Clinical Nephrology

SECOND EDITION

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Preface

One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient.

FRANCIS WELD PEABODY

This second edition of *Clinical Nephrology* has the same purposes as its predecessor. It was written with the nonnephrologist in mind. I hope the book will also help serve some of the needs of the subspecialty trainee. As the title implies, the emphasis is clinical. An effort has been made to indicate controversy when it exists, but my own perspective is given and labeled for what it is; in this way, its inherent limitations should be apparent. A relatively short list of suggested readings concludes almost every chapter. More detailed expositions of each subject, as well as reference materials, are available in several books, including *The Kidney,* edited by Brenner and Rector (W. B. Saunders, Philadelphia, 1976), and *Strauss and Welt's Diseases of the Kidney* (third edition), edited by Earley and Gottschalk (Little, Brown, Boston, 1979). The last section of this book is a handbook describing in detail methods for accomplishing many of the tests, procedures, and treatments mentioned throughout the text.

The major effort in preparing this second edition has been to bring up to date the body of knowledge. This required addition and deletion, as well as extensive modification. A new section, on the more common disorders of fluid and electrolyte metabolism, is included. The developments in nephrology demonstrate both the excitement and the frustration that are an inherent part of medicine. In many areas, especially in the glomerulopathies, there has been a gratifying burst of new information. At the

same time, it is difficult not to be disappointed by so many remaining unknowns and frustrated by the continuing limitations in effective direct treatment of the underlying kidney disease.

One of the pitfalls for author and reader in a subspecialty book is that the necessary emphasis may place an organ system in sharper focus than the patient. It is, of course, the individual person who must be treated, with a thorough consideration of the spiritual, emotional, physical, and social phenomena which are man. Although the same principle applies throughout the entire practice of medicine, nowhere is it more evident than in the care of patients with chronic renal failure.

This book is personal in many ways and carries with it a permanent sense of deep appreciation to many people: To my wife, children, and grandchild, to whom this book is dedicated, for being who they are and for the gift of love. To my parents and my brother, who have helped for more than half a century. To those teachers along the way who had the skill and who cared. To Dr. Maurice B. Strauss for his friendship, counsel, skill, wisdom, and knowledge, as well as for the educational opportunities he provided. To Dr. Jack D. Rosenbaum, who was the humane scholar and whose memory (and, I hope, influence) is always with me. To Dr. William B. Castle, who teaches by extraordinary example and whose insights and guidance have been generously shared through the years. To Dr. William J. Harrington, who gave when I had great need. To Dr. James F. Hammarsten, humanitarian and good friend. To Dr. R. Timothy Coussons, friend, colleague, loyal Vice-Chairman, and elegant clinician. And to all my students, house staff, and fellows, who allowed me the great privileges of teaching and learning together.

As in the last edition, I imposed on the friendship of experts to review and criticize each chapter. Their skill, interest, and willingness to help are greatly appreciated: Drs. William B. Blythe, Neal S. Bricker, R. Timothy Coussons, Murray Epstein, Donald T. Erwin, Richard J. Glassock, Christian E. Kaufman, Manuel Martinez-Maldonado, Jack Metcoff, Guido Perez, Robert W. Schrier, Carlos A. Vaamonde, and Robert Whang.

Dr. Victoriano Pardo, respected Professor of Pathology at the University of Miami School of Medicine, gave unstintingly of his expertise and efforts in the selection, description, and presentation of the material related to structure. The radiographs and radiologic guidance were thoughtfully provided by Dr. Bob G. Eaton, Professor and Vice-Chairman, Department of

Radiological Sciences, University of Oklahoma College of Medicine, and Dr. Manuel Viamonte, Jr., Professor of Radiology, University of Miami School of Medicine. The artwork was done primarily by Mr. Marcelino Obaya, whose patience and special skills are appreciated.

My deepest gratitude to Ms. Beverly Clarke, whose extraordinary editorial skills and love for this book were expressed in time, thought, true commitment, constructive criticism, and determination.

The combined efforts of these many people and others allowed me to enjoy writing the second edition of *Clinical Nephrology*.

S. P.

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I. GENERAL CONSIDERATIONS

1. Evaluation of the Patient

[The physician] will use scientific methods, he will for a time dismember his patient—isolate, for instance, his kidneys or his heart and observe their actions under very specialized conditions—but in the end he has to put these parts together in his "diagnosis." This "diagnosis" is his total conception of the relationships between the patient as a person, the disease as a part of the patient, and the patient as a part of the world in which he lives.

THOMAS ADDIS

Patients with renal abnormalities present in a number of ways: they may have symptoms directly referable to the urinary tract, or urinalysis or a test for blood urea nitrogen concentration performed for other reasons may show abnormal findings. Other patients have nonrenal manifestations of some generalized illness which may involve the kidney (e.g., diabetes mellitus, tuberculosis, and systemic lupus erythematosus). Without prior knowledge of renal disease, patients may have symptoms and signs of renal failure (e.g., hypertension, anemia, Kussmaul breathing, and "uremic" symptoms). Edema may be the reason patients with the nephrotic syndrome originally seek medical advice.

Whatever the means of presentation, the physician is concerned with the following questions: (1) Does the patient have renal disease? (2) What is the nature of the renal lesion; is it reversible or treatable, or both? (3) What is the status of renal function? (4) What is the outlook for the patient?

Let us consider a general approach to finding the answers to

these questions. This section deals mostly with highlights, more specific details being given in subsequent chapters.

Diagnostic Approach

In the diagnosis of renal disease, often the first step is the identification of the "type" of abnormal process, i.e., a "syndrome" rather than the specific disease causing the syndrome. Table 1 enumerates the more common syndromes in clinical nephrology. A variety of specific illnesses can result in either acute or chronic renal failure. And one of the practical problems is that sometimes in the initial presentation it is impossible to distinguish between acute and chronic renal lesions. The grouping of glomerular and vascular syndromes together indicates their similarities in clinical manifestations. In general they are characterized especially by proteinuria and gross or microscopic hematuria. The tubular and interstitial functions are normally so intertwined that often one cannot distinguish precisely their abnormal manifestations. The tubulointerstitial syndromes are associated with less marked proteinuria and more with pyuria and in some instances with evidence of defects in specific tubular functions.

Once a syndrome is identified, it is important to (1) evaluate renal function and (2) search for the specific cause of the syndrome. Sometimes, of course, the specific cause is evident from the outset. The next assessments include the estimation of prognosis, where it is possible, and the elaboration of a therapeutic program.

TABLE 1

Common Syndromes in Clinical Nephrology

Renal failure syndromes
Chronic renal failure
Acute renal failure
Glomerular-vascular syndromes
Acute nephritic syndrome
Nephrotic syndrome
Asymptomatic proteinuria (or hematuria)
Chronic glomerular (progressive) syndrome
Hypertension
Tubulointerstitial syndromes
"Interstitial nephritis" (including infection)
Obstructive nephropathy
Tubular defects (congenital and acquired)
Renal stones

As in virtually all aspects of clinical medicine, the search—that is, the problem-solving technique—begins with the history and physical examination.

Medical History

Obviously, symptoms directly referable to the urinary tract may provide clues to the nature and duration of illness. The implications of difficulty with urination, abnormal-appearing urine, frequency of urination, nocturia, or pain in the costovertebral angle, flank, or groin are well known. A detailed family history may be helpful, e.g., of hypertension, diabetes, gout, lupus, polycystic disease, hereditary nephritis (and/or the nerve deafness and visual symptoms that may occur in relatives of a patient with hereditary nephritis). A history of nephrotoxic agents, including antibiotics and analgesics, should be sought. Sometimes the patient has mild symptoms of systemic illness that afflict the kidney, e.g., gout and lupus. Concern with past pregnancies and possible urinary tract difficulties or instrumentation may provide clues.

In addition to these and other aspects, very commonly valuable data are submerged in past examinations done for purposes of insurance and employment or in the course of other illnesses. Often past blood pressure and the results of previous urinalyses, blood counts, and tests for blood urea nitrogen (BUN) can be determined. This aspect deserves considerable attention and potentially provides extraordinarily valuable information.

Physical Examination

Aside from the manifestations of uremia (see p. 119), which provide a clue to the presence of renal disease as well as to the level of renal function, other types of information may be gained. For example, nerve deafness and cataracts might suggest hereditary nephritis. The presence of heart murmur, fever, and splenomegaly indicates that the proteinuria and hematuria are probably due to infective endocarditis. There may be evidence of generalized disease (e.g., sarcoid, scleroderma, or lupus) that is causing the renal disease. Tenderness in the costovertebral angle may be a helpful sign. I prefer to test for this with the patient supine, resting on the examiner's hands, while the examiner presses with one finger precisely in the angle. Generally, tenderness of renal origin is sharply localized to the angle whereas in musculoskeletal conditions the tenderness is present

over a wider area. Bruits under the rib margin anteriorly suggest renal vascular disease. One may feel a hydronephrotic kidney or polycystic kidneys. If the patient is a male, it is well to watch him void in order to assess possible difficulty in emptying the bladder. Prompt voiding of a strong stream of urine readily discontinued is normal. On the other hand, difficulty in initiating urination under direct scrutiny may be due to disease of the lower tract or to the patient's inability to urinate while being observed.

There are several ways of determining the presence of residual urine, including catheterization after voiding as well as methods that do not require instrumentation. These are discussed in Part V, the Handbook (p. 559).

After the history and physical examination, and a search for past relevant information, certain laboratory procedures are valuable.

Laboratory Examination

This chapter considers only some principles along with certain selected aspects of laboratory examination. The Handbook contains more detailed descriptions of the various procedures, including urinalysis, the collection of a 24-hour urine, quantitative measurement of urinary protein, determination of renal function, urinary bacteriology, and others. *The reader is encouraged to peruse the Handbook for specific technical aspects of the tests referred to in this and subsequent chapters.*

Urinalysis is a simple, inexpensive test which generally reveals renal disease, if present, and in many instances directs the physician toward a specific diagnosis. However, the urine must be properly collected, the equipment must be accurate, and, most critically, the person performing the test must be skilled. It is still commonplace to find the following urinalysis on a patient's record:

Urinalysis:	Color	Amber
	Sp. Gr.	qns
	pH	6
	Sugar	0
	Protein	Trace
	Sediment	Occ. RBC, O-2WBC; occ. hyaline cast

I refer to it as the *all-purpose* urinalysis because of its infinite scope (it may be associated with a normal urinary tract or one

afflicted with a large spectrum of disease) and its possible aesthetic value in the patient's record. For the care of a patient, it is generally useless, while sometimes giving false comfort and denying the patient the potentially great value of a simple and extraordinarily helpful test.

The urine to be examined should be obtained following overnight dehydration (except in patients with known or suspected renal failure, in whom dehydration may be hazardous) in order to have some estimate of concentrating ability and to have a more meaningful setting for examining the sediment and testing for proteinuria.

While the urinalysis cannot provide a complete assessment of renal function, the *specific gravity* may serve as a guide before the results of more definitive tests are available. However, the specific gravity must be interpreted in the light of several factors: (1) Specific gravity is a measure of mass and density rather than total solute concentration (osmolality), and the physician is really interested in the latter. The reason specific gravity has *any* relation to osmolality is that the types of material in urine are normally limited to urea and salts. A dilute urine is defined as having a total solute concentration lower than that of plasma (280 to 300 mOsm per kilogram H_2O), and a urine is regarded as concentrated when its osmolality exceeds that of plasma. The range of urinary osmolality is between 40 and 1200 mOsm per kilogram H_2O. In terms of specific gravity, a urine of 1.008 or less is generally dilute, and one of more than 1.020 is concentrated. Between 1.008 and 1.020, however, far less reliable information is available. (2) Specific gravity is greatly influenced by glycosuria, dextran, and contrast materials used in pyelography; it is relatively less influenced by protein in the urine. (3) Concentrating ability cannot be tested meaningfully in the presence of either water or solute diuresis (e.g., after diuretic drugs). (4) The hydrometer must be an accurate, calibrated instrument, reading 1.000 with distilled water. The failure to calibrate with each use of this instrument is a common omission.

I am encouraged by the trend toward the use of more accurate and more directly interpretable tests of solute concentration. The osmometer, which measures solute concentration as a function of freezing-point depression, is excellent but is a good deal more expensive than a urinometer. I use a refractometer for routine purposes; it is simple, requires very small amounts of

urine, needs no correction for temperature, costs considerably less than an osmometer, and gives more meaningful data than an ordinary urinometer. Although calibrated to read specific gravity, the instrument measures a property of solutions that is more closely related to, although not identical with, total solute concentration.

The following is an example of the use of specific gravity as an index of renal function: If a dehydrated patient with strong stimulus to concentrate the urine has a specific gravity of 1.009, one can suspect renal functional impairment.

THE URINARY SEDIMENT

Addis, using a quantitative method, found that the normal adult during quiet activity might have as many as one million red blood cells (500,000 under age 12) per day (average 150,000 to 300,000), up to two million white blood cells per day (average 600,000 to 1,000,000), and 5000 to 10,000 casts per day (mostly narrow hyaline). It is evident from the figures that these elements will be found in normal urine, and the question resolves itself, at least in the case of the cells, into a determination of how many can be accepted as within the normal range. While a morning-voided, concentrated urine cannot provide quantitation, it is nevertheless of sufficient value so that more quantitative approaches are not generally needed. On occasion the semiquantitative data derived from the Addis count or its modifications are helpful—e.g., in evaluating an asymptomatic patient with borderline numbers of red blood cells in routine urinalysis and patients recovering from acute glomerulonephritis. There are data indicating that up to one, or possibly two, red blood cells per high-power field in a centrifuged sediment may be within the normal range. In the case of white blood cells, up to four per high-power field may be regarded as within normal limits. Arbitrary limits are pointless, and the great error in sampling should not be ignored. In a concentrated urine the absence of white blood cells and red blood cells is reassuring; their presence above a very few per high-power field suggests an abnormality requiring further evaluation. If a "random" urine is examined and it is *not* concentrated, a "normal" sediment gives no comfort and excludes nothing. Under the same circumstances, an abnormal urinalysis obviously has relevance.

Casts are molds of tubular lumina formed by the precipitation

of protein. Hyaline casts are apparently pure protein—largely the Tamm-Horsfall mucoprotein that is probably secreted by the cells of the ascending limb of the loop of Henle, distal tubule, and collecting duct. They are without known clinical significance. Cellular casts identify the kidney parenchyma as the site of disease; the red blood cell cast is virtually diagnostic of active glomerulonephritis; the white cell cast usually means interstitial nephritis including pyelonephritis. Granular casts are predominantly Tamm-Horsfall protein. Particles of protein precipitate after exercise or during fever and may account for the granular appearance. However, because granular casts may also be degenerated *cell* casts, they should generally be regarded with suspicion and interpreted in the light of the clinical situation and other findings in the urinalysis. Waxy casts probably represent a further stage of degeneration of cellular casts. Fatty casts are granular casts containing lipoid material. They tend to be found in the nephrotic syndrome. Renal failure casts are very broad casts originating in large parts of the collecting system during urinary stagnation.

The term *telescoped urine* is used to refer to the evidence in the sediment of the presence of all stages of glomerular disease. For example, the sediment might contain red cell casts, indicating active glomerulonephritis; tubular epithelial cells filled with fat (oval fat bodies), suggesting the nephrotic phase; granular and waxy casts, indicating degeneration of cell casts; and renal failure casts.

In some patients it may be helpful to examine the voided urine in "segments" in an effort to determine the source of abnormalities and particularly to determine the site of bleeding that results in microscopic hematuria. A two-glass test is useful here.

URINARY pH

There are many determinants of urinary pH including diet, pH of extracellular fluid, the concentration of potassium within the distal tubular cell, the ability of the distal tubule to form ammonia, urinary flow rate, and urinary tract infection with urea-splitting organisms. An alkaline pH suggests: urinary tract infection with urea-splitting organisms, usually *Proteus* and sometimes *Pseudomonas;* metabolic or respiratory alkalosis; renal tubular acidosis; or hyperaldosteronism. One can have a slightly acid urine with renal tubular acidosis or hyperaldo-