NEPHROTIC EDEMA: PATHOGENESIS AND TREATMENT

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Introduction

While the excretion of a small amount of protein in the urine may represent the first and only clue to the presence of underlying renal disease, by itself, it is clinically unimportant. If, however, protein excretion becomes massive, it becomes directly responsible for a complex series of circumstances involving albumin metabolism, lipids, transport proteins, coagulation components, and immunologic pathways which ultimately give rise to the clinical features of the nephrotic syndrome. Even though renal function in patients with nephrotic syndrome may remain normal for years, the metabolic complications account for much of the morbidity and even mortality in these patients. Once regarded as a single disease entity, the nephrotic syndrome is now known to be the common end point of a variety of disease processes either systemic in nature or primary to the kidney. The fundamental abnormality in all cases of the nephrotic syndrome is the increased passage of plasma protein across the glomerular capillary wall.

Mechanisms of Glomerular Proteinuria

The capillary bed which comprises the glomerulus possesses unique structural and functional characteristics which allows unrestricted passage of water and small solutes but poses an extremely efficient barrier to the passage of plasma proteins. The principle factors which account for this permselectivity of the glomerulus are the size selective properties of the glomerulus, the charge selective properties of the glomerulus, and hemodynamic factors which act across the glomerulus.

The size selective properties of the glomerulus have primarily been determined by examining the clearance of molecules of varying size which are uncharged and are neither secreted or reabsorbed by the renal tubule. Dextran, a polymer of D-glucose pyranose, has most commonly been used for this purpose since it is available in varying sizes and is known to be non-toxic when infused intravenously. The clearance of a given size dextran molecule is typically expressed as a fractional clearance relative to a marker known to be freely permeable across the basement membrane such as inulin. A fractional clearance of one would indicate that the given size dextran is as freely permeable as inulin. As values decline and approach zero it would indicate progressive hindrance in the ability of the molecule to traverse the glomerular basement membrane.

An example of this approach is given in Figure 1 in which the fractional dextran clearance profile was determined in twenty healthy adult volunteers (1). Dextrans with a molecular radius of <20 angstroms demonstrate no measurable restriction in crossing the glomerular capillary wall as indicated by the fractional clearance of 1.0. With increasing size, however, there is a progressive

decline in the permeance of the dextran as reflected by the rapid decline in the fractional clearance value. There is virtually no excretion of dextran molecules once the molecular radius exceeds 60 angstroms. Similar results have been reported in the rat, dog, and rabbit (2-4). The exact ultrastructural component of the basement membrane which accounts for this size selective property is not clear but probably resides in the basement membrane itself or within the slit diaghram between adjacent podocytes (5).

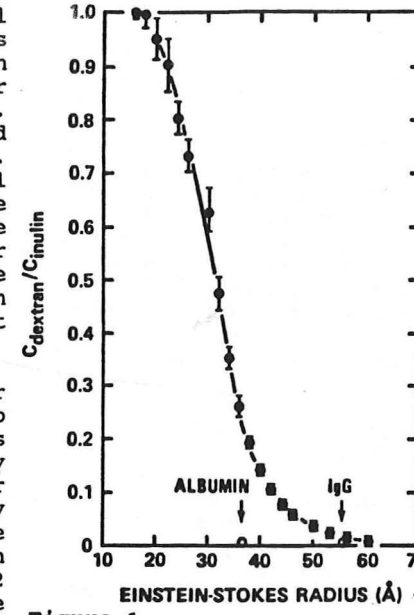

Figure 1

In addition to molecular size, molecular charge also influences the ability of solutes to cross the glomerular capillary wall. The importance of molecular charge was first appreciated by the observation that the clearance of albumin, a polyanion in physiologic solution, was some 2 orders of magnitude less than the clearance of a neutral dextran of similar size. Bohrer et al, tested the effects of molecular charge on the transglomerular passage of macromolecules by comparing the fractional clearance of neutral dextrans (solid circle) with that of dextrans affixed with either a negative (open circle) or positive charge (open triangle) (6-8). As shown in figure 2, for any given size dextran, the presence of a negative charge markedly decreases the fractional clearance of the molecule as compared to the uncharged specie. By contrast, the same sized molecule affixed with a positive charge demonstrates an increased fractional clearance. It is believed that the high density of fixed negative charges known to be present within the structures of the glomerular capillary wall provide an electrostatic barrier to circulating polyanions while facilitating the filtration of polycations (5). This would account for the finding that the filtration of albumin is restricted to a much greater extent than would be predicted from size considerations alone.

Hemodynamic factors also influence the transglomerular passage of proteins. For example, decreases in glomerular plasma flow have been shown to increase the fractional clearance of neutral dextrans. Under these conditions, the concentration of a relatively impermeant macromolecule rises along the length of the

glomerular capillary as water is removed by filtration. As the concentration rises, a more favorable diffusion gradient develops from the capillary lumen to Bowman's space. By contrast, under conditions of high plasma flow, the concentration of the relatively impermeant macromolecule tends not to rise such that a favorable diffusion gradient fails to develop. Such hemodynamic factors may account for the presence of transient or functional proteinuria which has been described in association with fever, exercise, or congestive heart failure (9).

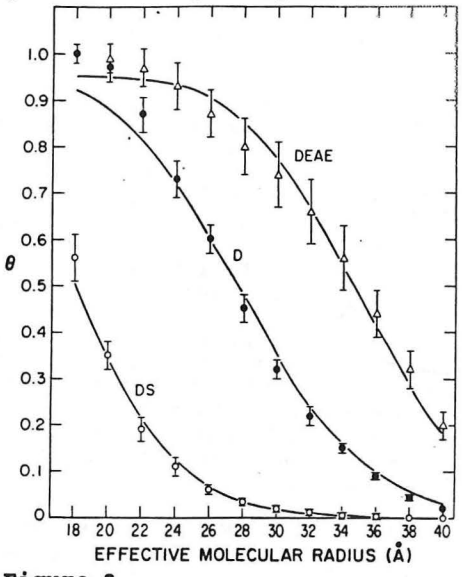

Figure 2

In these conditions a decrease in effective circulatory volume leads to a reduction in glomerular plasma flow. Despite the fall in glomerular plasma flow, the glomerular filtration rate is generally well preserved owing to an increase in intraglomerular pressure. Intraglomerular pressure is high under these conditions because of angiotensin II mediated constriction of the efferent arteriole. The increase in filtration fraction (glomerular filtration rate/glomerular plasma flow) which characterizes such states allows for the axial concentration of proteins along the length of the glomerular capillary to increase and thus provides a favorable concentration gradient for proteins to diffuse into the urinary space. As discussed below, the increase in circulating angiotensin II and increased intraglomerular pressure may also facilitate proteinuria by directly altering the porosity of the glomerular basement membrane.

To this point, a model that would best fit the dextran clearance data described above would predict that the normal glomerular capillary wall contains numerous identical cylindrical pores with a radius of approximately 55-60 angstroms. According to such a model, large proteins such as IgG (r=55 angstroms) would be unable to traverse the capillary wall by size constrains alone. Since the capillary wall is affixed with a large density of negative charges, small molecular weight proteins such as albumin (r=36 angstroms), which would be predicted to traverse the glomerular wall by size alone, are unable to cross the wall due to electrostatic repulsion. Based on this model, two factors could

theoretically account for the increased transglomerular passage of proteins in pathological states. First, there could be an increase in the total number of pores or an increase in the size of existing pores. Second, there could be loss of fixed negative charges such that the electrostatic barrier function was disrupted.

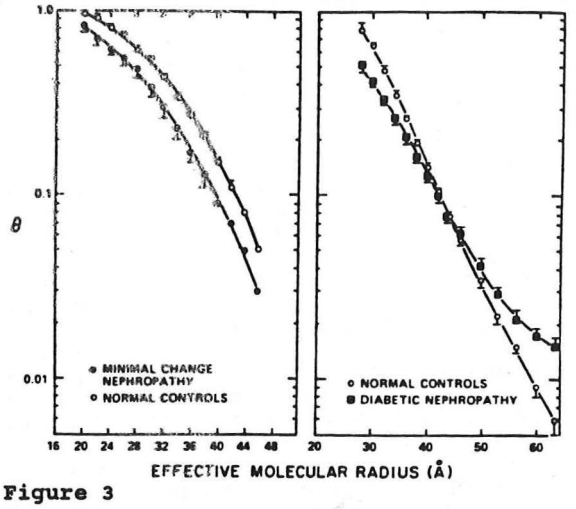

Figure 3

In an attempt to determine the extent to which the size and charge selective properties of the glomerulus are altered in disease states, dextran clearance studies have now been performed in patients with the nephrotic syndrome due to a variety of causes (10-12). In figure 3 (left), the fractional clearance profile of neutral dextrans in 10 adult patients with biopsy proven minimal change disease is compared to that in a group of 12 healthy controls. Despite the presence of massive proteinuria, the fractional clearance values were depressed below that found in the control group over the entire range of molecular sizes studied. This restriction in the transglomerular passage of dextrans is consistent with a reduction in the total number of pores and or a decrease in the mean pore size. To account for the increased transglomerular passage of albumin through pores of reduced number or size, a defect in the electrostatic barrier function must exist. In support of this possibility, biopsy specimens from 10 patients with minimal change disease demonstrated decreased uptake of a cationic stain consistent with a diminished glomerular content of polyanions (12). Thus, findings in minimal change disease would suggest that the glomerulus retains the ability to discriminate according to size but not molecular charge (13). The clinical correlate is the finding that these patients typically have a preponderance of albumin in the urine. The preservation of the size selective barrier largely excludes proteins which have a molecular radius of >60 angstroms such as IgG from entering Bowmans space. As a result, patients with minimal change disease are said to more commonly manifest selective proteinuria.

Similar studies have been performed in patients with nephrotic syndrome due to diabetic nephropathy, a disease in which the glomerular capillary architecture is more grossly distorted (10).

As shown in Figure 3 (right), the clearance of dextran molecules with relatively small molecular radii were depressed relative to the control patients similar to the findings in patients with minimal change disease. In contrast to patients with minimal change disease, however, the clearance of dextran molecules of larger size was elevated as compared to normal controls. In fact, this tendency for the fractional clearance to exceed control values became progressively magnified for dextrans with a molecular radii of >45 angstroms. These results are difficult to reconcile with the previous model in which the glomerular capillary wall is composed of a single population of pores of identical size. To account for the simultaneous occurrence of restricted passage of small molecules and enhanced passage of large molecules, Myers et al, has proposed a second model in which two population of pores exist (14). The largest part of the total glomerular membrane area is composed of normal pores which are either reduced in number or size and are responsible for the retention of dextrans with small molecular radii. The second population is small in total number but is composed of pores larger in size which are non-discriminatory and provide a shunt pathway for the dextrans of larger molecular radii to enter the urinary space. Presumably, this second population of large pores account for the 10 fold increase in IgG excretion measured in the diabetic patients as compared to patients with minimal change disease. In these diabetic patients, there is a loss in both the size and charge selective properties of the glomerular apparatus. Dextran clearance studies in other forms of glomerular disease in which the nephrotic syndrome is present seem to best fit with this later model in which two populations of pores exist (15,16).

Hypoalbuminemia

The determinants of plasma albumin concentration are the distribution of the body's albumin pool, albumin catabolism, hepatic albumin synthesis, and dietary protein intake. In addition to urinary loss, the hypoalbuminemia of the nephrotic syndrome involves some or are all of these homeostatic mechanisms.

Albumin Distribution- Under normal conditions approximately 50-70% of the total body albumin mass is located in the extravascular space, primarily in the interstitial space of muscle and skin (17). In nephrosis there is a mobilization of this extravascular pool into the intravascular space such that the extravascular pool is even more depleted than the intravascular albumin pool. As discussed in detail below, this redistribution of the body's albumin mass serves an important role in the initial defence against edema formation. Despite the redistribution of albumin into the intravascular space, continuous loss of albumin make this compensatory mechanism of limited utility in defending the serum albumin concentration.

Urinary loss of Albumin- In general, the greater the severity of

proteinuria, the lower the serum albumin concentration. There are patients, however, who manifest significant hypoalbuminemia even though urinary protein losses barely exceed what is considered by convention nephrotic range proteinuria (>3.5 gm/24 hours). Urinary loss of protein alone would not be predicted to result in hypoalbuminemia because the hepatic synthetic capacity for albumin should compensate for such losses. For example, patients who receive chronic ambulatory peritoneal dialysis sustain external losses of albumin in the dialysate which is equal in magnitude to urinary losses in many patients with nephrotic syndrome (6-8 gm/day) (18). As shown in figure 4, patients on CAPD generally maintain the serum albumin concentration about 1 gm/dl higher than patients with nephrotic syndrome despite comparable external albumin losses (19-21). In these patients, the hepatic synthetic rate presumably increases in proportion to the external loss such that the serum albumin concentration usually remains in the normal range. Since the liver normally synthesizes 12-14 gm of albumin daily and can increase this rate up to threefold when necessary, the development of hypoalbuminemia in nephrotic patients with relatively small amounts of urinary protein loss suggests either a blunted albumin synthetic rate or an increased rate of albumin catabolism.

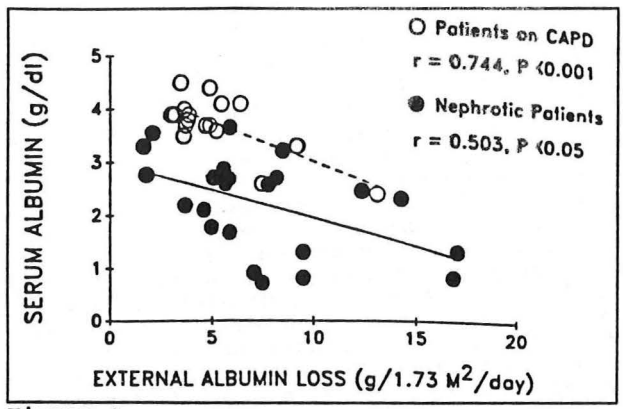

Figure 4

Albumin Catabolism- In other conditions characterized by hypoalbuminemia such as kwashiorkor, protein loosing enteropathy, and severe liver disease, both the absolute and fractional catabolic rate of albumin is reduced (17). In nephrotic patients the absolute catabolic rate of albumin is similarly decreased. By contrast, however, the fractional catabolic rate is increased in these patients and plays an important role in the maintenance of hypoalbuminemia (22,24). The primary site of this increased catabolism appears to reside in the kidney and, more specifically, results from tubular uptake and breakdown of filtered albumin.

Normally, the kidney is responsible for about 10% of total body albumin catabolism (24). Under conditions of increased glomerular permeability, large quantities of filtered albumin would

become subject to proximal tubular reabsorption and degradation. As a result, urinary albumin excretion would represent only a small fraction of the filtered load. In this regard, clearance studies in animals and humans with the nephrotic syndrome demonstrate that the amount of albumin filtered across the glomerular capillary membrane may exceed 50 grams per day (25,26). Since daily urine albumin excretion is typically much less in nephrotic patients, a considerable amount of filtered albumin may be catabolized within the renal tubules and therefore lost from the body pool. In fact, the kidney may be responsible for up to 50% of total body albumin catabolism in the nephrotic syndrome (24). A number of observations would support an important role for the kidney in the increased fractional catabolic rate of albumin. In rats with nephrotoxic serum nephritis, tubular absorption of albumin was found to be increased 10 fold in 50% of the animals (25). The demonstration of a dual transport system for albumin in the proximal tubule, one of which is described as low affinity but high capacity, would provide a mechanism for substantial albumin absorption and subsequent degradation (27). Morphologic studies in rats made nephrotic have demonstrated protein reabsorptive droplets containing albumin and globulin in proximal and distal tubular cells (28). In addition, lysozomal enzyme activity increases in tubular cells in response to increasing protein loads (29). Thus, urinary loss as well as increased fractional albumin metabolism contribute to the hypoalbuminemia of the nephrotic syndrome. The renal catabolism of proteins can account for some patients who demonstrate striking decreases in the serum albumin concentration and yet have levels of proteinuria which barely exceed the nephrotic range.

Hepatic Albumin Synthesis- As mentioned previously, the liver normally produces 12-14 grams of albumin per day but has the capacity to increase this production 2-3 fold. While hepatic albumin synthesis is generally increased in the nephrotic state, the response is inadequate for the degree of hypoalbuminemia present in most patients. This blunted response is depicted in figure 5 which shows the relationship between the rate of albumin synthesis

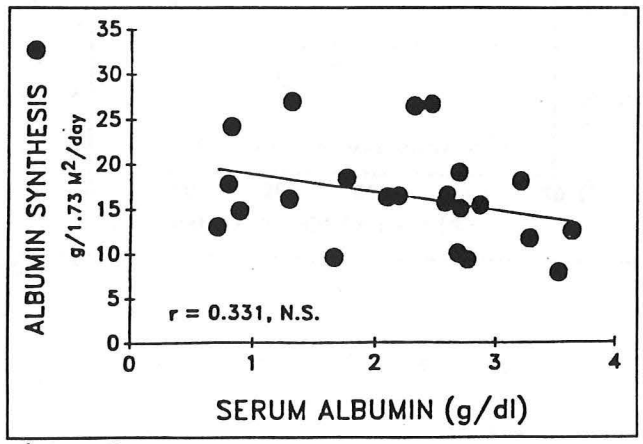

Figure 5

and the serum albumin concentration in a group of nephrotic patients (17). While the rate of albumin synthesis is increased in some patients, in others, the rate is decreased and overall, the synthetic rate bears no clear relationship to serum albumin concentration. One factor which may contribute to the impairment in hepatic albumin synthesis is the level of dietary protein intake. In this regard, increasing dietary protein intake has been shown to increase the rate of albumin synthesis in animals and humans with the nephrotic syndrome (20,30,31). Based on these results one would anticipate that increased protein intake should have a beneficial effect on albumin stores. Figure 6 shows the effect of increasing amounts of dietary protein on albumin synthetic rate, serum albumin concentration, and albumin catabolic rate in a rat model of nephrosis (32). In these animals, the albumin synthetic rate increased in parallel with increasing amounts of

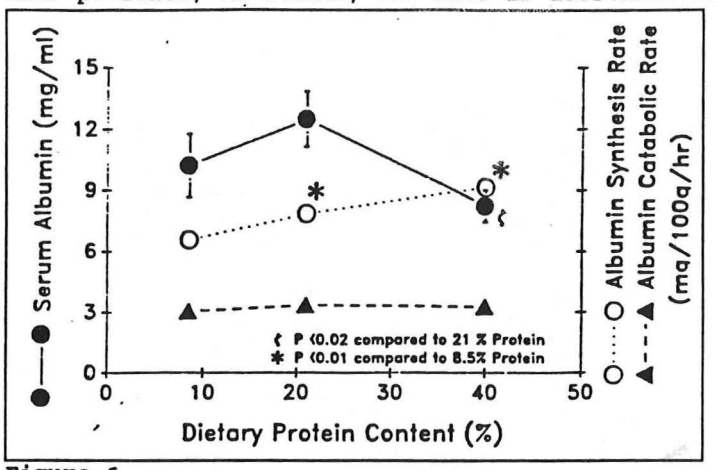

Figure 6

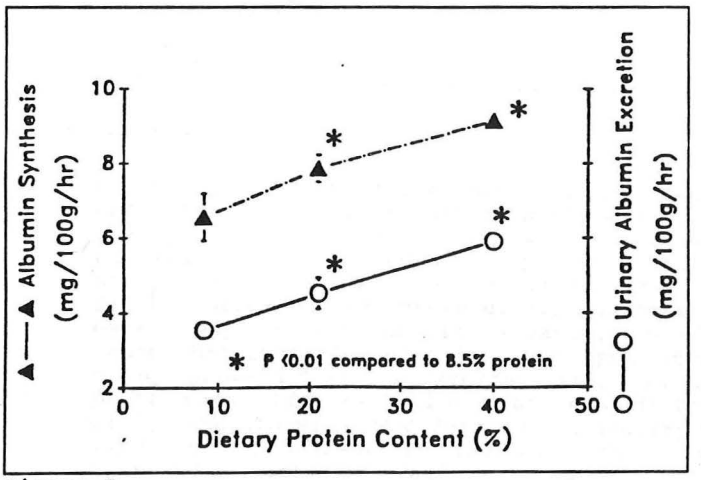

Figure 7

protein intake. Interestingly, the serum albumin concentration increased slightly in animals fed the 21% protein diet but decreased significantly in animals fed the 40% protein diet. The rate of albumin catabolism could not explain the fall in serum albumin concentration as it remained constant at all levels of protein intake. One factor which appears to have contributed to the decrease in serum albumin concentration at the higher protein diet is an increase in urinary albumin excretion. As shown in figure 7, while the rate of albumin synthesis increased with each increment in dietary protein, there was, in fact, a matching increase in urinary albumin excretion. A similar effect of increased dietary protein leading to an increase in urinary protein excretion has also been demonstrated in studies of nephrotic patients (33). As shown in figure 8, when dietary protein intake is changed from 0.8 gm/Kg/day to 1.6 gm/Kg/day, the rate of albumin synthesis increases but so does urinary albumin excretion. In addition, the fractional rate of albumin catabolism increases during the period of dietary protein supplementation. The net effect on the serum albumin concentration was a slight decrease. Conversely, patients changed from the high protein to the low protein diet exhibited a decrease in urinary protein excretion. Even though the albumin synthetic rate fell in this group the net effect on the serum albumin concentration was a slight increase. Rosenberg et al., performed a randomized, cross-over study in patients with a variety of glomerular diseases and found that ingestion of a low (0.55 gm protein/kg/day) compared to a high protein diet (2 gm/kg/day) resulted in a decrease in 24 hour protein excretion as well as a decrease in the fractional clearance of IgG and albumin. The decrease in dietary protein was associated with an improvement in the size selective properties of the glomerular capillary wall as evidenced by a significantly lower fractional clearance of larger sized dextrans (34).

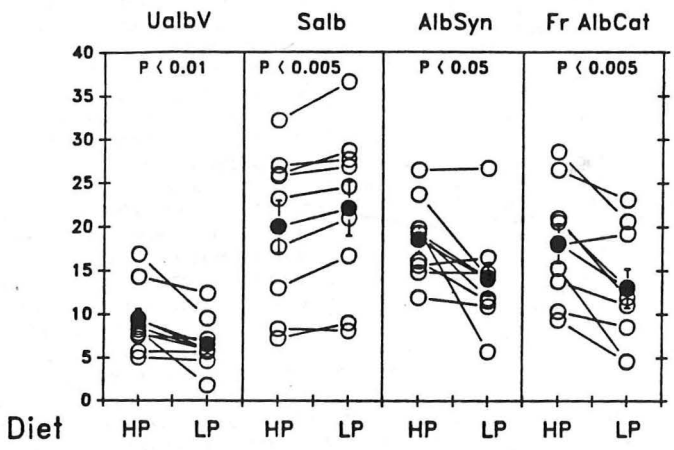

Figure 8

Edema Formation

The development of edema is one of the cardinal features of the nephrotic syndrome. The mechanism of its formation is not entirely understood. The classical view of edema formation in the nephrotic syndrome describes the process as an underfill mechanism (Figure 9). According to this theory, urinary loss of protein results in hypoalbuminemia and decreased plasma oncotic pressure. As a result, plasma water translocates from the intravascular space into the interstitial space. When the magnitude of this transudation is sufficiently great, clinically detectable edema develops. Reduction in intravascular volume elicits activation of effector mechanisms that signal renal salt and water retention in an attempt to restore plasma volume. The renal response leads to further dilution of plasma protein concentration thereby exaggerating the already reduced plasma oncotic pressure and further enhancing edema formation. In order for this formulation of edema genesis to be true, three critical predictions must be satisfied: 1) blood and plasma volume must be reduced during accumulation of edema; 2) measurement of neurohumoral effectors should reflect activation consequent to contraction of EABV; 3) maneuvers that increase plasma volume into the normal range should result in a natriuretic response. As discussed below, these predictions are satisfied in some patients, especially those with minimal-change nephrotic syndrome, whereas the majority of nephrotic patients fail to conform to this conceptual model.

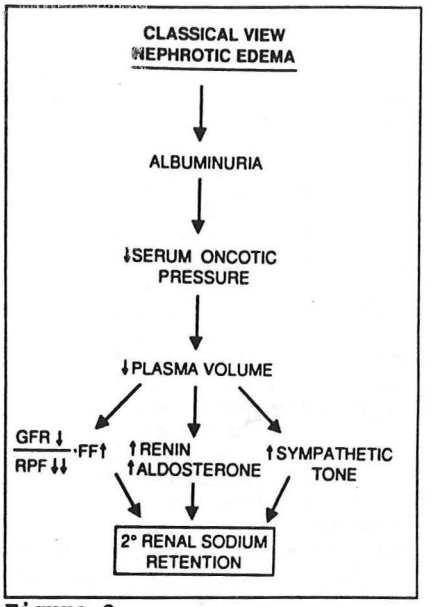

Figure 9

Blood and Plasma volume in the Nephrotic Syndrome

The classical view of edema formation assigns a pivotal role to decreased plasma volume serving as the afferent mechanism signalling renal salt and water retention. When measured directly plasma volume has indeed been low in a variable proportion of patients with nephrotic syndrome (35-37). Moreover, profound reductions in plasma volume leading to acute oliguric renal failure and hypovolemic shock has been reported (38,39).

Other studies, however, have failed to find a consistent reduction in blood and plasma volume in patients with nephrotic syndrome (40-43). In a survey of 10 studies, plasma volume measurements were analyzed in 217 nephrotic patients (44). In only one third of patients was plasma volume reduced whereas it was normal in 42 per cent and increased in 25 per cent. It has been suggested that conflicting measurements of plasma volume in patients with nephrotic syndrome can be reconciled by separating patients according to histologic class (45). In this regard, 4 patients with minimal change disease and normal creatinine clearance were found to have decreased plasma volume and elevated plasma renin activity and aldosterone levels. This group was compared to five patients with membranous or membranoproliferative lesions who had reduced creatinine clearances, normal or increased plasma volume and suppressed plasma renin activity. The authors concluded that edema formation in the latter group resulted from primary renal sodium retention while decreased effective circulatory volume and resultant secondary renal salt retention was the pathophysiologic mechanism of edema formation in those with minimal change disease. Other studies have failed to find such a correlation between histology and plasma volume measurements. In 10 patients with minimal change disease increased plasma volume was found prior to initiation of treatment (44). Following steroid induced remission both plasma volume and blood pressure fell accompanied by increases in plasma renin activity (114). Using plasma volume and plasma renin activity as indices of arterial filling, an underfill mechanism of edema formation would seem unlikely. Geers et al., studied 88 patients with the nephrotic syndrome in which 35 patients had minimal change disease as the underlying histologic diagnosis. As shown in figure 10, virtually all of the patients had either normal or increased plasma and blood volume (46).

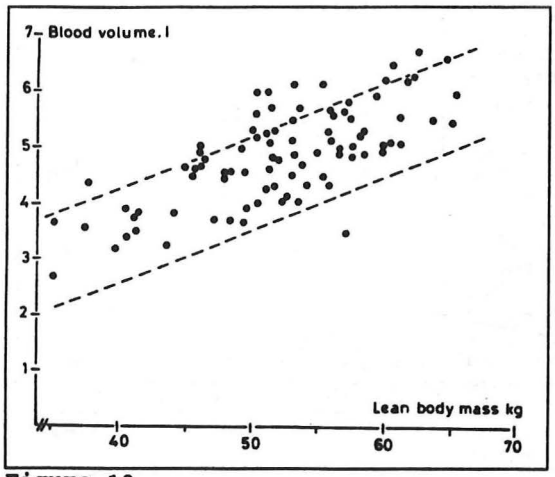

Figure 10

Neurohumoral Markers of Effective Circulatory Volume

Measurements of plasma renin activity and aldosterone

concentration have been utilized as a method to indirectly differentiate primary sodium retention from an underfill mechanism of edema formation in nephrotic patients. Elevated values would be expected if blood volume was decreased while suppressed values would occur in the setting of primary renal sodium retention and blood volume expansion. Plasma renin activity values collated from nine studies were normal or low in 64 of 123 patients investigated (47). Plasma aldosterone levels were also decreased in the majority of these patients. When measured with respect to salt intake or urinary sodium excretion no consistent relationship is found (48). While some studies have found elevated plasma renin activity and aldosterone concentrations in patients with minimal change diseases others have not (45,49). Geers et al., examined plasma renin activity with respect to blood volume and found no relationship in either patients with minimal change disease (open circles) or those with histologic lesions on light microscopy (solid circles) (Figure 11) (42). Although a higher proportion of patients with minimal change disease have elevated plasma renin and aldosterone levels as compared to those with histologic glomerular lesions these values tend to overlap (42). Moreover, blood volume, plasma volume, and filtration fraction are no different in patients with minimal change disease as compared to those with histologic lesions (42,49). Thus, measurement of various elements of the renin-angiotensin-aldosterone axis do not provide clear support for an underfill mechanism mediating renal sodium retention in nephrotic syndrome. It has been suggested that low plasma renin activity in some patients results from deficiency of substrate (50) although normal or increased substrate levels have been reported in nephrotic syndrome (51). A more likely explanation for the variable renin-aldosterone profiles in nephrotic syndrome is that renin release is inappropriate and influenced by intrarenal rather than systemic perturbations.

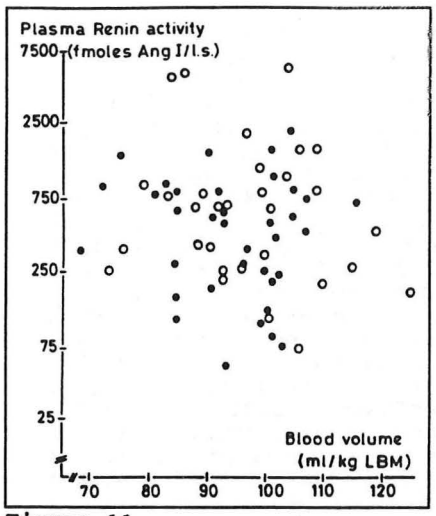

Figure 11

Effects of Manipulations

Another way which has been used to investigate the pathogenesis of sodium retention in the nephrotic syndrome is to examine renal sodium handling and hormonal indices of effective circulatory volume in response to expansion of the intravascular

blood volume. This has been primarily achieved by infusing albumin or expanding central blood volume by head-out body water immersion (HWI). The classical view of nephrotic edema would predict that expansion of the intravascular volume should correct renal salt and water retention. In children with minimal change disease, volume expansion induced by infusion of albumin was associated with significant declines in levels of plasma renin activity, AVP, aldosterone, and catecholamines (52,53). In addition, there was a significant increase in the glomerular filtration rate, urine flow, and sodium excretion. In a less homogenous group of adult patients with nephrotic syndrome, blood volumes were found to be low when expressed per kilogram wet weight (54). Plasma ADH was inversely correlated with blood volume and failed to decrease in response to a water load. When blood volume was expanded with 20% albumin, plasma levels of ADH fell accompanied by an augmented water diuresis. It was concluded that a contracted blood volume was responsible for the nonosmotic release of AVP. By contrast, other studies have found either no or only a minimal increase in urinary sodium excretion in response to infusion of hyperoncotic albumin (55). Studies utilizing HWI to expand blood volume have likewise produced conflicting results. Expansion of central blood volume by HWI in children with minimal change disease resulted in decreased levels of AVP, aldosterone, noradrenaline and plasma renin activity (52,56). These changes were accompanied by significant increases in urine flow and sodium excretion. Similarly, adult patients with a variety of histologic lesions subjected to HWI were found to have significant increases in urinary sodium excretion (57,58). By contrast. a more recent study in 10 patients with a variety of underlying glomerular diseases found only a blunted natriuretic response to HWI (59). While ANP levels rose to the same extent in control and nephrotic subjects, peak urinary sodium excretion and urine flow were one third that in the control group.

Table I. Arguments For 1° Sodium Retention

1. Blood volume normal or increased
2. Blood pressure often increased
3. Renin activity and aldosterone not ↑
4. Onset of natriuresis during recovery precedes rise in plasma protein
5. Sodium excretion modest in response to HWI or albumin infusion
6. Filtration fraction ↓
7. Sodium retention in unilateral nephrosis model only in diseased kidney

Several other experimental studies question the pivotal role assigned to hypoalbuminemia and reduced plasma oncotic pressure in the initiation of edema formation. For example, reducing plasma protein concentration in man (60) or experimental animals (61) with

plasmapheresis results in either no change or actually increases plasma volume. Moreover, patients with congenital analbuminemia do not necessarily develop edema (62).

In summary, available data would argue against a contracted plasma volume as the afferent mechanism initiating sodium retention in all patients with nephrotic syndrome. Rather some component of primary renal sodium retention appears to be operative in nephrotic syndrome with histologic glomerular lesions as well as in minimal change disease. Although children with minimal change nephrotic syndrome more often have low blood volume and increased renin-aldosterone profiles, coexistence of a primary impairment in renal sodium excretion cannot be excluded. In this regard, the natriuresis seen in patients recovering from minimal change disease occurs concurrently with a rise in filtration fraction (63). Furthermore, salt retention may resolve without improvement in hypoproteinemia (64). Even the natriuresis and correction of the neurohumoral counterregulatory profile afforded by HWI and albumin infusions may have resulted from central blood volume expansion sufficient to overcome a primary salt retaining state. Alternatively, both primary salt retention and an underfill mechanisms of edema formation may coexist in the same patient. For example, in the earliest stages of a glomerular disease salt retention by the kidney may be primary in origin. As hypoalbuminemia develops and becomes progressively severe, plasma volume may fall and result in an element of superimposed secondary salt retention. The coexistence of these two mechanisms may account for the lack of uniformity in hemodynamic as well as hormonal and neurocirculatory profiles in patients with the nephrotic syndrome.

Peripheral Capillary Mechanisms of Edema Formation

The presence of normal or increased plasma volume and the poor correlation between serum albumin concentration and the presence of clinically detectable edema are findings which argue against the classical view of edema formation in the nephrotic syndrome. These features can best be explained by examining the alterations which are known to occur in transcapillary exchange mechanisms in the setting of hypoproteinemia.

Table II. Edema Preventing Factors

1.	↑ Interstitial hydrostatic pressure
2.	↑ Lymph flow
3.	↓ Interstitial oncotic pressure
4.	↓ Permeability of capillary

Fluid movement within the capillary bed between intravascular and interstitial spaces is determined by the balance of Starling

forces between these two compartments:

$$J_v = K_f[(P_c - P_i) - (\pi_c - \pi_i)]$$

where J_v is fluid flux along the length of a capillary, K_f is the ultrafiltration coefficient, Pc is capillary hydrostatic pressure, P_i is interstitial hydrostatic pressure, π_c is capillary oncotic pressure, and π_i is interstitial oncotic pressure. On the arterial side of the capillary net hydrostatic pressure $P_c - P_i$ (ΔP) exceeds net colloid osmotic pressure ($\Delta\pi$) $\pi_c - \pi_i$ resulting in net filtration of fluid into the interstitial space. Due to an axial fall in capillary hydrostatic pressure, the balance of Starling forces at the venous end of the capillary ($\Delta\pi > \Delta p$) favor net reabsorption of fluid. In some tissues net hydrostatic pressure exceeds opposing net colloid osmotic pressure throughout the length of the capillary such that filtration occurs along its entire length (65). Net ultrafiltrate is returned to the circulation via lymphatic flow such that in steady state conditions total body capillary flux is equal to lymph flow; interstitial and intravascular volume remain stable and edema formation does not occur (66).

Absence of compensatory mechanisms would predict small changes in ΔP, $\Delta\pi$, or K_f to increase fluid transudation and result in clinically detectable edema. However, the poor correlation between plasma albumin concentration and edema formation suggest counterregulatory adjustments do occur in those forces that govern fluid exchange between the intravascular and interstitial space. One such factor relates to compliance characteristics of the interstitium (67). Under normal circumstances interstitial pressure ranges from -6 mmHg to 0 mmHg. Due to the noncompliant nature of this compartment small increases in interstitial volume result in large increases in interstitial pressure. Such increases in Pi act to oppose further transudation of fluid. In addition, increased interstitial pressure leads to a second factor that tends to prevent formation of edema, increase lymphatic flow. Lymph flow can increase many fold under conditions of augmented net capillary fluid filtration (66). In patients with edema resulting from heart failure or nephrosis, the disappearance rate of a subcutaneous injection of ^{131}I-albumin is markedly enhanced consistent with increased lymphatic flow (Figure 12) (68). A third factor which minimizes fluid filtration is reduction in interstitial oncotic pressure (69). Since transcapillary fluid flux consists primarily of a protein-free ultrafiltrate, interstitial protein concentration tends to become diluted. Moreover, increased lymphatic flow removes fluid and protein from the interstitial space and returns both to the

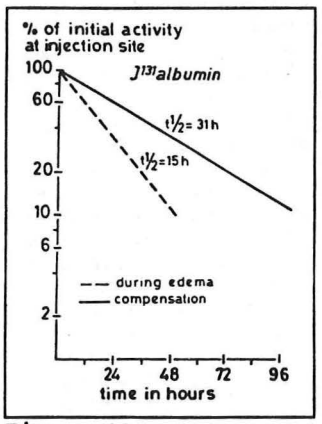

Figure 12

vascular compartment thereby further reducing interstitial oncotic pressure. A reduction in π_i serves to increase net colloid osmotic pressure between the capillary and interstitium favoring a reduction in capillary filtration. Finally, intrinsic permeability of the capillary may decrease under conditions of hypoalbuminemia further mitigating any fall in π_c along the capillary length (70). Thus, increased interstitial hydrostatic pressure, accelerated lymphatic flow, decreased interstitial oncotic pressure, and decreased albumin permeability all serve as the initial defense to formation of edema.

In normal humans plasma colloid oncotic pressure (COP) is about 24 mmHg and interstitial COP is about 12 mmHg creating a transcapillary COP gradient of about 12 mmHg (24). In the nephrotic syndrome COP of interstitial fluid falls in parallel with COP of plasma as hypoalbuminemia develops (71-74). This relationship is depicted in figure 13 in which plasma and tissue colloid osmotic pressure were found to decrease in parallel in rats with progressive hypoproteinemia (69). Patients studied both in remission and in relapse demonstrate almost equivalent changes in COP of plasma and interstitium at all levels of serum albumin (72). The maintenance of net COP within the normal range mitigates the potential driving force for transudation of fluid into the interstitial space. In consequence, blood volume is maintained and edema formation is avoided during early stages of nephrotic syndrome. Although net fluid filtration is increased, augmented lymph flow triggered by a rise in interstitial hydrostatic pressure returns fluid to the vascular compartment. Body albumin pools are redistributed such that a greater fraction than normal is located in the vascular compartment (24). Thus, a new equilibrium is established with only minimal increase in tissue fluid. The consequence of this new steady state is that defense mechanisms against edema formation are at their limit. Any further increase in net filtration pressure, as would occur with ongoing primary renal salt retention, will eventually overwhelm these defenses and result in fluid accumulation and edema formation. Similarly, a fall in plasma COP below 10-12 mmHg will also exhaust edema preventing factors. In this setting, the transcapillary COP gradient falls and fluid moves into and accumulates within the interstitial space.

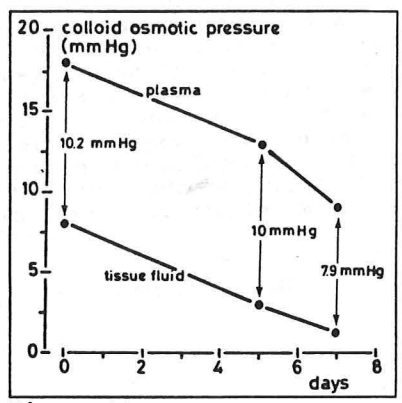

Figure 13

In summary, the reduction in serum oncotic pressure which accompanies the nephrotic syndrome would be predicted to alter Starling forces in a direction favoring net flux of fluid across the capillary bed. Despite this alteration, however, fluid tends not to accumulate within the interstitium because of increased lymphatic flow. In addition, the effect of decreased serum oncotic pressure is opposed by the parallel decline in interstitial oncotic pressure as well as an increase in interstitial hydrostatic pressure. If, however, the kidney begins to retain sodium in an unrelenting fashion, clinically apparent edema may become evident. This occurs because salt retention leads to an increase in capillary hydrostatic pressure at the very time those defense mechanisms normally employed to prevent edema have been maximized. Thus, edema formation in the nephrotic syndrome results from the combined effects of primary salt retention coupled with reduced defenses against edema.

EDEMA FORMATION IN THE NEPHROTIC SYNDROME

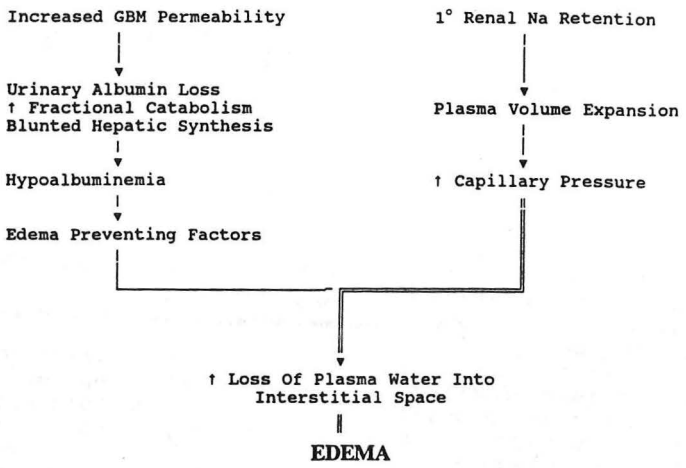

Figure 14 compares the change in mean arterial pressure and blood volume between nephrotic patients with hypoalbuminemia and chronic renal failure patients with normoalbuminemia as a function of varying extracellular fluid volume (75). In the hypoalbuminemic patients with the nephrotic syndrome, expansion of the extracellular fluid volume leads to immediate translocation of fluid into the extravascular space as evidenced by little change in mean arterial pressure or blood volume. Presumably, those factors which serve to prevent edema were already maximized and were overwhelmed by increases in capillary hydrostatic pressure which

occurred as the extracellular fluid volume expanded. By contrast, the patients with chronic renal failure, who were normoalbuminemic, developed an increase in mean arterial pressure and blood volume as extracellular fluid volume expanded. In these patients, fluid was retained in the vascular tree despite the increase in capillary hydrostatic pressure due to initial activation of edema preventing factors. At some point of extracellular fluid volume expansion, these factors would also become overwhelmed and these patients would then begin to develop clinically detectable edema.

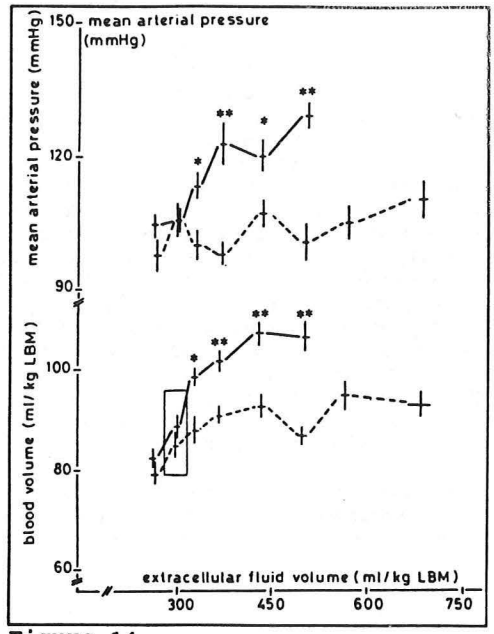

Figure 14

TREATMENT

The primary goal of therapy in the nephrotic syndrome is to treat the underlying disease process. In many instances the underlying pathologic process is either poorly or not at all responsive to available therapy. In these cases one has to direct therapy towards alleviating the manifestations of the nephrotic syndrome. Central in this goal is instituting therapy which decreases the degree of proteinuria.

Table III. Treatment of nephrotic edema

1. Immunosuppressive agents
2. Hypertensive agents (ACE inhib.)
3. Protein restriction
4. Nonsteroidal Agents (NSAIDS)
5. Nephrectomy
6. Diuretics

Angiotensin Converting Enzyme Inhibitors

In experimental models and in humans with the nephrotic syndrome, administration of angiotensin converting enzyme inhibitors have been shown to reduce the magnitude of proteinuria. Taguma et al., found that administration of captopril resulted in significant declines in protein excretion in a group of azotemic patients with diabetes (76). The decline in proteinuria was significant within two weeks of captopril administration and occurred without a change in blood pressure. A similar beneficial effect of angiotensin converting enzyme inhibitors has been seen in patients with other forms of glomerular diseases (77). In many of these diseases, solute clearance studies have indicated that the mechanism of proteinuria, in part, results from a disturbance in the normal size selective properties of the glomerular basement membrane. As discussed previously, increased transglomerular passage of protein appears to result from the shunting of protein through a population of pores which are small in number but large in size and are characterized by their failure to discriminate among solutes of larger size.

The converting enzyme inhibitors may be more effective than other antihypertensive regimens in reducing clinical proteinuria. In this regard, Heeg et al., compared the antiproteinuric effect of conventional antihypertensive agents with that of lisinopril in a group of patients with proteinuria from a variety of underlying renal diseases (77). Despite similar reductions in blood pressure after 8 weeks of therapy, only the patients treated with the angiotensin converting enzyme inhibitor exhibited significant declines in the amount of protein excretion (Figure 15).

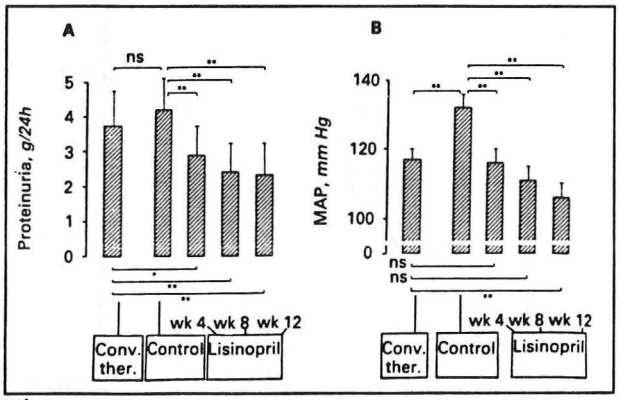

Figure 15

The beneficial effect observed with angiotensin converting enzyme inhibitors suggests that angiotensin II mediated effects may in some way be contributing to the permselective defect present in proteinuric states. In experimental models, infusion of angiotensin II selectively enhances the transglomerular transport

of dextrans of intermediate and large size (78). A similar effect is seen when endogenous angiotensin II production is increased by renal vein constriction (79). In this latter model, increased glomerular passage of large dextrans could be prevented by administration of an angiotensin II antagonist. Thus, an activated renin-angiotensin system appears to expand the shunt-like component of the glomerular basement membrane by shifting glomerular pores toward larger size. The mechanism by which angiotensin II leads to increased glomerular leakage of solutes may be related to the development of increased intraglomerular pressure as a result of preferential constriction of the efferent arteriole (78). The increased intraglomerular pressure may, in turn, lead to stretching of intercellular junctions or even partial detachment of cellular elements both of which could provide a reversible size selective defect. Alternatively, angiotensin converting enzyme inhibitors may affect the barrier function of the membrane directly (80). In this regard. angiotensin II receptors are known to be present on mesangial cells within the glomerulus. These cells are intimately associated with the glomerular capillary network and contain intracellular filaments which contract in the presence of angiotensin II. By stimulating these cells to contract, angiotensin II may cause conformational changes in the epithelial foot processes and perhaps changes in the slit-pore junction which account for the emergence of the shunt pathway. In either case, angiotensin converting enzyme inhibitors appear effective in restoring the size selective properties of the glomerulus toward normal such that the fraction of glomerular filtrate which was passing through the non-selective pathway is redirected through the normal population of pores.

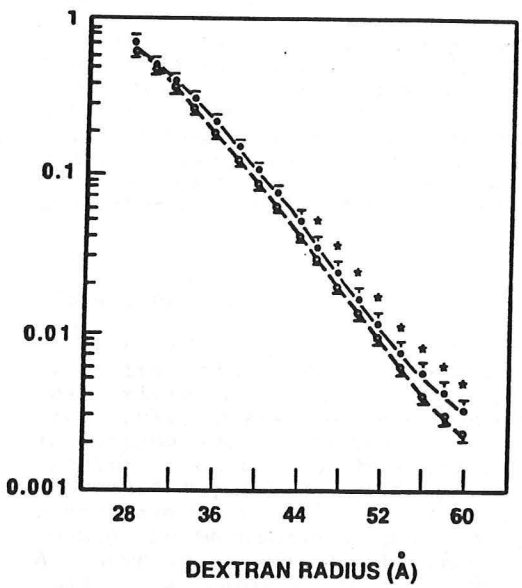

Figure 16

The effect of angiotensin converting enzyme inhibitors to enhance barrier size selectivity was recently demonstrated in a group of diabetic patients in whom dextran clearance studies were performed (82). In these

patients, administration of enalapril for 90 days significantly reduced total protein excretion and decreased the fractional clearance of albumin and IgG. Dextran clearance profiles showed a significant decline in the fractional clearance of solutes of larger size (46-60 Angstroms) (open circles). After a thirty day washout period, the beneficial effect of enalapril to lower the transglomerular dextran transport was entirely dissipated (Figure 16) (closed circles).

The effect of angiotensin converting enzyme inhibitors to reduce urinary protein excretion can be utilized to increase total body albumin stores. As discussed previously, the beneficial effect of a high protein diet to increase albumin synthesis is counterbalanced by increased proteinuria such that serum albumin concentration is not changed. Nephrotic rats fed a 21% protein diet who simultaneously were treated with either enalapril or captopril demonstrated significant decreases in urinary albumin excretion as well as a significant increase in the serum albumin concentration (83). By decreasing the amount of proteinuria, the beneficial effect of a high protein diet in increasing hepatic synthesis of albumin could become fully manifest. By contrast, control animals fed the same diet but not given an angiotensin converting enzyme showed no change in the serum albumin concentration.

The reduction in proteinuria achieved with angiotensin converting enzyme inhibitors has also been shown to attenuate the development of hyperlipidemia in the nephrotic syndrome. In nephrotic rats with Heymann nephritis fed a 40% protein diet, the serum cholesterol is increased approximately 100% as compared to control animals fed a 8.5% protein diet. If these animals are then given enalapril to reduce the amount of proteinuria, the serum cholesterol is reduced to control values.

Dietary Protein

In the past, patients with nephrotic syndrome were routinely prescribed high protein diets in an attempt to prevent protein malnutrition resulting from urinary protein losses. As discussed previously, diets high in protein have not been beneficial in increasing serum protein levels primarily because they provoke greater amounts of proteinuria negating the beneficial effect of increased hepatic albumin synthesis. By contrast, low protein diets have been shown in both experimental and clinical studies to reduce the magnitude of proteinuria in nephrotic states (85,86). As shown in figure 17, the institution of a low protein diet can lead to favorable effects on the size selective properties of the glomerular basement membrane as reflected by a decrease in the fractional clearance of large neutral dextrans (34).

The beneficial effect of a low protein diet is not related to changes in glomerular filtration rate and hence filtered load of protein. Rather, the clinical effect is similar to that observed with angiotensin converting enzyme inhibitors and suggests that these two maneuvers may share a common mechanism. In this regard, a low protein diet is associated with a decrease in plasma renin activity as well as decreased expression of the renin gene (87,88). Thus, a decrease in angiotensin II levels may underlie the antiproteinuric effects of both a low protein diet and converting enzyme inhibitors.

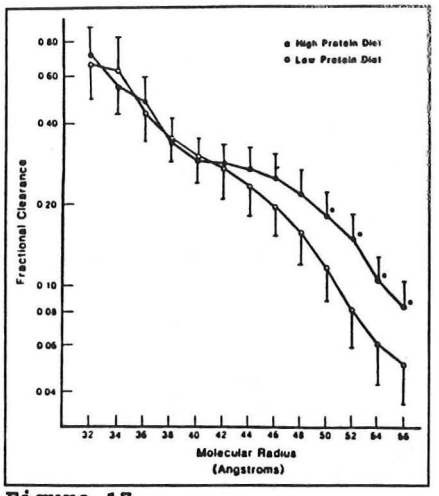

Figure 17

In support of this possibility, it has been shown that in rats with subtotal nephrectomy, acute blockade of the renin-angiotensin system reduces proteinuria only in animals ingesting a high protein diet (89,90). Similarly, in rats with immune complex nephropathy, administration of an angiotensin converting enzyme inhibitor reduced proteinuria only in the setting of a high protein intake and had no effect in animals fed a low protein diet (91). Finally, preliminary clinical findings in transplant patients suffering from chronic rejection have shown a greater antiproteinuric effect with angiotensin converting enzyme inhibitors in the setting of a high protein intake (92).

Based on these findings, a reasonable dietary protein intake for nephrotic patients is one containing 0.8 gm/kg/day. The protein should be of high biologic value. Once prescribed, careful attention should be taken to monitor the adequacy of nutrition by following parameters such as serum albumin, transferrin, and skin fold thickness.

Nonsteroidal Antiinflamatory Drugs

Nonsteroidal antiinflamatory agents have been found capable of reducing proteinuria in a variety of glomerular diseases (93). Unlike a low protein diet and angiotensin converting enzyme inhibitors, the reduction in proteinuria with nonsteroidal antiinflammatory agents is associated with a fall in the glomerular filtration rate. As a result these agents should only be used in

patients with intractable proteinuria who have failed to respond adequately to the other conservative forms of therapy. In some cases, the fall in the glomerular filtration rate can be dramatic resulting in acute renal failure.

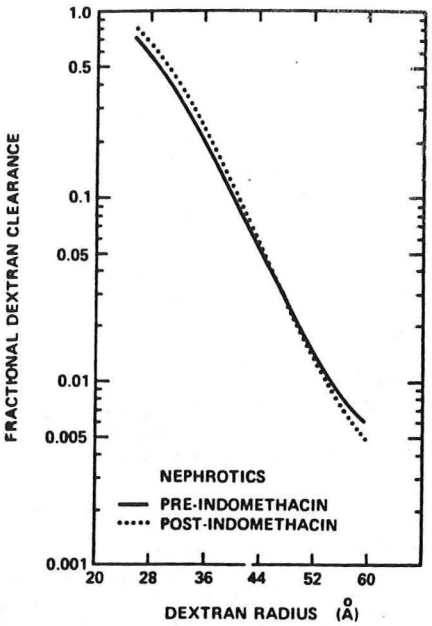

Figure 18

The mechanism by which these agents reduce proteinuria is multifactorial. The fall in glomerular filtration rate that accompanies the use of these agents can account for some of the antiproteinuric effect simply as a result of the decrease in filtered load. In addition, there is evidence to suggest that these agents decrease the amount of proteinuria by directly improving the intrinsic selectivity of the glomerular capillary wall. In support, clearance studies in nephrotic patients after treatment with indomethacin revealed a selective decline in the fractional clearance of solutes with a molecular radius of >50 angstroms (94). Similarly, Golbetz et al., examined the fractional clearance of uncharged dextrans in a group of nephrotic patients after treatment with indomethacin (95). In this study, the fractional clearance of dextrans 28-44 angstroms was increased whereas that of dextrans 50-60 angstroms was decreased (Figure 18). Thus, nonsteroidal antiinflammatory drugs are capable of decreasing proteinuria by restoring the barrier size selectivity of the glomerular basement membrane. The clinical usefulness of these agents, however, is limited by the tendency to decrease the glomerular filtration rate.

Nephrectomy

The most radical approach to eliminate proteinuria is surgical nephrectomy or destruction of remaining functional renal tissue. This form of therapy is reserved for those patients with significant renal failure in whom proteinuria continues in massive amounts and in whom the extrarenal manifestations of the nephrotic syndrome are incapacitating. For example, patients with end stage renal failure from amyloidosis or focal segmental

glomerulosclerosis may continue to exhibit severe and persistent proteinuria with resultant hypoalbuminemia. In turn, the low oncotic pressure may lead to loss of fluid from the intravascular space and result in life-threatening hypotension.

Measures which have been used to treat such patients have included bilateral surgical nephrectomy, gel-foam embolization of the kidneys, and renal ablation with stainless steel coils (96,98). A less invasive approach which has been reported effective is to achieve a medical nephrectomy by administering a nephrotoxic agent such as a mercurial salt (99). As shown in figure 13, infusion of sodium mercaptomerin has been used in an effective manner to decrease urinary protein excretion and increase serum protein concentration in severely nephrotic patients.

Diuretic Therapy

The initial approach to treating edema in the nephrotic syndrome is the institution of dietary salt and fluid restriction. The majority of patients, however, will ultimately require the institution of diuretic therapy to manage edema formation and prevent volume overload. In order to achieve a clinical response, many patients require large doses of loop diuretics even when the glomerular filtration rate is well preserved. The mechanism of the blunted response to loop diuretics which is frequently observed in patients with nephrotic patients is unknown.

Furosemide is one of the most commonly used diuretics in these patients and circulates 98% bound to albumin. The volume of distribution and clearance of total furosemide is inversely related to the serum albumin concentration. Based on studies in rats with analbuminemia, Inoue et al., suggested that the increased volume of distribution for furosemide caused decreased circulating levels of the drug and therefore limited the amount of drug reaching the renal tubule (100). In this same study, he described four patients who exhibited resistance to a single oral dose of furosemide but responded when given an

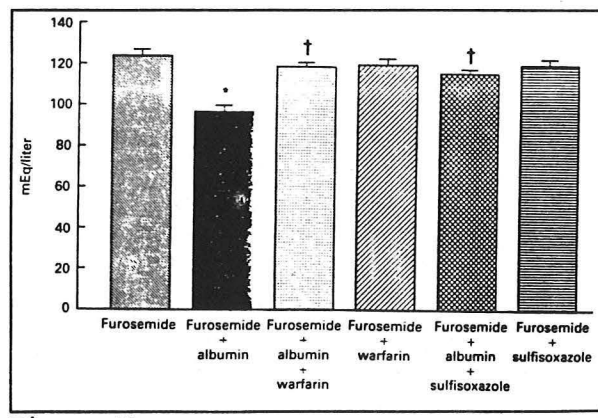

Figure 19

equivalent dose (30mg) that was complexed to albumin (6gm) and given intravenously.

Such a pharmacokinetic mechanism does not appear to account for resistance seen in the majority of humans with nephrotic syndrome since the total amount of diuretic delivered into the urine and its time course are identical in nephrotic and normal subjects (101). Given these findings, it has been suggested that diuretic resistance in the nephrotic syndrome is primarily due to a reduced ability of the renal tubule to respond to furosemide.

The mechanism of this blunted tubular response is unknown but may be related to the albuminuria present within the real tubule. In rats made nephrotic with puromycin aminonucleoside, Green and Merkin et al., found that 60-95% of furosemide excreted in the urine was bound to urinary protein making it potentially unaccessible to interact with its nephron site of action (102). Using micropuncture techniques in the same animal model, Kirchner et al., came to similar conclusions (103). That is, with increasing amounts of protein in the urine, the greater the amount of diuretic bound, resulting in less furosemide to be available to exert a pharmacologic effect. In support of this conclusion, the same investigators found that the addition of competitive inhibitors of furosemide-albumin binding restored the potency of the diuretic (Figure 19) (104). Whether, in addition, there exists an intrinsic defect in the loop segment in the setting of the nephrotic syndrome could not be determined from these studies.

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