The Pathologic Physiology of Chronic Bright’s Disease*

An Exposition of the “Intact Nephron Hypothesis”

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The course of advancing chronic renal disease is characterized by the development of a constellation of clinical, biochemical and physiologic derangements. These derangements may ultimately involve many organs and organ systems; however, the fundamental event underlying their development is the progressive destruction of nephrons. Although the causal relationship between intrinsic renal disease and the complex abnormalities of the uremic state was recognized by Bright more than twelve decades ago [1], the precise nature of the events leading from the initial destruction of nephrons to the picture of terminal uremia is yet to be fully understood. Until it becomes possible to prevent the various forms of chronic renal disease or to interrupt their inexorable progression, a major requisite to effective concepts of therapy is the clarification of the sequential events in pathologic physiology. In this regard it is essential to define clearly the functional capacity, range of operation and limitations of the diseased kidney. The present discussion consists of a review of recent experimental observations relating to these considerations.

THE TERM “CHRONIC BRIGHT’S DISEASE”

The observations of Bright, establishing the relationship between chronic renal disease and the clinical abnormalities of the uremic state [1], may well be regarded as the beginning of the modern era of the study of diseases of the kidney. It seems appropriate, therefore, that the term, chronic Bright’s disease, is generally employed (and will so be used in the present discussion) as a generic expression for all the chronic pathologic disorders of the kidney that lead to progressive renal failure. In this context the term assumes conceptual as well as historic significance, for it tends to group together a number of diseases of diverse etiology, differing pathogenesis and widely varying pathologic characteristics. A singular term implies the existence of a common denominator in these disease entities which supersedes their differences. There is now abundant evidence, both clinical and experimental, to support the view that the many different forms of chronic

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† Several examples of these exceptions may be cited: (1) During the natural history of chronic glomerulonephritis, lupus nephritis and certain other chronic renal diseases, a marked increase in glomerular permeability to protein may result in the evolution of a nephrotic syndrome. (2) Acute glomerulitis (e.g., secondary to an acute exacerbation of chronic glomerulonephritis, malignant hypertension, etc.) may modify glomerular tubular balance in the residual functioning nephrons of the diseased kidney and evoke corresponding functional changes. (3) A number of disease entities exist in which disproportionate involvement in one or more specific tubular functions may dominate the clinical picture [2].
renal disease may give rise to the same pattern of chemical and functional derangements, the evolution of which relates principally to the rapidity and extent of nephron destruction. Although in certain instances specific alterations in function may correlate with involvement of a particular site of the nephron, the major parameters of function are similar in all forms of chronic Bright's disease, and in general the more advanced the pathologic process becomes, the less evident are the differentiating features. From the functional point of view, therefore, consideration of the various forms of chronic renal disease as members of a unified group serves to emphasize the fact that the evolution of abnormalities is in most instances independent of etiology or details of morphologic change; moreover, it suggests that the functional capacity of the residual nephrons of the diseased kidney is largely independent of the specific form of renal disease. Accordingly, in the present discussion, concepts of pathologic physiology will be considered without systematic reference to the etiology of the underlying renal disease.

THE FUNCTIONAL CAPACITY OF THE DISEASED KIDNEY

General Considerations. In the normal subject the renal contribution to homeostasis is shared by approximately 2 million nephrons. In chronic Bright's disease the total nephron population diminishes progressively. Interpretation of the contribution to homeostasis must therefore involve two considerations: one, the consequences of nephron destruction and two, the functional capacity of the persisting nephrons. The decrease in the number of nephrons is clearly responsible for many of the abnormalities that develop in the patient; the persisting nephrons permit the patient to survive.

THE CONSEQUENCES OF NEPHRON DESTRUCTION

Because the over-all functional capacity of a kidney relates to the total number of intact functioning nephrons, the ablation of nephrons has definite and predictable consequences.

The Increasing Demands on the Residual Nephrons. As the number of constituent nephrons decreases, each residual nephron must perform a greater fraction of total renal function. If balance of any specific solute is to be maintained (and retention in body fluids avoided) on a constant intake, the quantity excreted by each nephron must increase as the total population of functioning nephrons decreases. The facility with which this is accomplished varies with the nature of the particular mechanism responsible for renal excretion.

Substances excreted by active transport mechanisms: Balance and plasma concentrations of solutes which are either secreted or reabsorbed by active tubular transport mechanisms may be maintained within normal limits only if the rate of transport per nephron is altered as the number of nephrons contributing to function diminishes. For substances which are excreted principally by tubular secretion, constancy of body fluid levels demands an increased secretory rate per nephron. For substances which are actively reabsorbed, reabsorption per nephron must decrease if balance is to be maintained on a given intake. For the majority of transport systems thus far studied, appropriate adaptive changes in excretion occur, and abnormalities in body fluid concentrations of the specific solutes are minimized or, in some instances, prevented until the late stages of chronic Bright's disease. Examples of two such adaptations may be cited.

Potassium is excreted principally by tubular secretion [3]. On any given dietary intake of potassium each nephron in the normal kidney must excrete approximately 1 two-millionth of the total quantity. In

* Such a unified approach in no way minimizes the importance of recognizing the differentiating features in etiology, pathogenesis and pathologic characteristics. However, a discussion of these considerations is beyond the scope of the present paper.
the patient with only 200,000 functioning nephrons, all other factors remaining constant, the same potassium intake demands that each nephron increase its excretion rate by tenfold. The diseased kidney must therefore function at a level that the normal kidney is called upon to achieve only rarely. This is ordinarily achieved, and hyperkalemia is an infrequent occurrence until the terminal stages of chronic Bright’s disease [4].

Phosphate represents a substance which is reabsorbed by an active tubular transport mechanism [5,6]. In the normal subject approximately 85 to 90 per cent of the filtered phosphate is reabsorbed and the amount excreted is balanced with intake and metabolic needs so as to maintain constancy of plasma phosphorus concentrations. As the nephron population (and hence total glomerular filtration rate [GFR]) diminishes, the filtered load of phosphate falls in parallel. Were the transport mechanisms to continue to reabsorb 85 to 90 per cent of the filtered phosphate, excretion would decrease progressively and retention of phosphate would occur early in the course of chronic Bright’s disease. (At a filtration rate of 50 mL/minute and a plasma phosphate level of 4 mg. per cent, reabsorption of 85 per cent of the filtered load would permit excretion of approximately 450 mg/day rather than the 700 to 800 mg. required to maintain balance on a normal diet.) However, phosphate reabsorption in the residual nephrons does not remain constant but decreases in a manner so precise as to allow a diminished number of nephrons to continue to maintain phosphorus balance. Plasma phosphate concentrations may remain normal until the filtration rate falls as low as 25 mL/minute [7]. At this level of renal function approximately 50 per cent of the filtered phosphate must be excreted in order to preserve normal plasma levels. At lower levels of GFR suppression of reabsorption is not sufficiently great to prevent phosphate retention on a normal phosphorus intake. * Thus hyperphosphatemia ultimately appears, but only after the nephron population is markedly reduced.

Substances excreted by glomerular filtration: For substances which are excreted predominantly by glomerular filtration, without the intervention of active transport mechanisms, a decrease in the number of nephrons must result in retention in body fluids if the rate of acquisition remains constant. This is illustrated by the progressive rise in plasma concentrations of two end products of metabolism, urea and creatinine. Both substances enter body fluids at a relatively constant rate in normal and uremic subjects if the dietary intake and cellular catabolism remain constant. The major determinant of the amount excreted is the glomerular filtration rate. Thus the total amount entering the functioning nephrons (i.e., the filtered load) represents the product of the plasma concentration times the glomerular filtration rate. In a person with normal kidneys, plasma levels remain essentially stable over prolonged periods by virtue of the fact that the amount excreted each day equals the amount acquired. In the patient with chronic Bright’s disease, each period of nephron destruction is accompanied by a corresponding decrease in total glomerular filtration rate. † The filtered load of urea or creatinine is thereby decreased, and this in turn results in a decrease in the total amount excreted. With a constant rate of production and a decreased rate of excretion, retention is an inevitable consequence.

As the plasma levels rise the filtered load entering each residual nephron increases until ultimately the rate of excretion again equals the rate of production. At this point a new steady state is established and plasma levels will stabilize (although at a higher than normal level) until additional destruction of nephrons causes a further decrease in the total filtration rate. If nephrons are destroyed continu-

* At a filtration rate of 10 mL/minute and a plasma phosphate concentration of 4 mg. per cent, the excretion into the urine of 100 per cent of the filtered phosphate would equal only 575 mg/twenty-four hours.

† The possibility that GFR per residual nephron may increase as an adaptive change in the diseased kidney will be discussed in a subsequent section.
ously, urea and creatinine concentrations rise progressively. If nephron destruction is intermittent, the rise occurs in a step-wise pattern.

The effects of nephron destruction on the patterns of excretion of other substances (principally sodium chloride and water) will be considered in detail subsequently.

**The Decreased Range of Excretion.** A second major consequence of the destruction of nephrons is a decrease in the range of excretion for any given substance. Although each individual nephron in the diseased kidney may be capable of increasing or decreasing the excretion rates of specific solutes or of water in response to the needs of the patient, the absolute change in excretion rates is determined by the product of the change per nephron times the total number of functioning nephrons. Hence, the fewer the remaining nephrons, the smaller will be the range over which excretion rates of any substance may vary. The upper limit of excretion for all substances will be decreased. Moreover, because of the adaptive changes that enable a decreased number of nephrons to excrete relatively normal amounts of sodium, chloride and water for long periods (these will be considered subsequently), the ability to decrease excretion rates is also restricted. Thus the lower limit of excretion is above that of the normal subject, and an obligatory renal excretion of salt and water may continue despite an inadequate intake and/or loss of body fluids through sweating, vomiting or diarrhea.*

It is apparent that the functional capacity of the residual nephrons of the diseased kidney determines the degree to which homeostasis is preserved. It thus becomes essential to examine in detail the quantitative aspects of renal function of the diseased kidney.

**THE FUNCTIONAL CAPACITY OF THE SURVIVING NEPHRONS OF THE DISEASED KIDNEY**

**A Statement of Conflicting Views.** The degree to which function is preserved in the persisting nephrons of the chronically diseased kidney has become the subject of much controversy. Perhaps the most widely held view is that morphologic disorganization of the renal parenchyma results in extensive abnormalities in intrinsic renal functions. Specific functional limitations in the diseased kidney (e.g., inability to concentrate and dilute urine, inability to excrete a sodium-free urine, and the like) are generally attributed to anatomic involvement of active sites in the persisting nephrons. Within recent years an increasing amount of evidence has accrued which seriously challenges this concept. The observations from many sources suggest that the surviving nephrons of the diseased kidney largely retain their essential functional integrity. Accordingly, a thesis diametrically opposite to the conventional view has arisen. According to this thesis the nephrons in the diseased kidney are reduced in number but possess essentially normal functional characteristics. The limitations of the diseased kidney would therefore relate not to intrinsic functional defects but rather to a predictable series of events that evolve when a decreasing population of relatively normal nephrons must maintain homeostasis.

Resolution of this conflict has important practical implications. If the functional systems of the diseased kidney deteriorate in a chaotic manner any attempts to develop a unified concept of pathologic physiology and to derive therefrom a rational therapeutic program would be complicated, perhaps hopelessly so. However, if the surviving nephrons in the diseased kidney are basically intact, a clear definition of the capacity and range of operation of these units at any given stage of chronic renal disease may permit a formulation of sound principles of therapy.

**THE "INTACT NEPHRON" HYPOTHESIS**

A number of investigators in the past have alluded to the possibil-

* The concept of an upper and lower limit of excretion rates has been admirably developed and discussed by Talbot and associates [8,9].
state are minimized. It thus becomes possible to study the diseased kidney in an essentially normal internal environment.

If the conventional view is correct, morphologic derangements of the persisting nephrons should result in abnormalities of function in the diseased kidney irrespective of the presence of an intact kidney or of the status of body fluids. However, if the intrinsic functional capacity is preserved, the capabilities of nephrons of the diseased kidney should remain comparable to those of the intact organ.

Three different forms of chronic renal disease have been studied: (1) a chemically induced lesion, aminonucleoside-nephritis [18]; (2) anti-kidney serum glomerulonephritis [19]; and (3) pyelonephritis [20]. All three lesions resulted in marked contraction of the renal mass and in severe architectural distortion of the persisting nephrons. The variation in the site of the nephron principally involved and in the extent of involvement created a spectrum of anatomic derangements analogous to that seen in the various forms of chronic Bright’s disease.

The induction of disease, irrespective of the type, was associated with an absolute decrease in values for all renal functions in the experimental kidney. A representative set of measurements of glomerular filtration rate and renal plasma flow in three dogs, each with a different form of renal disease, is shown in Figure 1. The decrease in values implies that the number of functioning nephrons has decreased. The critical considerations, however, concern the functional capacity of the remaining nephrons. The experimental observations which have a direct bearing on this issue are presented in the following paragraphs.

* This appraisal is permitted by analysis of: (1) the reproducibility of clearance values for the diseased kidney under steady-state conditions; (2) the patterns of change in the diseased kidney as compared with the normal kidney during changing experimental conditions; and (3) the relationship between clearance ratios (e.g., GFR/ERPF, GFR/TmPAH, etc.) for the diseased versus the normal kidney in serial studies under a variety of experimental conditions.

The Relationship Between Glomerular and Tubular Function in the Diseased Kidney. It has frequently been contended that the residual nephrons of the diseased kidney may include (1) units in which the glomeruli are largely destroyed but in which the tubules retain functional ability (alloglomerular tubules) and (2) units in which the glomeruli have normal filtering capacity but are attached to damaged tubules that serve largely as conduits which transport the glomerular filtrate in an essentially unmodified form into the urine (atubular glomeruli). That neither of these anomalies exists in the diseased kidney in the experimental animal is suggested by the following observations in which the relationships between glomerular and tubular function in the diseased organ are contrasted with those in the intact kidney.

Filtration fractions. The filtration fraction provides a measurement of the volume of glomerular filtrate formed per unit of effective renal plasma flow. If there is a detectable population of relatively aglomerular tubules in the diseased kidney, filtration fractions will be less for the diseased than for the intact kidney. Conversely an appreciable number of atubular glomeruli would result in abnormally high filtration fractions for the diseased organ.

In Figure 2A serial measurements of filtration fractions are shown for three representative dogs with unilateral renal disease. The values for the diseased kidneys are compared with those simultaneously obtained for the intact organs over periods up to eight months. The comparability of values for the individual kidneys of each dog, at any given time, is striking. This observation is inconsistent with the presence of an appreciable number of anomalous nephrons.

GFR/TmPAH ratios. The secretion of paraminohippurate (PAH) occurs in the proximal tubule and is limited by a maximal rate of
transport ($T_{\text{mPaH}}$ [5]). By comparing glomerular function (GFR) with $T_{\text{mPaH}}$ it is possible to examine a functional relationship between glomeruli and their attached tubules.

In Figure 2B the ratios of glomerular filtration rate to $T_{\text{mPaH}}$ are shown for the diseased and normal kidneys of three representative dogs. The values for the individual kidneys of each dog are essentially equal. These observations indicate that the relationship of the filtering capacity to the tubular secretory capacity is the same in the nephrons of the diseased kidney as in those of the normal kidney. This, then, represents another point in evidence against the existence of anomalous nephrons.

**GFR/$T_{\text{m}}$ glucose ratios.** The maximum rate of glucose reabsorption may also be employed as a reflection of tubular function, and the ratio of GFR to $T_{\text{mGlucose}}$ provides another means of comparing glomerular with tubular function. In Figure 2C ratios for GFR/$T_{\text{mGlucose}}$ are shown for the separate kidneys of three dogs with unilateral renal disease. In each instance the values for the normal and diseased kidney are essentially the same. These data thus provide additional evidence against the anomalous nephron thesis.

**The Homogeneity of the Nephron Population in the Diseased Kidney.** It has long been contended that the morphologic changes in the residual nephrons of the diseased kidney convert a relatively homogeneous population of nephrons into a heterogeneous group characterized by a spectrum of functional disorders [26,27]. One method for evaluating the homogeneity of the nephron population consists of the measurement of glucose excretion during progressively rising plasma glucose concentrations [28,29]. The rationale for employing this technic, the glucose titration curve, in the dog with unilateral renal disease is as follows: If there is a greater degree of heterogeneity in the diseased kidney than in the normal organ discrepancies should emerge in the respective patterns of glucose excretion. In nephrons with normal glomeruli and impaired proximal tubules, filtered glucose should be poorly reabsorbed and glucose should appear in the urine at relatively low plasma concentrations. Conversely, in nephrons with damaged glomeruli but normal tubules (hence a decreased GFR/nephron) the amount of filtered glucose might remain less than the reabsorptive threshold of the attached tubules until extremely high plasma concentrations are obtained. Glucose reabsorption would then continue in the diseased kidney long after the $T_{\text{m}}$ for the normal organ had been reached. The simultaneous existence of both forms of abnormal nephrons could also be detected. Glucose would appear in the urine of the diseased kidney before it does in that of the normal kidney, and glucose reabsorption would continue in the diseased kidney after the threshold had been reached for the intact organ.

Glucose titration curves have recently been obtained for animals with unilateral renal disease [23]. In Figure 3A a representative glucose titration curve is shown for a dog with a severe renal lesion in one kidney. Glucose concentrations were gradually increased from 120 mg. per cent to 840 mg. per cent. It may be seen that glucose reabsorption was complete in the diseased as well as in the intact kidney until the respective Tm's were reached. Moreover, once the filtered load of glucose exceeded the Tm level, no increment of glucose reabsorption occurred in either kidney. Finally, it may be seen (Fig. 3B) that $T_{\text{m}}$ was reached at essentially the same plasma glucose concentration in the diseased as in the normal kidney.

These results lend strong support to the "intact nephron hypothesis." The inability to demonstrate any degree of functional heterogeneity in the diseased kidney suggests that nephrons which are markedly damaged may be lost from the population of functioning nephrons, whereas nephrons that continue to operate retain a remarkably uniform relationship between glomerular and tubular function. To evaluate further the integrity of the persisting nephrons of the diseased kidney a number of other parameters of function must be examined.

**SUMMARY**

Clinical and experimental data relating to the functional capacity of the surviving nephrons of the chronically diseased kidney for the most part support the thesis that these nephrons retain their essential functional integrity regardless of the nature of the underlying form of chronic Bright's disease. There are instances in which specific alterations of function correlate with pathologic involvement of a particular site of the nephron but these appear to represent the exceptions, and in general the more advanced the disease becomes, the less evident are the differentiating features.

Studies on dogs with unilateral renal disease indicate that the functional capacity of the nephrons of the diseased kidney parallels that of the nephrons of the contralateral normal kidney. These data tend to exclude widespread intrinsic damage to the functioning nephrons by the underlying pathologic processes. From these observations, as well as from certain supporting clinical and experimental observations, it is suggested that the majority of surviving nephrons in the patient with bilateral renal disease similarly are functionally intact. Concepts of the
pathologic physiology of the kidney, based on the “intact nephron hypothesis,” are presented.

Within the framework of this hypothesis it is concluded that (1) the diseased kidney consists of a diminished number of nephrons, most of which retain essentially normal functional abilities; (2) certain of the apparent abnormalities in function in bilateral renal disease may relate to adaptive changes imposed by the decreased nephron population and the attendant derangements in body fluids rather than to structural distortion of nephrons; (3) the over-all flexibility of the diseased kidney decreases as the number of constituent nephrons decreases; but (4) there is an orderly and predictable pattern of excretion for all substances.

REFERENCES