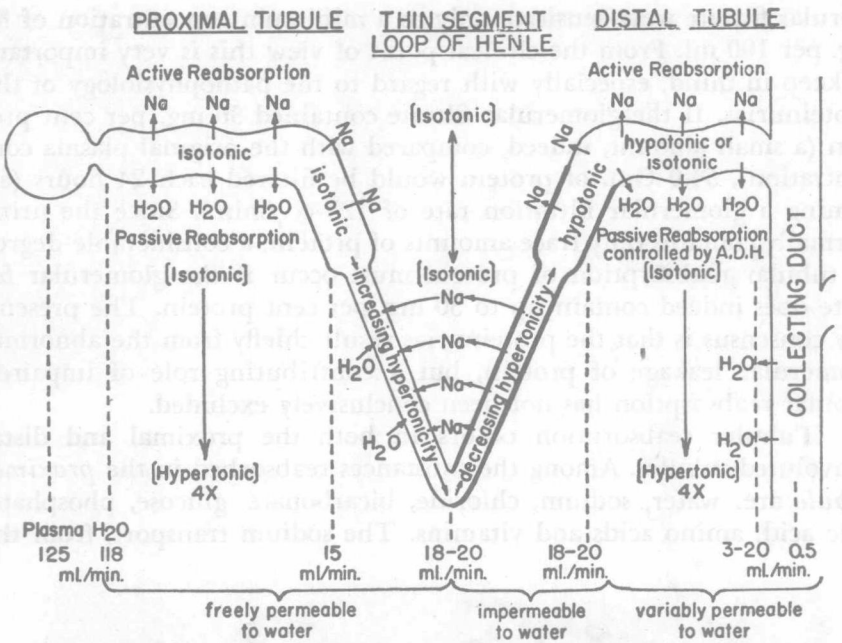

Fig. 3. The functional organization of the nephron in relation to reabsorption of sodium and water and formation of dilute and concentrated urine. The diagram incorporates views of Wirz, Hargitay, and Kuhn, Gottschalk, and Berliner. (From Pitts, R. F., The Physiological Basis of Diuretic Therapy, Charles C Thomas.)

lumen into the tubule cell, is believed to be "active"; that is, the net movement of the ion is believed to be from a lower to a higher electrochemical potential. On the other hand, the transport of chloride and bicarbonate is believed to be "passive," from a higher to a lower electrochemical transport.

About 85 per cent of the filtered water is believed to be reabsorbed in the proximal tubule, and this reabsorption of water is believed to be a consequence of the osmotic pressure of the reabsorbed solute. That is to say, the reabsorption of solute in this portion of the nephron is the primary event, and that of water is secondary. The contents of the tubular fluid in the proximal segment are isotonic with plasma (minus its proteins) (Fig. 3).

The concepts concerning the functions of the loop of Henle have undergone radical changes in recent years. Direct aspiration and analysis of the fluid within the first part of the distal tubule have shown it to be hypotonic to plasma, even when the final urine is hypertonic. This finding has been interpreted to mean that the loop of Henle is the site for the reabsorption of sodium, leaving solute-free water behind to account for the aforementioned hypotonic contents of the first portion of the distal tubule (cf. discussion of "countercurrent" hypothesis of urinary concentration in Appendix 2).

The distal tubule reabsorbs sodium as well as water. Although the