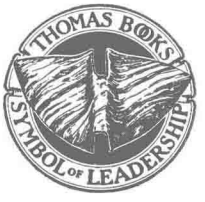
URINE
and the
URINARY SEDIMENT

A PRACTICAL MANUAL AND ATLAS

By

RICHARD W. LIPPMAN, B.S., M.D.

Fellow of the John Simon Guggenheim Memorial Foundation



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FOREWORD

IT IS THE purpose of this monograph to serve as a practical guide in the clinician's examination of urine and the urinary sediment and as a record of methods and interpretations that have evolved during a long period of careful observation. No attempt has been made to produce an exhaustive compilation of methods or of photographs that include all conceivable conditions.

It would be presumptuous for the author to present this book solely as the result of his own experience. The principal original contribution is a collection of photographs, in color, which preserve subtle differences in shade and refraction that make the reproductions recognizably similar to actual observations through the microscope. These photographs of material in an ordinary hemocytometer chamber were taken with simple equipment and with the high dry (4 mm.) or low dry (10 mm.) objective, giving a magnification at the eyepiece of 440x or 100x respectively. The reader must remember with some charity that photomicrography of the urinary sediment suffers from an inherent limitation: size of the objects relative to depth of focus. In actual observation, the observer's hand constantly adjusts the fine focus and his eye constantly integrates the images. The camera captures only one focal plane, selected by the observer's best judgment.

It was the author's good fortune to be associated with Dr. Thomas Addis, first as a Medical School Postgraduate Fellow at the Clinic for Renal Disease of the Stanford University School of Medicine, and later as a friend. Many of the interpretive comments concur with Dr. Addis's opinions and observations. It was impossible, however, to resolve some differences of opinion, since the writing was performed after Dr. Addis's untimely death. Dr. Addis believed deeply in the need for unifying theory and practice. He was constantly seeking for ways that would make the information derived from precise observation accessible to the clinician and applicable to the patient. It is this goal that the book seeks to serve.

R.W.L.

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R.W.L.

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CHAPTER I

PROTEINURIA AND ELEMENTS OF THE URINARY SEDIMENT

INTRODUCTION

IN SPITE OF his careful observation and keen interpretation, which led to the first clinical correlation of proteinuria and anasarca with demonstrable renal disease, Richard Bright did not describe or mention the elements of the urinary sediment. This is a circumstance of peculiar interest since Bright was fully aware of the existence of a urinary deposit and worked a century and a half after the microscope was invented, when microscopic observations of various tissues and fluids were being pursued with great enthusiasm. In 1827 Bright (39) stated:

> "During some part of the progress of these cases of anasarca, I have in almost all instances found a great tendency to throw off the red particles of the blood by the kidneys, betrayed by various degrees of haematuria from the simple dingy colour of the urine, which is easily recognized; or the slight brown deposit; to the completely bloody urine, when the whole appears to be little but blood, and when not unfrequently a thick ropy deposit is found at the bottom of the vessel."

The importance of urinary sediment in the diagnosis of renal disease was recognized, however, even during Bright's lifetime, for in 1846 Golding Bird could say (32):

> "Albumen is occasionally found in the urine in a coagulated state, and presenting a tubular vermicular appearance. . . . It is of common occurrence in Bright's disease, even in the earlier stages, and the deposit appears to be made up of fibrinous (albuminous) casts of the uriniferous tubules of the kidney. . . . Urine containing these bodies, lets them fall by repose in the form of a dirty-white sediment, easily diffused by agitation, and not unlike mucus. A solution of potass dissolves and gelatinizes the deposit. . . . This deposit may be regarded as pathognomonic of Bright's disease."

The initial discovery of urinary casts as microscopic structures is difficult

to credit. Several observations were made almost simultaneously, first in France by Vigla in 1837 (213), then Rayer (158), and shortly afterwards in Germany by Nasse (129), and Simon (192).

The consideration of proteinuria in renal disease is inseparable from consideration of the urinary sediment. Although Bright was not the first to observe proteinuria, he was the first to correlate its occurrence with renal disease that could be demonstrated at autopsy. Few basic advances in comprehending clinical proteinuria were made until Addis introduced simple, quantitative methods for the clinical laboratory examination of patients with renal disease and, by quantitative measurements, followed the changes in proteinuria that occurred during the progress of renal diseases.

Recent emphasis placed by Papanicolaou upon the examination of desquamations from the surface of internal organs should also direct attention to a frequently forgotten fact: the urinary sediment is partially derived from just such desquamations. Careful study of its composition and histologic elements, with their derivatives, offers a direct avenue for approaching the condition of the kidney.

As urine descends from the glomerular membrane, during its passage down the nephron, through collecting tubules and thence along the macroscopic ducts, its composition is altered and the conditions of its environment change. While functions of the passage walls, especially of the renal tubule cells, alter its composition, the urine in turn affects the epithelial membrane containing it. By understanding these reciprocal effects, a representation of conditions in upper reaches of the excretory system may be obtained from voided urine.

One may compare the urinary stream to a mountain stream. Arising from a conglomeration of rivulets, water is constantly seeping into its bed, yet simultaneously dissolves a portion of the bed itself which is carried down stream. Even discrete particles are swept along, and these may be deposited in lower, more gentle reaches of the river, or they may abrasively erode canyons as they rush on their way. From the study of channels and their structure, from studying the composition of water as it flows downward toward the sea, many inferences may be made concerning the mountains in which the stream originated. The urine and its sediment likewise reflect their origin, although the changes produced in their miniscule descent possess added complexity since the bed of the urinary stream is composed of living cells.

PROTEINURIA

In 1931 Bieter (30) demonstrated that proteinuria was dependent upon the presence of glomeruli and, consequently, that protein entered the urine by passage through the glomerular membrane. He found that the toad fish, *Opsanus tau,* a fish without glomeruli, did not produce urine containing

protein even after severe renal damage. On the contrary, other fishes with glomeruli could easily be made to excrete urinary protein by damaging the kidney. Webster and her associates (221) perfused the frog kidney with hemoglobin-Ringer solution. In the frog, the circulation is arranged so that the glomeruli are supplied almost exclusively from the aorta through the renal arteries, while the tubules receive their blood supply exclusively from the renal portal vein. Hemoglobinuria could be produced only by perfusion of the glomeruli. While Bieter and Webster showed that glomeruli were essential to the production of proteinuria, it remained to be ascertained whether the normal glomerular membrane allows the passage of some protein, or whether protein appears in the glomerular filtrate only after injury to the filtering membrane.

Since the mid-19th century, when Bowman (36) and Ludwig (117) first suggested theories of renal function based upon their observations of structure, urine formation was believed to start by ultra-filtration of plasma through the glomerular membrane. This semi-permeable membrane prevented protein from escaping into the glomerular urine, a belief that was strengthened by investigations of Wearn and Richards (220) in the frog. Walker, Oliver and their associates (215, 216) were able to obtain samples of urine from the glomeruli and from the proximal tubules of rats and guinea pigs with micro-pipettes. The specimens obtained in this fashion were inconsistent. Some contained a moderately high concentration of protein. This was attributed to trauma. Other specimens were "protein-free." However, the method of analysis could not reveal protein concentrations less than 30 mg. per 100 ml., in some instances, and 80 mg. per 100 ml. in others. It was concluded that normal glomerular fluid contains either no protein or only very small amounts.

No other biological filtrate is actually protein-free. Tears, spinal fluid and edema fluid all contain small amounts of protein, 20 to 40 mg. per 100 ml. or more. There has been a growing body of indirect evidence to support the belief that, under normal conditions in the kidney, protein is filtered through the glomerular membrane in a low concentration (157). However, the total quantity is great because of the large volume of glomerular filtrate. In man, if the filtrate protein concentration were only 20 mg. per 100 ml., with a glomerular filtration rate of 180 liters per day,* a total of 36 g. would pass

* Although a value of this magnitude is generally accepted by renal physiologists, it seems incredible on first consideration and depends on the validity of measurements by inulin clearances (198). Some support for the credibility of this value can be found in electron microscopy of the renal tubules, by which Pease (147, 148) has shown infolded membranes at the basal region of tubular cells and cytoplasmic processes which compose the brush border. If these observations are not found to be artifacts, as the new technique of electron microscopy is mastered, the surface available for reabsorption from the tubular lumen would be vast enough to explain how 99% of the glomerular filtrate can be reabsorbed.

the glomerular membrane. Since very small quantities of protein appear in voided urine, most of the filtered amount must be absorbed by the tubule cells (64, 155). That such protein absorption occurs in the proximal tubules has been demonstrated with colored azoproteins by Smetana (195, 196), with various proteins by Oliver (133, 138, 139, 140, 205) and with hemoglobin by Rather (156) and others (169, 178, 230). Rhodin (160) has also demonstrated protein absorption droplets and studied them with electron microscopy.

This new concept leads to the belief that proteinuria can no longer be regarded as evidence only of a change in permeability of the glomerular membrane. On the contrary, while proteinuria *may* result from such altered permeability (108, 112), it may also result from a diminished capacity for the tubular absorption of protein (7, 108, 112), an increase in the glomerular filtration rate, a change in the nature of serum proteins rendering them more readily filterable (6), or, as Addis has suggested (13), a diminished rate for the tubular "digestion" or disposal of protein. It is interesting to note that the highest degrees of proteinuria occur, in the nephrotic syndrome, with pathologic lesions that are most prominent in the tubules, although evidence for increased glomerular permeability has also been found (45a).

PROTEINURIA VERSUS ALBUMINURIA

The occurrence of protein in the urine has historically been named "albuminuria." This term originated at a time when proteins were not susceptible to differentiation and the word "albumen" was a generic term applying to any protein. In present usage, albumin refers to a protein fraction which, while not homogeneous by all criteria, may at least be differentiated from other protein fractions by certain physical and chemical characteristics. Reference to urinary protein as "albumin" is an anachronism which has served to confuse thought concerning the significance of proteinuria.

Many different proteins may appear in the urine. The most common ones, of course, are serum albumin and globulin. In normal individuals, the relatively minute quantities of urinary protein have been shown by electrophoresis to be distributed in the same spectrum as the serum proteins, though in different proportions (123, 162). Albumin, beta, and gamma globulins are present in smaller proportion, while alpha globulins are in larger proportion than in the serum. Mucoproteins and glycoproteins are also present in small quantities (37, 162).

In patients with proteinuria it has long been known that globulins appeared, as well as albumin, although the relative quantities were a matter for dispute (45, 79, 87) until the introduction of electrophoresis. Recent studies have shown that in some conditions, as in nephrosis (33, 118), the urinary protein distribution resembles closely the proportions of normal

serum proteins. In other conditions, as in calculous disease of the urinary tract (37), the urinary protein distribution remains similar to that in normal individuals, which differs from the serum protein, as described above.

When the glomerular membrane suffers a marked increase in permeability to protein, fractions of large molecular size may appear in the glomerular filtrate. Thus fibrinogen appears in the urine after the administration of renin in experimental animals (16). Under certain circumstances, abnormal proteins such as Bence-Jones' protein, to which a normal glomerular membrane is highly permeable, appear in the urine. After prolonged Bence-Jones' proteinuria, the glomerular membrane may suffer damage with increased permeability, or the tubule cells may become "saturated," so that normal serum proteins, albumin and globulin, appear as well. Although hemoglobin does not normally appear in the urine, hemoglobinuria may occur following massive intravascular hemolysis. In addition, other proteins appear in the urine under special conditions. For example, it has been shown by Addis and his associates (7) that many proteins and modified proteins appear in the urine when administered parenterally to the rat in sufficient quantity. Qualitatively similar to this phenomenon is the appearance of massive proteinuria after the intravenous administration to patients of human albumin in large quantities (145, 211).

DEGREE OF PROTEINURIA

Knowledge of the protein excretion rate is often of considerable value in arriving at a diagnosis concerning renal disease (Table 1). This circumstance is often unrecognized because the ease with which a quantitative protein determination can be performed upon urine is not commonly known. Most laboratories and clinicians still rely upon a qualitative report of protein in the urine as 0 to 4 plus. As will be indicated in the section on technique, the qualitative test for protein may be modified by adventitious conditions so that the significance of a rate is obscured. Furthermore, after the protein concentration has reached a degree termed "4 plus" no further distinction is possible. Since a reading of "4 plus" may be obtained with a relatively low rate of protein excretion, much valuable insight of clinical importance is lost.

The degenerative tubular lesion, regardless of the etiologic factor, is characterized by the highest rates of proteinuria. When the protein excretion rate exceeds 7.00 g./24 hrs., knowing little else, the observer can be almost certain that degenerative tubular disease is present. The proteinuria associated with bacterial infection is usually of moderate degree, ranging from 2.00 to 5.00 g./24 hrs., depending upon the severity and duration of the infection. Vascular diseases in general, including arteriolosclerosis, arteriosclerosis and abnormalities due to vascular anomalies, usually pro-

duce relatively low rates of proteinuria, from 0.500 to 4.00 g./24 hrs. One exception to the latter statement is malignant hypertension, in which occasionally rates of proteinuria reach as high as 10.00 to 15.00 g./24 hrs. Proteinuria rates exceeding 20 g./24 hrs. are rare, unless they follow the massive administration of human albumin intravenously in patients with the nephrotic syndrome.

SIGNIFICANCE OF PROTEINURIA AND ITS CONSEQUENCES

The occurrence of proteinuria is the best single indicator of a renal abnormality. For this reason, the qualitative test for protein is a useful screening procedure for the detection of renal abnormalities. Proteinuria does not ordinarily occur as the result of abnormalities or infections of the lower urinary tract.* Consequently, when pyuria is observed in the absence of proteinuria it can be inferred with reasonable assurance that the pus originates in the lower urinary tract and that the kidney is not involved.

There is divided opinion concerning the possible consequence of prolonged proteinuria, although most observers are agreed that proteinuria of short duration probably does not, in itself, cause permanent damage to the kidney. Studies performed upon patients in the degenerative stage of glomerular nephritis with the nephrotic syndrome, who received massive doses of albumin intravenously for the treatment of edema, have not shown conclusively the presence or absence of any change in renal function, other than acute and temporary changes immediately during albumin administration (145, 211). Baxter and Cotzias (22) produced proteinuria in rats by the intraperitoneal administration of human albumin and other protein fractions. After six weeks of such administration, they were unable to find evidence of diminished renal function or histologic evidence of renal damage other than occasional casts obstructing the tubules. They interpreted such findings to indicate that the occurrence of proteinuria, in itself, is a benign condition that does not materially affect the kidney. Similar experiments performed in our laboratory showed that at the end of six weeks the number of casts obstructing renal tubules became appreciable and was increasing. This observation suggests that, if the experiment were carried on for a longer time, evidence of renal damage would increase and become significant, with the atrophy of nephrons behind obstructed tubules.

The increased protein concentration in tubular urine, which must accompany proteinuria, favors the precipitation of protein and the formation

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* In occasional cases an exudative lesion of the lower urinary tract may cause a slight proteinuria. Since one ml. of undiluted serum contains only 60 to 70 mg. protein, it is obvious that only severe exudation can produce a perceptible proteinuria.

of casts. Such an association is reflected in the fact that proteinuria and cylindruria, in general, occur together. Only rarely does proteinuria occur without significant cylindruria, when the other factors affecting precipitation are compensatorily altered. After the administration of albumin intravenously to patients with the nephrotic syndrome, there is a marked increase in the degree of proteinuria, with a concomitant increase in the number of desquamated tubule cells that appear in the urinary sediment. At times, after albumin administration, a many-fold increase in the rate of tubule cell excretion is noted. When the rate of proteinuria diminishes, the rate of tubule cell excretion returns to or near the previous level. It is difficult to believe that such a marked increase in tubule cell excretion is unrelated to the increased rate of proteinuria, with the additional absorption load that is placed upon the tubule cells.

BENIGN PROTEINURIA

Although proteinuria usually indicates the presence of a renal lesion, it does not necessarily indicate a lesion of clinical or prognostic importance. Under the classification "benign proteinuria" may be placed a number of conditions. Their principal importance lies in the clinical confusion they produce. Nomenclature has varied, influenced by the bias of the writer, and this group includes orthostatic, postural, lordotic, physiological proteinuria, etc. The proteinurias often associated with fever (207) and sometimes with salicylate administration are also benign, in that they are transient and lead to no renal damage. In all of these conditions the proteinuria is transient, or at least inconstant, and of relatively small magnitude, usually less than 1.00 g./24 hrs. In none of these conditions can permanent anatomical damage be attributed to the proteinuria, although Rytand (171) has suggested that there is transient tubular degeneration, since cylindruria, hematuria, and desquamation of tubular epithelium may infrequently occur in conjunction with orthostatic proteinuria.

Several different theories, none wholly satisfactory, have been advanced to explain the transient occurrence of proteinuria in the erect posture, often, but not always, associated with an exaggerated lordosis of the lumbar spine. The excellent study of Bull led to the postulation that inferior rotation of the anterior surface of the liver, in the erect lordotic posture, with compression of the inferior vena cava against the spine, may cause passive renal hyperemia (42). Excessive mobility of the renal pedicle, with ptosis of the kidney in the erect posture (170, 171), may be another cause of passive hyperemia. Various congenital vascular anomalies have also been implicated. In dogs, Wegria and his associates (223) showed that proteinuria could be produced by elevation of the pressure in the renal vein, through application of a clamp. This phenomenon was reversible.

Greiner and Henry (69) have shown in human subjects that proteinuria resulted when blood was pooled in the extremities by use of a tilt-table. The proteinuria was prevented if the legs were mechanically massaged to prevent blood pooling. It was suggested that postural proteinuria results from renal vasoconstriction, with diminished renal plasma flow, as a reflex response to decreased blood content of the thoracic viscera. However, King and Baldwin have shown that the decrease in renal plasma flow and in the glomerular filtration rate occurs in erect lordosis without relation to the occurrence of orthostatic proteinuria (89).

The effects of orthostasis may be observed to a less pronounced degree in all normal individuals, as well as in all those with renal disease, since the rate of protein excretion nearly always increases in the erect position. There also is an *increase in the excretion rate of all formed elements* of the sediment (42).

In orthostatic proteinuria the protein excretion rate rarely exceeds 1.00 g./24 hrs. and decreases to a normal level in recumbency, during the night. Rarely, the orthostatic effect may be reversed, so that protein appears in the urine during recumbency and not when the subject is erect.

The proteinuria which follows exercise has been attributed to increased glomerular permeability, as a result of increased blood acidity. Javitt and Miller (81) found that renal blood flow, measured by clearance methods, was diminished after exercise, and this was also considered to be a factor in the production of proteinuria.

Proteinuria can be produced in man by the administration of epinephrine and norepinephrine (89a, 100c). Although emotional stress has not been shown to produce proteinuria, it is reasonable to suppose that an emotional stress with the liberation of adrenal medullary hormones could induce transient proteinuria. Such transient proteinuria might also accompany other conditions of stress in which the liberation of adrenal medullary hormones might be anticipated. Proteinuria which occurs with heavy exercise and intrapartum proteinuria (125b) might also be explained on a similar basis.

Löwgren (114) has revived the old idea of Quincke (152) that benign proteinuria results from the leakage of lymph into the urine at the calyceal fornices. This suggestion of a "post-renal" mechanism is provocative but is not well-supported by the experiments presented.

SIGNIFICANCE OF CASTS

Casts are cylindrical bodies appearing in the urinary sediment, so named because their shape represents an actual cast of the tubular lumen. They may be formed anywhere along the course of the nephron by precipitation of protein or by conglutination of material within the lumen. It is