TEXTBOOK OF RENAL PATHOPHYSIOLOGY

edited by
Franklyn G. Knox M.D. Ph.D.

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Professor of Physiology and of Medicine, Mayo Medical School; Chairman, Department of Physiology and Biophysics; and Consultant, Division of Nephrology and Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

with 18 contributors

MEDICAL DEPARTMENT
HARPER & ROW, PUBLISHERS
HAGERSTOWN, MARYLAND
NEW YORK, SAN FRANCISCO, LONDON

Printed in the United States of America. For information address Medical Department, Harper & Row, Publishers, Inc., 2350 Virginia Avenue, Hagerstown, Maryland 21740.

Library of Congress Cataloging in Publication Data
Main entry under title:

Textbook of renal pathophysiology.

Includes bibliographies and index.
1. Kidneys—Diseases. 2. Kidneys. I. Knox, Franklyn G., 1937–
RC904.T45 616.6′1′07 78–17430
ISBN 0–06–141450–6

78 79 80 81 82 83 10 9 8 7 6 5 4 3 2 1

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Foreword

Despite the fact that early death from kidney and genitourinary disease has been recognized by the medical profession for several centuries, the prevalence and mortality of renal disease are still not well documented in the United States; however, estimates are that more than 60,000 persons die each year from some renal or genitourinary disorder. Disability and morbidity from nephrologic and urologic problems are even more common—urinary tract infection is probably the single most frequent cause of loss of work days in women, and urolithiasis remains one of the major causes of hospital admissions. Appreciation of the importance of early detection, appropriate diagnostic evaluation, and prompt and continued treatment in the prevention of so-called end-stage renal disease has just begun. Importantly, many major medical centers have made commitments to develop research and educational programs in nephrology, urology, and the related basic sciences in order to improve health care and medical care in renal and genitourinary diseases.

Aware that disorders of the kidney remained a "frontier in medicine," the Board of Governors of the Mayo Clinic in 1962 undertook a formal commitment to improve patient care, develop educational programs, and support clinical investigation and basic research in renal disease through the establishment of a Division of Nephrology in the Department of Internal Medicine.

Because of the Mayo tradition of "first commitment" to patient care, the initial initiatives of this Division were to establish a renal and electrolyte laboratory, a renal nutrition service, and an artificial kidney center for a conjoint dialysis–transplantation program in association with the Department of Urology and the Department of Surgery. Trainees were sent to other centers in the United States, Canada, Germany, and England to develop special expertise in hypertension, renal lithiasis, mineral metabolism, urinary tract infection, renal immunopathology, and vascular smooth muscle and renal physiology. Clinical and basic investigators were recruited to establish a nephrology research laboratory, a clinical pharmacology unit, and a mineral research laboratory. These investigators have contributed strongly to national medical meetings and to the medical literature.

From 1962 to 1977 the nephrology program at Mayo expanded from several cardiologists who provided care for some persons with renal disease to a divisional staff and faculty of 20 full-time individuals. Highly sought-after clinical and research fellowship programs have permitted training of more than 50 nephrologists and related basic scientists. An extensive program is now provided in patient care, education, and research in renal disease, as was visualized by the governing body of Mayo Foundation. The Editor of this text and the individuals who have written the several chapters are principals in the development of the patient-care, educational, and research programs in renal and genitourinary diseases at Mayo.

This volume strongly reflects the commitments and expertise of the members of the Division of Nephrology. The initial chapters are concerned with the structure and function of the kidney and its role in maintaining normal water and electrolyte homeostasis and body composition. Consideration is given to the endocrine functions of the kidney, particularly as these relate to blood pressure regulation and control. Subsequent chapters deal with the pathophysiology and management of common renal problems including stone disease, urinary tract infection, tubular and glomerular disorders, and end-stage renal disease. Although the book is written especially for the undergraduate student, it will serve as an excellent source of information for the practicing physician who needs to supplement his or her knowledge of renal pathophysiology, water and electrolyte metabolism, and acid-base disorders.

The Editor, Dr. Knox, has established a position on the cutting edge of research in renal physiology. In this publication he has assembled a highly skilled and experienced group of investigators, teachers, and practitioners who have provided an outstanding text for students of renal disease.

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Preface

This volume on renal pathophysiology is a new textbook for use in medical school curricula. Although it may find a home in any curricular setting, it is particularly directed toward integrated curricula which take a multidisciplinary approach to the kidney. An overview of the basic sciences underlying renal function and disease precedes introductions to the clinical discipline of nephrology. Material has been selected with particular emphasis toward relevance to the practice of medicine. Consequently, the pathophysiology underlying common disorders of the kidney is particularly well covered. For example, although renal stone disease is a prevalent and important part of medical practice, most texts do not deal with this subject in an adequate fashion. In the present text, two chapters are devoted to urolithiasis, one in the basic pathophysiology and a second in more applied aspects. Accordingly, the text may be particularly useful as a primary source material for the first two years of an integrated medical school curriculum and as a reference source for subsequent continued training.

We believe that the cohesive presentation of the material is a unique strength of this book, and this has been made possible by the contributions from members of the same faculty of the Mayo Medical School, the editorial craftsmanship of Dr. Werner Heidel, and the outstanding illustrative work of William Westwood. The excellent editorial assistance of Mrs. Deanna Servick is also acknowledged, as is the handsome cover designed by Jim Garrity.

Franklyn G. Knox, M.D., Ph.D.

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CHAPTER 1

Historical Basis of Renal Pathophysiology

Charles G. Roland

In general, knowledge accumulates gradually. Nevertheless, it is common practice to accord special credit to a few individuals who seem to have made exceptional contributions. In historical circles this is called the "great man" theory of history. It is, of course, a form of hero worship, and it is too simplistic to be acceptable to professional historians. Yet the approach is useful because of its very simplicity. In this chapter, several of our predecessors will serve as foci, their eras being convenient points at which to step aside from the stream of history and to attempt to outline the state of renal physiologic knowledge then current.

Within the three main sections of this chapter, then—ancient and medieval times, renaissance advances, and modern precursors—we will direct our attention at such notables as Aristotle, Galen, Malpighi, Bowman, Bright, Ludwig, and Cushny. This attention to a few persons should not be misunderstood. Many hundreds of physicians and scientists have contributed, over the years, to our knowledge of how the kidney works. Indeed, every chapter in this book is history in the sense that each presents its up-to-date summary based—explicitly or implicitly—on an accumulation of accomplishment. By common scientific convention, our intellectual underpinnings are acknowledged by references to the literature. But those references, again by convention that is unstated but clear, are cut off at a certain point in the relatively recent past. It is no longer necessary or appropriate to note that Harvey discovered the circulation of the blood unless one is writing "history." Much of the history of any discipline becomes a given. But we have felt that the givens deserve some explicit reference. Hence, this chapter.

ANCIENT AND MEDIEVAL TIMES

There is a great temptation to mock the ancients for their primitive beliefs and suppositions. But retrospective wisdom is a pernicious conceit. The ancients were neither stupid nor blind; they simply began with a data base that is vastly different from ours today. And we should take no overweening pride in our possession of our lode of information—almost all of it came from the efforts of our predecessors. We do indeed stand on the shoulders of our ancestors.

ARISTOTLE

Perhaps Aristotle can be considered briefly as a typical example of the prescientific, theoretic approach to explanation. Aristotle believed the kidneys to be a sort of frill: "The kidneys when they are present exist not of actual necessity, but as matters of greater finish and perfection" (1). Their presence, he concluded, enables the bladder to perform its function with greater perfection. The bladder, which he thus considered much more important than the kidneys, he related to the presence of blood in the lungs. Animals with lungs containing blood are thirstier than other animals (insects and fishes, for example), and drinking greater quantities of fluid results inevitably in increased amounts of liquid residue. The stomach cannot cope with the large volume of residue, so "the residual fluid must therefore of necessity have a receptacle of its own; and thus it comes to pass that all animals whose lung contains blood are provided with a bladder" (1).

HIPPOCRATES

So far as records exist, they show that rational clinical medicine began with the Hippocratic school (ca. 400 B.C.). Not surprisingly, then, it is in the Hippocratic writings that we first find instructions on how to examine the urine and what to look for. The following excerpt shows that the field was thoroughly studied:

> The urine is best when the sediment is white, smooth, and consistent during the whole time, until the disease come to a crisis, for it indicates freedom from danger, and an illness of short duration; but if deficient, and if it be sometimes passed clear, and sometimes with a white and smooth sediment, the disease will be more protracted, and not so void of danger. . . . Clouds carried about in the urine are good when white, but bad if black. . . . The most deadly of all kinds of urine are the fetid, watery, black, and thick; in adult men and women the black is of all kinds of urine the worst, but in children, the watery (15).

The *Aphorisms* of Hippocrates also include many references to the state of the urine and its relation to prognosis. The comparison with Aristotle is illuminating. Aristotle wanted theory. The Hippocratic school tried to interrelate observations of sick persons in order to be able to predict what might befall other patients with similar constellations of symptoms and signs. Irrespective of the ultimate importance of theory it is hardly surprising that the sturdy pragmatism of Hippocrates and his followers has found continuing support and empathy from physicians for almost 2400 years.

Before considering the contributions of Galen, at least passing reference should be made to Celsus (5). This physician seems to have been the earliest to recommend measuring the amount of a patient's drink and of his urine. Thus, about the time of Christ, quantification entered the field of renal physiology.

GALEN

Galen (ca. 130–ca. 200), I would suggest, represents the beginning of experimental method. Although some students of history have sneered at Galen's ignorance, more appropriately we might admire the advances this remarkable man made. He strongly encouraged, by precept and admonition, the practice of experimentation. As we shall see, he applied this concept to his understanding of the excretory system and helped to eliminate from further serious consideration the highly theoretic hypotheses of his predecessors. He knew the kidneys, ureters, and bladder of man and other mammals from personal dissection (12). Moreover, he used vivisection of animals to demonstrate function.

When he analyzed what he called true natural faculties—the physiology of the body organs—he used precisely described animal experimentation to illustrate the foolishness (as he put it) of Asclepiades, who claimed that the ureters served no function and that fluid wastes pass into the bladder by being resolved into vapors; these vapors, Asclepiades claimed, were in some undefined manner condensed when they reached the bladder and formed urine. Galen, to refute what he considered to be "nonsensical talk" (11a), ligated the ureters and subsequently showed them to be greatly distended, whereas the bladder was empty. This and other experiments showed clearly the gross relationships among kidneys, ureters, and bladder.

Given this, how was urine secreted? Galen here reached the limit of experimental possibility in his time and retreated—as happens still today, on occasion—to sheer logic:

> For, surely everyone sees that either the kidneys must attract the urine, or the veins must propel it—if, that is, it does not move of itself. But if the veins did exert a propulsive action when they contract, they would squeeze out into the kidneys not merely the urine, but along with it the whole of the blood which they contain. And if this is impossible, as we shall show, the remaining explanation is that the kidneys do exert traction (11b).

Traction, or attraction, was Galen's fundamental explanation for urinary excretion. He expressed the view that the kidney could attract waste products from blood not only through the renal vein but also via other, ill-defined routes. He adduced ingenious arguments to support his theory. But his arguments were only that. He supported himself by ridiculing Lycus, for example, who maintained that urine simply represented the residual matter from the nutrition of the kidney. Lycus was wrong, and Galen showed his error convincingly, but Galen had no firmer basis to support the theory of attraction.

Galen may not have known what "attraction" consisted of; obviously, he had no conception of tubular secretion and reabsorption. But he did emphasize what gross anatomic and physiologic studies could prove. Urine was *not* drawn into the kidneys or the bladder as a response to some internal vacuum. Nor was urine a vaporous substance somehow condensing in the bladder. Clearly, urine was formed in the kidneys, flowed through the ureters, was stored temporarily in the bladder, and was ultimately excreted.

From that empiric base, Galen was drawn to propose:

> The parts situated near the alimentary canal, by virtue of their appropriateness of quality, draw in the imbibed food for their own purposes, then the parts next to them in their turn snatch it away, then those next again take it from these, until it reaches the vena cava, whence finally the kidneys attract that part of it which is proper to them (11c).

The "appropriateness of quality" and "that part . . . which is proper to them" were abstractions that could be explicated rationally only when a whole new experimental approach was possible. Microscopy offered the first new insight, albeit a strictly anatomic one. And that approach was impossible till more than a millenium after Galen. But microscopy is a significant indicator of the beginning of the medical renaissance, and that renaissance was earliest and most fully exemplified, for nephrologic physiology, in Malpighi.

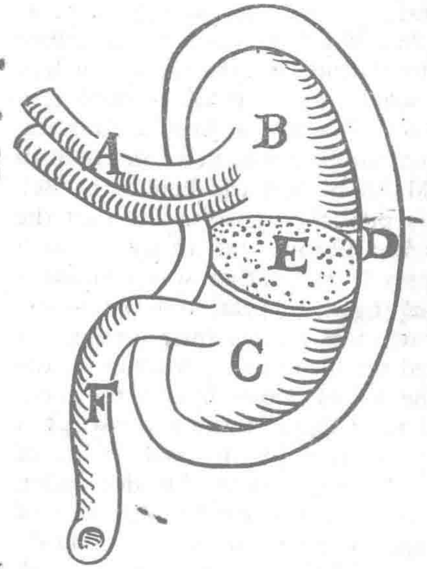
RENAISSANCE ADVANCES

Totally arbitrarily, I have designated as the "renaissance" in renal physiology that period that began with Malpighi and ended with Bowman. But before considering Malpighi's contributions, asides about Vesalius and Paracelsus seem warranted.

Vesalius (1514–1564) has been criticized by some writers—perhaps most notably and recently by the late Homer Smith—for misrepresenting the anatomy of the kidney in *De Humani Corporis Fabrica*. Smith remarked that Vesalius described the structure of the kidneys "quite fancifully, as hollow organs each divided by a sieve-like membrane into two compartments" (21a), the blood flowing into the upper compartment and clear urine flowing from the other chamber to the bladder. Vesalius, it is true, does present such a drawing (Fig. 1–1). But he accompanies it, and another showing a different view, with the comment that he thereby "attempted to represent the false teaching of physicians on the straining of the urine" (19). He also included several quite accurate drawings of the gross internal structure of the dog's kidney; he did not use the human kidney because he considered it too fatty to display the absurdity of the "sieve theory."

Paracelsus (1493–1541) deserves mention here because this great and peculiar man made a first, hesitating, confused effort to perform chemical analysis of the urine. His efforts are noteworthy only as pointing a direction; actual results were few. And his followers, unfortunately, further obscured Paracelsus' contribution by carrying it to a

Fig. 1–1. Illustration from Vesalius. (*De Humani Corporis Fabrica*, liber V, "De Renibus," Basel, 1543)



ludicrous extreme. They proposed that urine could be heated in a special container (Fig. 1–2) and that the ensuing clouds or sediments distributed themselves in the cylinder so as to correspond to the diseased part of the body. Thus a sediment concentrated in area 19 presumably should be construed to reveal the presence of a disorder of the knees. We might categorize this system as "urinary phrenology." But one important point was made; it had become acceptable for practitioners of physic to attempt chemical studies upon the urine.

More serious chemists, such as van Helmont, ridiculed "chemical dissection." But more important, they began serious efforts to quantitate urinary examination, efforts that are epitomized in van Helmont's introduction of what we now know as the test for specific gravity.

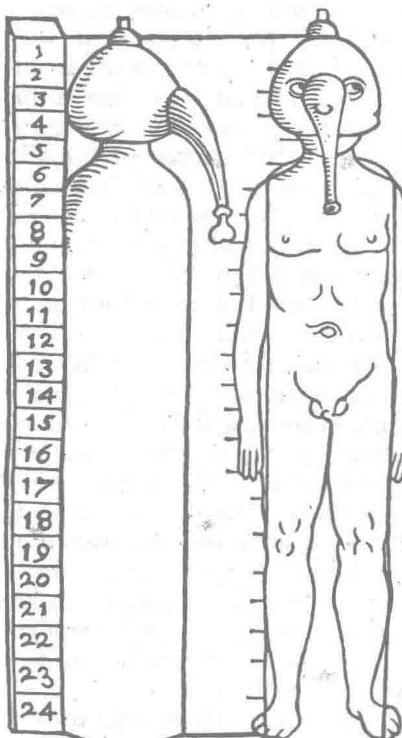


Fig. 1–2. In "chemical uroscopy," developed by followers of Paracelsus, the level of sediment laid down in this container after urine was distilled in it purportedly showed the position of an anatomic disorder. (*Aurora Thesaurusque Philosophorum Paracelsi,* 1577)

MARCELLO MALPIGHI

Van Leeuwenhoeck and Galileo are the names perhaps most prominently associated with the introduction of lens combinations that ultimately permitted microscopy. But Malpighi (1628–1694) played the most significant early role in advancing our knowledge of the fine anatomy of the kidney.

Malpighi was a Bolognese who lived, learned, and taught in Bologna for 59 of his 66 years. He received his medical degree in 1653, and 4 years later he began his career of research and teaching (14).

Many of his works are of continuing significance and interest—perhaps most especially *De Pulmonibus,* in which he described capillary circulation in the lungs. Chief among his works for a renal physiologist, however, is *De Viscerum Structura Exercitatio Anatomica,* published at Bonn in 1666. In this work, Malpighi had the benefit of Bellini's recently published observation that the kidney was not fibrous (as many contemporaries believed) but rather was composed of radially arranged, minute, hollow tubules. Malpighi announces in his introduction: "I never reached my idea of the structure of the kidney by the aid of books, but by the long, patient, and varied use of the microscope. I have gotten the rest by the deductions of reason . . ." (14). Certainly his dedication to the necessity of experimenting—and of repeating experiments to be sure the observations are valid—was vigorously pursued. Two years before his death he wrote to Baglivi: ". . . et osservandosi cosa di curioso, sarà necessario repplicarla più volte per accertarsi del vero" (20). (If something interesting is found, it is necessary to repeat the experiment several times to be sure of the truth.)

Malpighi's great contribution, of course, was recognizing and describing what have come to be known as malpighian corpuscles—the glomeruli of the kidney.

> . . . in all kidneys which up to this time I have been able to get, I have detected a number of very small glands. These I have observed in quadrupeds, turtles, and always in man himself. In order to see these glands, black fluid mixed with spirit of wine should be injected through the renal artery until the whole kidney swells, and the exterior grows black. If now the capsule of the kidney be removed, the glands immediately meet the naked eye. . . . And when the kidney is sectioned in the same manner as before, longitudinally, between the bundles of the

urinary vessels and the narrow spaces formed by them, one will see these same innumerable glands attached like apples to the blood vessels . . . (14).

He supposed that the "innumerable" glands corresponded in number to the tubules or urinary vessels. The glands clearly were connected with the arterial system, and also with the veins, although Malpighi was never able to identify the glands as capillary tufts.

Malpighi could not detect the exact relationship between the glands and the ureters, but he inferred that relationship. He did describe the renal papillae, suggesting that human kidneys usually contained 12, and he believed that the urine entered the pelvis through these papillae.

The function of the kidney could not, of course, be observed in the 17th century. Malpighi attempted what he categorized as a "satisfactorily probable" answer to the question of how the urine is derived from the blood. One's satisfaction cannot help but be strained a little, however. He hypothesized that substances that are to be excreted are of such a size and shape as to be able to traverse the "little pores and small spaces" of the excretory apparatus. So they are excreted. Those things that the body is to retain are of some different size or shape and cannot pass through and are retained in the bloodstream.

As Smith points out (21b), this is essentially a restatement of the then contemporary theory of filtration through selective pores. Bellini and others had supported the same theory. Its weaknesses are obvious. But many decades would pass before the theory could be sculpted into a closer approximation of what we now believe to be true.

Gout

An aside may be appropriate here. The dramatic peripheral manifestations of gout long distracted physicians from the important relation between gout and the kidney. In this chapter, only a few highlights of this recognition can be made

Perhaps the beginning of our real understanding of the renal handling of uric acid and the urates dates from 1797. In that year, William Hyde Wollaston published in the *Philosophical Transactions* an account of his analysis "of gouty concretions, and of four new urinary calculi" (23). Wollaston credited Scheele with having analyzed one species of bladder stone and finding it composed largely of "a peculiar concrete acid" called lithic acid.

The term **lithic acid** has vanished (although its etymologic relation to **lithiasis** and similar words is obvious), and we now call this substance uric acid. Wollaston subjected chalk deposits from gouty patients, and a variety of bladder stones, to treatment with various acids, alkalies, and heat. After various procedures, he found that the bulk of the deposit remained and possessed all the characteristics of lithic acid. Moreover, Wollaston was by no means easily satisfied in this matter. He took lithic acid, triturated it with some mineral alkali, added warm water, and found that the product had every chemical appearance of "gouty matter."

When he studied bladder stones, Wollaston found lithic acid in some of these, although the proportion varied. Interestingly, he also described "triple crystals" in the form of "a short trilateral prism, having one angle a right angle, and the other two equal, terminated by a pyramid of three or six sides." Are these the urate crystals identified in synovial fluid in 1961 (16)?

Crystals also interested the next student of this subject whom I shall discuss here, A. B. Garrod. Just 50 years after Wollaston, Garrod wrote a paper enunciating several basic relationships that have proved important in advancing our knowledge both of gout and of renal physiology (13).

Garrod studied the concentration of uric acid in the blood and the urine of patients with gout and with other disorders. He observed that patients who had gout and tophaceous deposits always had uric acid in the blood and always had a deficiency of uric acid in the urine. Further, Garrod suggested that the chalklike deposits found in gouty patients represent a means by which the body eliminates uric acid when it cannot do so via the urine. In other disorders of the kidney, uric acid might be excreted in normal quantities or it might not, but the likelihood related more to the severity of the disease than to its type. That is, if the kidney was sufficiently damaged by a disease other than gout, uric acid excretion *could* be interfered with, just as could the excretion (and reabsorption) of any other urinary constituent.

Garrod discusses "four-sided prisms of urate of soda." These crystals Garrod found in abundance in concretions taken from various parts of the body in patients with gout. He appends drawings of these crystals (Wollaston did not), and although it is difficult to reconcile the verbal descriptions of these crystals by the two men, there would seem a strong case to assume that they were, indeed, seeing the same thing.

From this point, the story of studies of uric acid handling by the kidney becomes part of the general story of renal physiology, to the advantage of our knowledge of both areas. And this relationship should carry us on to the time of Bowman. However, one other name must appear here, to maintain chronologic integrity.

RICHARD BRIGHT

No matter the orientation of his study, the historian must introduce the name of Bright when discussing the accretion of our knowledge about the kidney and its function. In this book, devoted to renal pathophysiology, Bright's feat of uniting the observation of coagulable urine in dropsical patients with the observation of granular kidneys found in patients at autopsy is exemplary. It epitomizes the great 19th-century medical contribution, heralded by Morgagni's *De Sedibus et Causis Morborum*, of using dead-house studies to clarify and categorize clinical disease.

Richard Bright (1789–1858) was born in Bristol. His father, a wealthy banker, gave him an excellent education and the opportunity to travel—an opportunity he used to advantage, not only publishing an account of one journey but illustrating it with highly competent sketches from his own pen.

This same artistic ability served him well in his medical career, too. After graduating from Edinburgh in 1813 he traveled and studied, but ultimately settled in London. There, in 1820, he became an assistant physician at Guy's Hospital. Thus was created the third part of that great triumvirate of Guy's—Addison, Hodgkin, and Bright.

Bright made many significant observations and served his institution with distinction. But without question, his observations on kidney disease were his definitive work. As Nixon has pointed out, in one epoch-making monograph:

> . . . he described the uraemic symptoms, cerebral haemorrhage, loss of sight, the hard pulse, oedema, pleural, pericardial, and peritoneal effusions, bronchitis, cardiac hypertrophy, and the enteritis which may attend the disease (17).

The elaboration of all this innovative work was a book entitled *Report of Medical Cases, Selected with a View of Illustrating the Symptoms and Cure of Diseases by a Reference to Morbid Anatomy*, published in London in 1827.

Physicians before Bright had observed albuminuria—the earliest on record seems to be Frederick Dekkers, who wrote in 1694. Dekkers observed that the urine from "consumptives and emaciated people" is clear when unboiled but becomes milky when heated. Adding acetic acid at this stage caused the precipitation of a "white rennet" (9). But Dekkers and other early workers did not make the association with specific disease.

In Bright's book he refers to several known causes of albuminuria, such as compression of major veins. He goes on, however, to make the fundamental statement that "I have never yet examined the body of a patient dying with dropsy attended with coagulable urine, in whom some obvious derangement was not discovered in the kidneys" (4a).

Bright had begun studying this relationship 12 years earlier, but most of his detailed investigations took place between 1825 and 1827. In his *Reports*, he gave complete case histories and autopsy studies of numerous patients. In the very first instance, he describes the kidneys as being "completely granulated throughout . . . externally the surface rough and uneven; internally all traces of the natural organization nearly gone" (4b).

Thus we find Bright correlating kidney disease with abnormally constituted urine. But before these important observations could be pursued much further, a great deal more needed to be known about the fine structure of the kidney. And it is, therefore, appropriate here to resume the main thread of the text by considering William Bowman.

WILLIAM BOWMAN

Although Frederik Ruysch reported, in 1729, that Malpighi's glands were twisted, entwined arterioles, the relationship between the arterioles and the tubules of Bellini remained in doubt more than a century longer. Then a classic paper appeared. It was Bowman's "On the Structure and Use of the Malpighian Bodies of the Kidney, with Observations on the Circulation Through That Gland" (2).

William Bowman (1816–1892) engaged almost exclusively in anatomic and physio-