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Vol. 1

Harvey C. Gonick M.D. Editor

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PREFACE

> For education the lesson is clear: its prime objective must be to increase the individual's "cope-ability"—the speed and economy with which he can adapt to continual change.
>
> Alvin Toffler, *Future Shock*

Nephrology has indeed come of age as a subspecialty of internal medicine. Not only are there several excellent textbooks and journals in this field, but also symposia addressed to specific areas within nephrology appear each year. Why then yet another treatise? Nephrology is still a rapidly evolving field in which the busy clinician may easily fall behind if he does not have ready access to new information. This problem is of course not unique to nephrology, but is equally pertinent to all fields in which the rate of explosion of knowledge exceeds the capacity of the postgraduate to assimilate recent data and apply it in his daily work.

In addressing ourselves to this issue, we sought to provide a partial solution by creating an annual volume in which the literature within the disciplines of nephrology published within the preceding year was reviewed by an authority in each area, and placed in the perspective of existing knowledge. After much deliberation, certain ground rules were established. Each contributor agreed to survey all of the English language literature within the assigned year (October 1, 1975 to September 30, 1976), and to orient his presentation toward the clinician. Thus clinical studies were to be emphasized over animal experimentation, and animal studies were to be discussed in the context of the relevant clinical problem. The contributors had complete freedom to express their own views of the validity and significance of these articles. To the extent possible, the style was to be informal and informative. Each chapter was to begin with an introduction reviewing the state-of-the-art in that discipline prior to the year's articles. The individual chapters were to be illustrated by figures and tables reprinted from selected key articles, and on occasion, by original material from the contributors.

I believe that we have come close to satisfying these objectives. As this was the first volume, flexibility was allowed in the assigned year in order that important articles appearing a few months before or after the review dates could be included. Also earlier pertinent references have been included to provide a background for discussion. It proved somewhat difficult to limit the basic researchers in our group in their discussion of critical animal experiments. In certain chapters it was possible to review every article published within the review period, but in others, because of the extensive amount of material, it was necessary to delete articles which in the opinion of the contributor did not add significantly to the knowledge in the field. Thus, this review cannot be considered to be exhaustive in scope. There is also considerable variability in chapter lengths reflecting, in part, the degree of current interest, and therefore, investigation in each discipline.

The contributors and I consider that we have benefited from this intensive review of articles related to our special fields of interest. We hope that we have

presented the information to you, the reader, in a manner that is easily assimilated. The proximity of the contributors has made it possible for us to coordinate our efforts and interact more closely than is usually the case in multiauthored publications, and we think that the publication has benefited from these continued discussions. We apologize to those authors whose contributions we may have deliberately or inadvertently deleted, and extend our appreciation to those authors and publishers who have graciously permitted the use of their data and figures.

To Dr. Charles Kleeman, Professor of Medicine and Chief of Nephrology at U.C.L.A. Medical Center, we extend our deepest appreciation for his leadership and guidance. Many of us had Dr. Kleeman as our mentor and have greatly benefited from his stimulating and innovative approaches to new problems. We also thank Ms. Peggy Wilson, Medical Editor at Houghton Mifflin Professional Publishers, for her generous and sustained efforts in the development and completion of this project.

Harvey C. Gonick, Editor
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Chapter 1

SODIUM METABOLISM AND VOLUME REGULATION

MICHAEL A. KIRSCHENBAUM AND
HARVEY C. GONICK

It is very clear that the kidney must play a dominant role in the volume regulation of the extracellular fluid compartment. Regardless of the dietary intake of solute and water, it is the kidney that performs the fine regulation of both the amount and concentration of the various ions in the extracellular space. This chapter contains an analysis of much of what has been published during this past year concerning both the renal handling of sodium and the factors which control the extracellular fluid volume. We will attempt to separate the many aspects of sodium regulation into somewhat arbitrary subdivisions but it will become apparent that there is considerable overlap. Renal hemodynamics will be included in this chapter because of the intimate relationship between renal blood flow and sodium excretion. Much of this year's literature has consisted of studies performed either in animal models or in isolated tissue preparations. To allow for a better understanding of the data, we will try to explain and simplify the techniques used in these studies. Renal hemodynamics and tubular physiology will be discussed beginning with glomerular filtration and then segmentally traversing the entire length of the nephron. There has been considerable recent interest both in determining the possible physiologic role(s) of a group of naturally occurring acidic lipids, the prostaglandins, and in further delineating other circulating natriuretic factors. As a final chapter component, these interesting compounds are discussed in separate sections due to the volume of original articles published this year.

GLOMERULAR FILTRATION

Over one hundred years ago, Carl Ludwig suggested that the formation of a plasma ultrafiltrate initiated the process of urine formation. At the turn of the century, Starling, using imagination more than direct measurements, described the balance of forces which defined filtration at the glomerular capillary. Using these principles, the rate of ultrafiltrate formation could be expressed by relating the forces which tend to favor transcapillary movement of fluid into Bowman's space, i.e., the difference in the mean hydrostatic pressure between the glomerular capillary ($\overline{P}_{GC}$) and Bowman's space (P_T), and the forces which favor movement of fluid back into the glomerular capillary, i.e., the mean oncotic pressure within the glomerular capillary ($\overline{\Pi}_{GC}$) and the oncotic pressure within Bowman's space (Π_T). At the level of the nephron, the rate of plasma ultrafiltrate formation can then be expressed by the formula:

$$SNGFR = K_f\{(\overline{P}_{GC} - P_T) - (\overline{\Pi}_{GC} - \Pi_T)\}$$

where SNGFR is the single nephron glomerular filtration rate and K_f is the ultrafiltration coefficient (referred to again in this section).

Two factors allowed Brenner and his associates (1971) to measure $\overline{P}_{GC}$ more precisely (1). In Munich, Klaus Thurau had discovered a mutant strain of Wistar rats that possessed numerous surface glomeruli, while other researchers had developed sensitive servo-nulling devices permitting more accurate estimation of hydrostatic pressures within the accessible portions of the nephron. Using these newly determined values for the hydrostatic pressure within the glomerular capillary, which were significantly lower than those previously estimated by stop-flow measurements, the magnitude of the net ultrafiltration pressure (P_{UF}) could now be more accurately defined. In the Munich-Wistar rat, P_{UF} at the afferent end of the glomerular capillary was calculated to be 15 mmHg (i.e., $\overline{P}_{GC}$ = 45 mmHg, minus P_T = 10 mmHg, minus the pressure exerted by the protein concentration of plasma = 20 mmHg). As filtration proceeds along the length of the glomerular capillary, the protein concentration within the capillary, $\overline{\Pi}_{GC}$, begins to increase due to the ultrafiltration of a relatively protein-free fluid. Thus at some point along the glomerular capillary, where the force exerted by the concentration of protein within the capillary increases 15 mmHg over that at the afferent end, filtration ceases and filtration equilibrium has been reached. In additional studies, Brenner and his associates noted that changes in oncotic pressure ($\Delta\Pi$) appeared to have a significantly greater effect on SNGFR than did changes in hydrostatic pressure. Since changes in glomerular capillary blood flow could significantly alter $\Delta\Pi$, it became apparent that, at least in this mutant strain of rat, glomerular ultrafiltration was plasma flow dependent.

During this past year, Ott and his associates (2) have questioned whether these findings in the rat are applicable to other mammals. In studies performed in the dog, the authors studied glomerular dynamics using similar techniques to those used in the rat. Since dogs do not possess surface glomeruli, direct pressure measurements were impossible and glomerular capillary hydrostatic pressure had to be estimated using stop-flow techniques. In this procedure, the movement of proximal tubular fluid is stopped with an oil droplet and the pressure proximal to this block is allowed to equilibrate with that in the glomerular capillary. Since this pressure is transmitted to an accessible portion of the nephron, it can be measured using routine techniques. This method was validated in the species of rats with surface glomeruli. Using these techniques, the authors showed that P_{UF} at the end of the glomerular capillary was more than 12 mmHg and not zero as in the rat. From these data the authors suggested that in the dog and perhaps other mammalian species, filtration equilibrium is not reached and that glomerular filtration may not be as dependent on renal plasma flow as it appears to be in the rat. These data may characterize glomerular dynamics in the dog, but Maddox and coworkers (3) have recently shown that measurements made in squirrel monkeys, a species closer to man than is the dog, closely resemble those obtained in the rat.

The results of the studies by Brenner and his associates have been questioned by Kallskog and his coworkers (4) in Sweden. Using nonmutant Sprague-Dawley rats in which an occasional glomerular capillary has been identified, significantly greater values for $\overline{P}_{GC}$ have been obtained and filtration pressure equilibrium has not been noted during hydropenia. However, considering all of these findings, there seems to be overwhelming evidence from several laboratories that the conclusions drawn from the data of Brenner and his associates are the most reasonable at this time and best explain the intricacies of glomerular filtration. A recent review by Brenner, Baylis, and Deen (5) summarizes these and other aspects of the movement of fluid and solute across the glomerular capillary.

In three separate studies this past year, the effects of various vasoactive compounds and increased ureteral pressure on the determinants of glomerular filtration were investigated. In the first of these studies, Blantz and his coworkers (6) evaluated the effect of a 20 mmHg elevation of ureteral pressure in the mutant strain of Wistar rats. Using methods we

have previously discussed, Blantz showed a somewhat complex series of alterations in many of the determinants of glomerular filtration. The authors found no significant increase in single nephron plasma flow. In the dog and other species, increased ureteral pressure can increase whole kidney plasma flow, but since in this study only the superficial nephron plasma flow was evaluated, a large change in blood flow to more inner cortical nephrons could have been missed. Indeed, several laboratories have shown a redistribution of blood flow to inner cortical nephrons associated with increased ureteral pressure. Nevertheless, no changes in plasma flow were noted in superficial nephrons.

When Blantz and coworkers examined the effect of increased ureteral pressure on the determinants of glomerular ultrafiltration, they noted that SNGFR fell in both hydropenic and plasma-expanded rats, although the cause for this reduction seemed to be different in each group. In the plasma-expanded rats (in filtration disequilibrium), the fall in SNGFR was due largely to the fall in the hydrostatic pressure across the glomerular membrane (ΔP) apparently due to the increase in P_T—the pressure within the tubule reflecting the increase in ureteral pressure. In hydropenia (in filtration equilibrium), the increase in P_T was balanced by a similar increase in $\overline{P}_{GC}$ reflecting an increase in hydrostatic pressure within the renal circulation distal to the glomerulus. Thus there was no change in ΔP. Since SNGFR was noted to fall without apparent changes in ΔP or oncotic pressure within the glomerular capillary, Blantz questioned whether there could be a change in the ultrafiltration coefficient, K_f. This factor is the product of the surface area of the glomerular capillary and the glomerular hydraulic permeability. Since calculation of the ultrafiltration coefficient can only be made during periods of filtration disequilibrium and since we have previously noted that during hydropenia, the rat attains filtration equilibrium, speculation about changes in K_f can only remain as such.

In a second study, Blantz and his associates (7) evaluated the effect of angiotensin II infusion on glomerular dynamics. Again the rats were plasma-expanded to allow glomerular ultrafiltration coefficient measurements by pushing the rat into filtration disequilibrium. Using doses of both synthetic and endogenous angiotensin II which did not affect systemic blood pressure, renal blood flow fell significantly as would be predicted. On the glomerular level, ΔP increased significantly primarily due to an increase in $\overline{P}_{GC}$. This increase was noted to be of sufficient magnitude to offset the fall in single nephron plasma flow. Once again the authors looked for changes in K_f which could explain the fall in SNGFR seen with an angiotensin II infusion. Since the rats were in filtration disequilibrium, changes in K_f could be calculated and were found to be decreased compared to control animals, thus accounting in part for the fall in SNGFR. These studies suggest that angiotensin II may have the ability to change the permeability of the glomerular capillary by altering the ultrafiltration coefficient.

In a final study, Baylis and her associates (8) evaluated the effect of three renal vasodilators (acetylcholine, bradykinin, and prostaglandin-E_1) on glomerular dynamics in the Wistar rat. The administration of each of these agents in mildly vasodepressive doses resulted in an increase in nephron plasma flow but no significant change in SNGFR. The increase in nephron plasma flow was apparently due to decreases in resistance in both afferent and efferent arterioles, with the greatest change in the afferent. Since in the rat plasma flow dependence of glomerular ultrafiltration has been demonstrated, the constancy of SNGFR in the face of significant increases in nephron plasma flow led the authors to look for possible alterations in K_f. Since the administration of all three agents caused filtration disequilibrium, K_f could be calculated. With the infusion of each of these drugs, K_f was noted to decrease slightly. Of interest is the observation that the colloid osmotic pressure in the efferent arteriole (π_e) fell consistently in all of the animals studied but the expected fall in proximal tubular reabsorption associated with a fall in π_e was not noted. The authors suggested that the increase in plasma flow in the efferent arteriole as well as an unmeasured increase in interstitial hydraulic pressure could have opposed the effect of a fall in π_e to obviate any change in the absolute rate of

fluid reabsorption in the proximal tubule.

Farquhar's (9) review of the ultrastructure of the glomerular capillary yields further information concerning the anatomical barrier to filtration. With the use of transmission electron microscopy the ultrastructure of this capillary was defined: (*a*) the capillary endothelial cell with its endothelial fenestrae, (*b*) a thick basement membrane with three distinct layers, and (*c*) a complex arrangement of three generations of fingerlike projections from the epithelial cells which seem to act as a spine for the capillary unit. Intimately associated with this unit is the mesangium, a group of cells which have a phagocytic and perhaps a supportive role. In her review, Farquhar gives the arguments for and against each of these structures being the ultimate barrier to filtration. She concludes that the basement membrane is the primary filtration barrier. Additional evidence is presented elsewhere (5) that filtration selectiveness (especially for large polyanions, e.g., albumin), may be due to the sialoglycoprotein coating on the foot processes of the glomerular endothelial cells.

RENAL BLOOD FLOW

The renal circulation is unique in that it is not only able to autoregulate itself with great efficiency over a wide range of perfusion pressures, but also it is able to redistribute blood flow to different cortical areas. Since the blood supply to the medulla is derived from the postglomerular circulation of inner cortical nephrons, any stimulus which causes a redistribution of blood flow to these inner cortical nephrons could have a very significant effect on electrolyte excretion. There has been considerable speculation as to the possible relationship between sodium excretion and the distribution of cortical blood flow. It has been suggested that a redistribution of renal cortical blood flow to juxtamedullary nephrons (thereby increasing medullary blood flow) was associated with decreased sodium excretion. Since this theory was proposed, considerable evidence has been presented to suggest that redistribution to inner cortical nephrons may not have a direct relationship to sodium excretion and may have other significance.

Many techniques that estimate regional blood flow within the renal cortex have been described. Two methods are the most commonly used and will be discussed here briefly before reviewing the literature. The first of these methods utilizes an inert radioactive gas (such as ^{85}Kr or ^{133}Xe) which is injected into the renal artery. Following injection, the radioactive gas rapidly accumulates within the kidney, then is more slowly "washed out." The exit of the gas from the kidney is characterized by a multiexponential curve which is then subjected to compartmental analysis yielding various components. These components are then related to anatomical regions within the kidney. The major criticism of this method concerns the accuracy of ascribing the decay curve components to specific anatomical regions. Additional criticisms of this method are outlined elsewhere (10). The second commonly used method of determining the cortical distribution of blood flow uses 15μ diameter latex spheres which are impregnated with various nuclides. Because of their size, these microspheres are completely trapped in the preglomerular and glomerular circulation and reflect glomerular perfusion at the time of injection. This method has also been criticized particularly with regard to the rheologic properties of the microspheres and their possible subjection to axial streaming which under some circumstances might falsely overestimate outer cortical blood flow.

During this past year there has been considerable continued investigation into the significance of the redistribution of cortical blood flow. Westenfelder and coworkers (11) studied the significance of an experimental model of congestive heart failure in dogs with regard to the distribution of renal blood flow. It had been suggested that a redistribution of renal blood flow to inner cortical nephrons is associated with sodium retention, and that this alteration in renal hemodynamics could play an important role in the formation of chronic edematous states. In this study, the intrarenal distribution of blood flow, measured by the radioactive microsphere method, was evaluated before and after the construction of an aortocaval fistula in dogs, a model of high-output cardiac failure. The average weight gain

of the 17 dogs studied was 3.4 kg (20% increase), and all of the animals developed edema and/or ascites. Total renal blood flow fell significantly from a mean of 400 to 224 ml/min after the development of generalized edema, and the glomerular filtration rate fell from 71 to 53 ml/min. Urinary sodium excretion fell from 182 to 14 μEq/min. However, despite these marked changes in renal function associated with the development of significant expansion of the extracellular fluid volume, no redistribution of cortical blood flow could be demonstrated. Several of these animals were also given furosemide, which has previously been shown to redistribute cortical blood flow to midcortical nephrons in nonedematous anesthetized dogs, and the results in these conscious edematous dogs were quite similar. It would appear from this study that, at least in this aortocaval fistula model of congestive heart failure as measured by the microsphere method, no role for the redistribution of cortical blood flow could be found in the generation of chronic edema.

In another study utilizing the microsphere technique, the relationship of hemorrhage and intrarenal blood flow was examined (12). In previous studies, many laboratories have demonstrated that hemorrhage in the dog is associated with a redistribution of cortical blood flow to juxtamedullary nephrons. In their study Data and coworkers (12) reconfirmed this observation, but when they pretreated dogs with indomethacin, an inhibitor of prostaglandin synthesis, they were able to block the redistribution to inner cortical nephrons. The authors suggested that the changes in inner cortical vascular resistance which accounted for the redistribution of cortical blood flow were dependent on the intrarenal release of prostaglandins. These results are not surprising since numerous laboratories have demonstrated that inhibition of prostaglandin synthesis in pentobarbital-anesthetized dogs is associated with an increase in renal resistance and a redistribution of blood flow to outer cortical nephrons. These findings become difficult to fully evaluate because many explanations of the data other than the authors' are possible. Prostaglandin inhibition, for example, is not associated with a change in renal resistance when the dog is studied without pentobarbital anesthesia. Burger, Hopkins, Tulloch, and Hollenberg (13) further investigated the role of barbiturate anesthesia in modulating the effect of angiotensin on the renal vasculature in dogs. The xenon washout method was used to estimate total renal blood flow. These studies confirm the observation that barbiturate anesthesia consistently increases renal resistance and reduces renal blood flow. This reduction in renal blood flow could not be blocked with α-adrenergic blockade (presumably ruling out norepinephrine release mediating this phenomenon). A high-salt diet which suppresses renin release, as well as three agents which interfere with the renin-angiotensin axis, resulted in an increase in renal blood flow. Thus the prior study, which evaluated the effect of prostaglandin inhibition in pentobarbital-anesthetized dogs, as well as other studies investigating renal hemodynamics during barbiturate anesthesia, must be evaluated with the knowledge that these anesthetic agents in themselves have hemodynamic effects probably mediated through the renin-angiotensin axis.

PROXIMAL TUBULE

The mechanisms of proximal sodium and fluid transport in the nephron have been reviewed by two of the leading investigators in this field, Windhager and Giebisch (14). We will briefly summarize this review to act as a reference for the remainder of this section.

Approximately 60% of the plasma ultrafiltrate entering the proximal tubule is reabsorbed isosmotically with respect to plasma in this nephron segment. It is generally assumed that the active process of sodium reabsorption supplies the energy for the movement of both solute and water. The evidence that all solute and fluid movement across the proximal tubule is dependent upon the active transport of sodium is far from conclusive. Several observations support active sodium reabsorption: (*a*) it must proceed against an electrical potential gradient which would tend to keep sodium within the lumen; (*b*) it is blocked by maneuvers which could inhibit sodium transport (e.g., ouabain); and (*c*) it can, under certain

circumstances, occur against significant concentration gradients (e.g., mannitol diuresis). (The relationship of the movement of other ions such as chloride, bicarbonate and hydrogen will be discussed later in this section.) The cells of the proximal tubule are aligned in a rather intricate fashion with their luminal membranes joined by so-called tight junctions which potentially could act as a significant barrier to solute and fluid transport. Between these tight junctions and the contraluminal membrane is an intercellular compartment. Active sodium transport occurs at these lateral intercellular and antiluminal membranes. As sodium enters this paracellular channel, it increases the tonicity of the fluid and water then moves into this area in response to the osmotic gradient. Fluid then can pass either into the peritubular capillaries or leak back into the tubule through the tight junctions. Indeed, these low resistance paracellular channels may account for the majority of the passive ion movement in the proximal tubule. Knowing the proposed sites of movement of solute and water, we can now discuss some of the factors which may influence this movement. Considerable data suggest that the proximal tubule has little inherent ability to vary the rate of solute and water movement. The same Starling forces which control glomerular filtration may be operative in fluid reabsorption back into the peritubular capillary, and there seems to be a direct relationship between colloid osmotic pressure in the peritubular capillary and absolute fluid reabsorption. We will return to this concept later in the discussion.

In a two-part article this past year, Green and Giebisch (15,16) investigated the role of other ions in relation to the reabsorption of sodium in the proximal tubule. In the first of these studies (15), the authors evaluated bicarbonate and chloride using a microperfusion technique in which they could vary both the luminal and peritubular fluid composition of individual nephrons while observing the net transepithelial volume and sodium flux. When acetate was substituted for bicarbonate on both sides of the membrane, a 40% decrease in sodium and water reabsorption was noted. When bicarbonate was again deleted and a chloride gradient created across the membrane, an insignificant change in sodium and volume flux was noted. The chloride gradient was estimated to be responsible for at most only 20% of sodium reabsorption. In addition, glucose appeared to have no effect on sodium flux and the substitution of choline for sodium in the luminal perfusate abolished sodium and volume flux completely. Thus we have additional evidence that sodium indeed is the actively transported ion; that bicarbonate ions exert a major effect on the rate of proximal tubular sodium and water transport; and that a chloride concentration gradient accounts for only a small proportion of sodium and fluid reabsorption. These conclusions have been drawn from data obtained by microperfusion of the accessible portion of proximal convoluted tubules of superficial nephrons. Sodium transport in the first part of the proximal tubule, in the proximal straight tubule, and in the proximal tubules of all other nephrons not at the outer cortex could not be sampled and these results may not necessarily reflect the function of all proximal tubules within the kidney.

In their second article (16) Green and Giebisch used similar simultaneous tubular and capillary microperfusion techniques to assess the role of hydrogen ions in sodium transport. In summary, as they observed that there was no firm association between hydrogen ion secretion by the proximal tubule and sodium reabsorption, they postulated several other mechanisms by which bicarbonate could stimulate sodium and water transport.

Using somewhat different techniques, Burg and Green (17) addressed the same question as Green and Giebisch. These investigators used an isolated perfused segment of the proximal tubule to study sodium and water transport. In this model, rabbit outer cortical proximal convoluted tubules were dissected free from slices of cortex. They were cannulated and perfused at low rates which approximate those usually seen in these segments. The composition of both the perfusate and bath surrounding these segments could be varied. When various cations other than sodium (e.g., lithium, choline, or tetramethyl ammonium) were substituted in both the bath and perfusate, the rate of

fluid absorption fell to zero. Potassium substitution for sodium in the bath also caused fluid reabsorption to drop to zero. When potassium was omitted only from the perfusate and replaced by sodium, the rate of fluid reabsorption fell 20%. When chloride was substituted for bicarbonate (Fig. 1), fluid reabsorption fell significantly as was noted in the previous study. However, replacing chloride by either nitrate or perchlorate did not substantially change fluid transport. Thus again, evidence is provided that fluid reabsorption is dependent upon the presence of sodium, and that the absence of bicarbonate, but not chloride, inhibits fluid transport. The inhibitory effect of removing potassium from the bath may be due to the potassium requirement of Na^+-K^+-activated ATPase needed for sodium transport.

In 1843, Carl Ludwig formulated the basis for our current theories of tubular reabsorption. He suggested that reabsorption occurred as a result of: (*a*) the fall in hydrostatic pressure in the peritubular capillaries; and (*b*) the rise in postglomerular capillary oncotic pressure above systemic pressure caused by the removal of a relatively protein-free ultrafiltrate at the glomerulus. Over one hundred years have passed, but this formulation still appears to be the most likely. These and other historical notes can be found in a recent editorial review by Bresler (18).

In more recent studies, the effects of changes in both hydrostatic and oncotic pressure have been investigated. The role of oncotic pressure changes was evaluated this past year by Conger and his coworkers (19). In their study, the authors microperfused peritubular capillaries of rat proximal tubules with either protein-free or hyperoncotic protein solutions. Large variations in the protein concentration of peritubular perfusates had little to no effect on the rate of proximal reabsorption (Figs. 2 and 3). These data are surprising since several other laboratories have found quite the opposite. The reasons for these findings may be that only superficial nephrons were sampled or that the effect of changes in protein concentration may occur in nephron segments distal to those sampled in this study.

In another study, Sato (20) evaluated some of the artifacts of micropuncture which can lead to spurious data while reexamining the role of changes in ion composition and hydrostatic forces which might affect the rate of proximal tubular fluid reabsorption. A bicarbonate-free perfusate decreased fluid absorption nearly 50%, confirming that bicarbonate is a major factor in sodium and volume reabsorption. When Sato examined the role of hydrostatic pressure, he found that increased luminal pressure was not a driving force for fluid reabsorption but that increased contraluminal pressure strongly inhibited fluid reabsorption. Thus proximal sodium and fluid reabsorption may not be explainable by changes in Starling forces alone. A complex series of events involving changes in both hydrostatic and oncotic pressure in the tubular lumen, paracellular channels, interstitial spaces, and peritubular capillaries along with the potential for back-leakage across the so-called tight junctions may be involved.

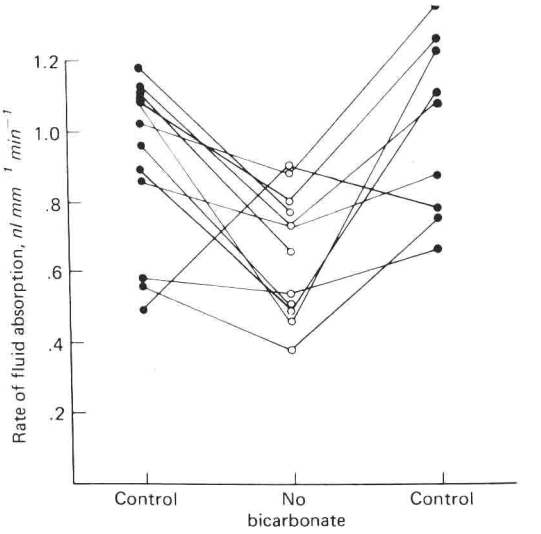

Figure 1. Effect of bicarbonate on proximal convoluted tubules. Bicarbonate was replaced by chloride in both the perfusate and bath and the solutions (gassed with 100% O_2) were maintained at pH 7.4 by the nonbicarbonate buffers present. (Reprinted by permission of the authors and the International Society of Nephrology from: Burg and Green. Role of monovalent ions in the reabsorption of fluid by isolated perfused proximal renal tubules of the rabbit. Kidney Int. 10:221-228, 1976.)

DISTAL NEPHRON

Formation of a dilute urine is a function of the distal nephron. During a maximal water diuresis, antidiuretic hormone

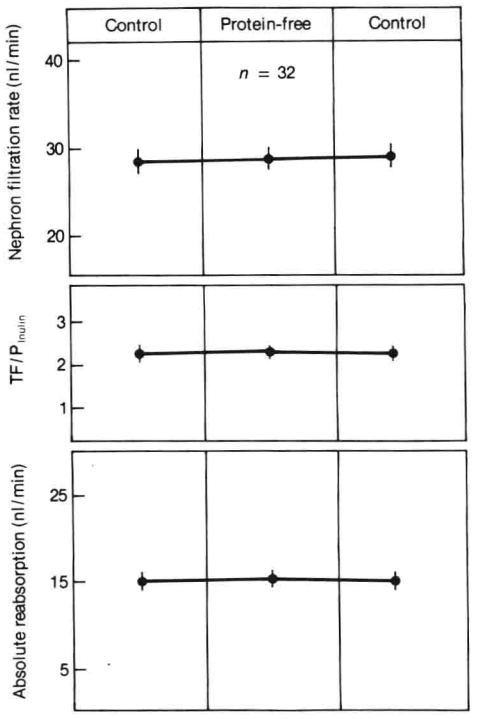

Figure 2. Relation between nephron filtration rates, TF/P inulin ratios and absolute reabsorption rates for collections from late proximal tubules during normal capillary blood flow (control, left panels), during capillary perfusion with protein-free solution (center panels) and after return of normal blood flow to the capillary bed (control, right panels). Results are shown as mean value ±1 SEM for 32 perfusion studies. (Reprinted by permission of the authors and The Medical Research Society and the Biochemical Society from: Conger et al. A study in vivo of peritubular oncotic pressure and proximal tubular reabsorption in the rat. Clin. Sci. Molec. Med. 51:379-392, 1976.)

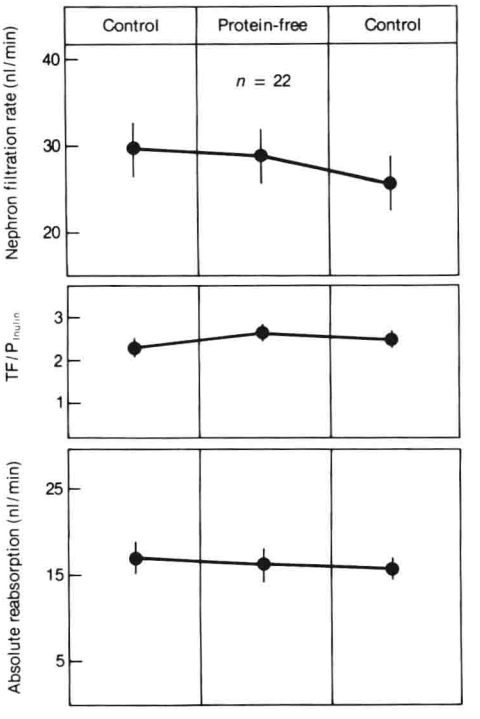

Figure 3. Relation between nephron filtration rates, TF/P inulin ratios and absolute reabsorption rates for 22 collections from late proximal tubules during pre- and post-control periods and capillary perfusion with high-protein plasma. Results are expressed as in Fig. 2. (Reprinted by permission of the authors and The Medical Research Society and the Biochemical Society from: Conger et al. A study in vivo of peritubular oncotic pressure and proximal tubular reabsorption in the rat. Clin. Sci. Molec. Med. 51:379-392, 1976.)

(ADH) release is suppressed and the distal nephron becomes relatively impermeable to water while it remains permeable to sodium. The reduced ability of this part of the nephron to reabsorb sodium may be a major factor involved in the natriuresis seen with expansion of extracellular fluid volume. Indeed, several laboratories have demonstrated a reduced distal sodium reabsorption during saline-loading (21-23). Danovitch and Bricker (21) have reexamined the influence of volume expansion on the function of the distal nephron. The authors chose to use clearance techniques to estimate distal delivery of filtrate because of the limitations of direct micropuncture techniques in this area of the nephron. The rate of formation of solute-free water (C_{H_2O}) factored by the glomerular filtration rate (GFR) during a maximal water diuresis (when the distal nephron is impermeable to water), is an estimate of the magnitude of sodium reabsorption in this segment. Since proximal nephron reabsorption is isotonic, filtrate delivered to the distal nephron is also isotonic. During a maximal water diuresis any free-water generated must be a reflection of the reabsorption of sodium. The authors used three separate terms to estimate the rate of filtrate delivery to the distal nephron. The first is the volume of urine excreted factored by GFR (V/GFR). In a maximal water diuresis, the volume of fluid reaching the distal nephron will be excreted without further reabsorption. The volume of urine excreted will represent the volume of filtrate reaching this water-impermeable segment. The second term is the fractional

excretion of sodium added to the fractional free-water clearance

$$(C_{Na}/GFR + C_{H_2O}/GFR).$$

In the absence of ADH, no water will be reabsorbed beyond the proximal tubule and the total free-water generated reflects the reabsorption of sodium in the distal nephron. Their final term for distal delivery is the fractional excretion of chloride added to the fractional free-water clearance ($C_{Cl}/GFR + C_{H_2O}/GFR$). The rationale for this expression is the assumption that like sodium, free-water generation is due to the distal reabsorption of chloride ion with sodium. In their study, distal delivery was enhanced with acetazolamide, a diuretic which decreases proximal reabsorption of sodium bicarbonate, or by either moderate or marked expansion of the extracellular fluid volume with saline. The results showed that using these estimates of distal delivery the rate of sodium reabsorption decreased as distal delivery increased by either acetazolamide administration or saline-loading. Of the three terms, the "chloride term," $C_{Cl}/GFR + C_{H_2O}/GFR$, seemed to reflect these changes best. Inherent in this study are many assumptions which may not be correct. The distal nephron is more than likely always permeable to water to some degree even in the absence of ADH. Not all of the sodium delivered to the distal nephron may be available for reabsorption and that which is exchanged for potassium will underestimate the clearance of sodium and will underestimate distal delivery. The administration of acetazolamide results in enhanced sodium bicarbonate delivery to the distal nephron with bicarbonate being substantially less permeable than chloride throughout the nephron. With all of these problems, however, the directional changes in the data of Danovitch and Bricker seem to agree with other laboratories using various techniques (including micropuncture) and reinforce the idea that the distal nephron plays a decisive role in the final regulation of sodium balance.

The final two articles which we will review in this section are by Sonnenberg (22, 23) and relate to the function of the collecting duct. Although viewed by Homer Smith as merely a conduit for the passage of urine, recent studies demonstrate a marked ability of this part of the nephron to alter both the solute and fluid composition of the urine. Direct cannulation studies of the medullary collecting duct have added substantial information about this region of the nephron which is inaccessible to direct micropuncture techniques. In direct cannulation, a fine polyethylene catheter is introduced into the distal end of the duct of Bellini of a rat papilla and passed into the medullary collecting duct. Fluid can be withdrawn at any level and the position of the catheter can be related to an anatomical area postmortem. Using these techniques, Sonnenberg and Wilson (22) investigated the role of the medullary collecting duct in postobstructive diuresis. After relief of acute ureteral obstruction, a transient diuresis is noted which cannot be explained by the elevation of BUN or other solutes. Some authors have suggested the presence of a natriuretic substance in this setting and others have speculated on a change in the distal handling of sodium and water. The authors evaluated 24 hours of bilateral obstruction, reinfusion of urine into normal rats and unilateral obstruction with and without the reinfusion of urine from the contralateral kidney. The release of bilateral obstruction was associated with a diuresis-natriuresis. When collecting duct transport was studied, net addition of sodium was noted despite reduced delivery of filtrate from more proximal parts of the nephron. When the authors evaluated collecting duct sodium transport during reinfusion of urine into the circulation, a similar diuresis and natriuresis was noted but no increase in the net addition of sodium was seen. The increase in sodium excretion was due primarily to increased delivery of filtrate from the proximal nephron. Under certain circumstances, the distal nephron seems to participate in enhanced sodium excretion. Whether this increase in sodium excretion represents a decrease in mucosal to serosal sodium transport, increased back-diffusion, changes in permeability, or some other poorly defined mechanism is not clear.

In the final study, Sonnenberg (23) used the same microcatheterization technique to examine collecting duct function in deoxycorticosterone acetate (DOCA)-treated rats. It is known that within a few days after administration of mineralocorti-