

Mechanisms of Disease

The nephrotic syndrome

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Introduction

The definition of nephrotic syndrome is proteinuria accompanied by hypoalbuminaemia and oedema. This, however, is not a direct chain of events. In the presence of normal liver albumin synthesis, nephrotic range of proteinuria (> 3.5 g/24 h) should not cause hypoalbuminaemia, and a low plasma albumin concentration itself does not result in oedema formation except in the presence of sodium retention. The cause of this sodium retention remains unknown, but is probably due to some intrarenal mechanism.

Mechanisms of proteinuria

By measuring the clearances of charged and neutral dextrans of known molecular weights and comparing them to inulin it is possible to study glomerular capillary permeability. Such studies show that in normal animals both molecular charge and size influence the transglomerular passage of circulating macromolecules. Thus, the filtration of the negatively charged albumin is restricted to a much greater extent than is that of a neutral macromolecule of the same size (Chang *et al.*, 1975). This is due to the existence of fixed negative charges on the glomerular capillary wall as demonstrated by the use of cationic 'stains' such as colloidal iron and ruthenium red (Latta *et al.*, 1975; Kanwar & Farquhar, 1979).

Studies in rats with nephrotoxic serum nephritis or aminonucleoside-induced nephrosis have shown that, at any given molecular size, negatively charged dextran sulphate fractional clearances are greater than those in normal rats (Bennett *et al.*, 1976; Bohrer *et al.*, 1977). This suggests that albuminuria in these disorders is due to a reduction in the fixed negative charges on the diseased glomerular capillary wall. Further support for this theory comes from the finding of

reduced binding of cationic stains to anionic sites of the glomerular capillary wall in aminonucleoside-treated rats (Michael *et al.*, 1970).

In man, there is also evidence of depleted glomerular polyanion in almost all glomerular diseases associated with proteinuria (Blau & Haas, 1973). This loss of glomerular electrostatic barrier function would allow the leak of the negatively charged albumin into the urine. There is also increasing evidence that the different protein selectivity found in different causes of nephrotic syndrome can be explained by the fact that in minimal change glomerulonephritis there remains an intact size-selective barrier, while in other glomerular lesions this barrier becomes leaky (Deen *et al.*, 1982).

Hypoalbuminaemia and proteinuria

The liver of a normal 70 kg person can synthesize albumin at the rate of 8–14 g/d (Rothschild *et al.*, 1972), yet in nephrotic syndrome, hypoalbuminaemia occurs with considerably lower urinary protein excretion rates. Nephrotic range proteinuria is usually defined as greater than 5 g/d and nephrotic syndrome can occur with a urinary protein excretion as low as 3.5 g/d. Although in some patients urinary protein losses may exceed the normal rate of synthesis of albumin by the liver, it is not clear why hypoalbuminaemia should occur in those patients with lesser degrees of proteinuria. There are three possible explanations: (1) albumin synthesis could be diminished; (2) non-renal losses of albumin could occur; or (3) albumin catabolism could be enhanced.

There is no evidence of decreased albumin synthesis in patients with nephrotic syndrome. Studies using radioiodinated albumin have shown that albumin synthesis in patients with nephrotic syndrome is either normal or slightly increased (Gitlin *et al.*, 1956; Jensen *et al.*, 1967). Non-renal losses of albumin may occur,

probably through the gastrointestinal tract, though the evidence is conflicting. Jensen *et al.* (1967) and Yssing *et al.* (1969) in their studies found no evidence of increased gastrointestinal losses but a later study by Schultze *et al.* (1980) using ^{51}Cr -albumin did show moderate to severe gastrointestinal protein losses in many patients with nephrotic syndrome.

The most likely explanation of the hypoalbuminaemia of nephrotic syndrome, however, is increased catabolism of albumin, probably by the kidney. Studies in both animal models (Katz *et al.*, 1963) and in patients with nephrotic syndrome (Jensen *et al.*, 1967) have demonstrated an increase in fractional albumin catabolism. The most likely site of this increased albumin catabolism is the kidney since there appears to be a direct relationship between renal albumin catabolism and quantitative proteinuria (Katz *et al.*, 1963), and bilateral nephrectomy causes at least a 50% fall in the rate of plasma albumin breakdown in rats with aminonucleoside or nephrotoxic serum-induced nephrotic syndrome (Katz *et al.*, 1964).

The site of this increased renal albumin catabolism is probably the proximal tubule. Radioiodinated albumin has been clearly demonstrated to be taken up by proximal tubule cells and perhaps then metabolized by lysosomes (Maunsbach, 1966). Proximal tubule cells have been shown to be able to metabolize a variety of plasma proteins (Waldmann *et al.*, 1972). Micropuncture studies, however, have failed to confirm that significant albumin catabolism occurs at the proximal tubule. Studies in both aminonucleoside-induced (Oken *et al.*, 1971, 1972; Lewy & Pesce, 1973) and nephrotoxic serum-induced nephrotic syndrome (Landwehr *et al.*, 1977) also gave no evidence that proximal tubular absorption plays a major role in albumin catabolism. However, Cortney *et al.* (1970) did find significant proximal tubular albumin absorption after injecting radioiodinated albumin into the proximal tubule.

Although the evidence is conflicting it would appear that the most likely explanation for the discrepancy between the hepatic capacity to synthesize albumin and the degree of albuminuria in many patients with nephrotic syndrome remains the increased albumin catabolism by the kidney, plus, possibly in some patients, increased gastrointestinal protein losses.

Hypoalbuminaemia and oedema formation

By Starling's law, the formation of interstitial fluid is dependent upon the balance between the hydrostatic and the oncotic pressures in the intravascular and interstitial fluid spaces, so, theoretically, oedema should occur when the plasma albumin concentration, and consequently the oncotic pressure, are low. A low

plasma albumin concentration, however, is not always accompanied by oedema formation. Even patients with analbuminaemia are not oedematous and, in fact, can have an exaggerated natriuresis in response to a small saline load (Bennhold *et al.*, 1960). Similarly, severe hypoalbuminaemia induced in animals by plasmapheresis does not produce any change in urinary sodium excretion (Vereerstraeten & Toussaint, 1969).

Volume receptors have not been detected in the interstitial space, so control of the volume of the interstitial fluid compartment appears to be by the interplay of a number of local automatic mechanisms (Aukland & Nicolaysen, 1981). One of the primary factors preventing oedema formation is structural resistance against volume changes making the interstitial space relatively noncompliant. Guyton (1965) found that at near normal interstitial volumes, small increases in interstitial volume cause large increases in interstitial pressure which would oppose further transudation of fluid into the interstitial space. However, once interstitial pressure reaches a critical value, as the interstitial volume increases further, the subsequent increments in interstitial pressure are much smaller. The lymphatics also play a role in preventing oedema formation. Lymph flow has been shown to increase following oedema formation in many different oedema states (Hollander *et al.*, 1961; Zweifach, 1972). Erdmann *et al.* (1975) showed that during steady state elevations of pulmonary micro-vascular hydrostatic pressure, lymph flow increased while the lymph protein concentration decreased, reflecting washout of interstitial protein. The consequent decrease in interstitial oncotic pressure, by increasing the oncotic pressure gradient across the capillary wall would also help to prevent further oedema formation. One further mechanism which may protect against oedema formation is that the capillary wall appears to become less permeable to albumin in the presence of hypoalbuminaemia (Wraight, 1974; Aukland & Nicolaysen, 1981). This would tend to prevent a further fall in plasma oncotic pressure along the capillary and therefore minimize oedema formation.

These control mechanisms preventing oedema formation have also been observed in patients with nephrotic syndrome. Increased lymphatic flow has been observed in patients with nephrotic syndrome (Hollander *et al.*, 1961; Zweifach, 1972). Furthermore, using wick techniques, Noddeland *et al.* (1980) found that the interstitial oncotic pressure fell during oedema formation in patients with nephrotic syndrome, presumably because of washout of the interstitial protein by the increased lymphatic flow. From these observations, it is apparent that generalized oedema only occurs in the presence of hypoalbuminaemia when there is a stimulus for the kidney to retain sodium and water since all the local control mechanisms act to reduce the oedema.

Mechanisms of sodium retention in nephrotic syndrome

The mechanisms causing sodium retention in nephrotic syndrome remain controversial. The classic pathophysiological explanation is that the fall in plasma albumin and, thereby, oncotic pressure leads to a transudation of fluid across the capillaries and a reduction of blood volume which then stimulates the renin-angiotensin-aldosterone system to retain sodium. Early studies on patients with nephrotic syndrome supported this idea since they demonstrated in many patients a low blood volume, high plasma renin activity, or raised urinary aldosterone (Hopper *et al.*, 1970; Luetscher & Johnson, 1954; Oliver & Owings, 1967; Veyrat *et al.*, 1964). Few of these measurements were carried out when patients were retaining sodium.

To study the mechanism of sodium retention in nephrotic syndrome, it is essential that the patients studied are accumulating sodium, i.e. sodium output is less than sodium intake with a consequent gain in weight each day. Patients who are oedematous, but are not gaining weight each day, although sodium overloaded, are in sodium balance, i.e. sodium excretion is equal to sodium intake.

Recent studies in patients with the nephrotic syndrome, who were retaining sodium, have shown that about half of the patients have a normal or high blood volume and low or normal plasma renin activity and aldosterone (Kelsch *et al.*, 1972; Meltzer *et al.*, 1979; Dorhout Mees *et al.*, 1979; Brown *et al.*, 1982a,b). We have now studied 18 patients all of whom were retaining sodium. While 10 of these 18 patients did have an elevated plasma renin activity, the other 8 patients had a low or normal plasma renin activity and a low or normal plasma aldosterone; 5 of these 8 patients had a normal or elevated blood volume. There was therefore no evidence of stimulation of the renin-angiotensin-aldosterone system in these 8 patients, so some other mechanism is probably responsible for the observed sodium retention.

From these studies, it does appear that in some patients with nephrotic syndrome, stimulation of the renin-angiotensin-aldosterone system does occur as a compensatory phenomenon to a low blood volume, but it is possible that even in these patients there is some other mechanism causing the sodium retention. If the raised angiotensin II and aldosterone does indeed cause the sodium retention in these patients, there must be some explanation as to why the usual 'escape' phenomenon seen after prolonged infusions of angiotensin II (Ames *et al.*, 1965) and aldosterone (August *et al.*, 1958; Barger *et al.*, 1958) into normal subjects does not occur.

Studies in rats with aminonucleoside-induced nephrotic syndrome show that oedema can develop despite bilateral adrenalectomy (Kalant *et al.*, 1962).

More direct evidence about the role of angiotensin II and aldosterone in the sodium retention of nephrotic syndrome is obtained by blocking the renin-angiotensin-aldosterone system. Indeed, in normal subjects, it has been shown that angiotensin-converting enzyme inhibition preventing the formation of angiotensin II causes a marked natriuresis (McCaa *et al.*, 1978; MacGregor *et al.*, 1980). This is in marked contrast to the effect of giving the angiotensin-converting enzyme inhibitor, captopril, to patients with nephrotic syndrome (Brown *et al.*, 1982b, 1984), when there was no increase in urinary sodium excretion and patients continued to retain sodium and gain weight. Even nephrotic patients with elevated plasma renin activity and plasma aldosterone continued to retain sodium when given captopril, despite plasma aldosterone falling to normal.

Volume expanding patients with nephrotic syndrome is another method of determining whether the sodium retention is related to the low blood volume stimulating the renin-angiotensin-aldosterone system. Following albumin infusion, there is a rise in plasma albumin and expansion of the blood volume, yet patients continue to retain sodium (Janeway *et al.*, 1944; Luetscher, 1944; Luetscher *et al.*, 1949) despite a fall in plasma renin activity and plasma aldosterone from high to extremely low levels (Brown *et al.*, 1982b).

Recently, it has been found that patients with nephrotic syndrome have a natriuresis and a fall in plasma renin activity and plasma aldosterone following short term water immersion regardless of whether the plasma renin activity or plasma aldosterone was elevated before immersion (Berlyne *et al.*, 1981; Krishna & Danovitch, 1982). In normal subjects, water immersion also causes a natriuresis which is associated with an expansion of the central blood volume (Epstein, 1976) and a rapid fall in plasma renin activity and plasma aldosterone (Epstein & Saruta, 1971). It is unlikely that the onset of this natriuresis is caused by the fall in aldosterone since aldosterone action has a half-life of at least 30 min. Furthermore, pharmacological doses of mineralocorticoids do not abolish the natriuresis of water immersion in normal man (Epstein *et al.*, 1973). Studies in normal man suggest that this natriuresis is due to expansion of central blood volume and the release of a natriuretic hormone (Epstein *et al.*, 1978). This is probably also true in nephrotic patients, since the natriuresis induced by water immersion is directly related to the pre-immersion plasma volume (Krishna & Danovitch, 1982).

In patients with nephrotic syndrome due to minimal change glomerulonephritis, steroid-induced remission causes a massive natriuresis up to a urinary sodium excretion of 600 mmol/24 h (Brown *et al.*, 1985). Studying such patients, especially if they are known to have initial high plasma renin activity and low blood

volume, would establish whether the switching off of the stimulus for sodium retention at the onset of natriuresis is caused by changes in the renin-angiotensin-aldosterone system. Oliver (1963) found that the onset of natriuresis occurred without any change in plasma albumin or blood volume. In a recent study of 6 patients undergoing steroid-induced remission we also found that plasma albumin and blood volume remain low even at the height of the natriuresis. During the natriuresis, there was a fall from high to normal levels in plasma renin activity and plasma aldosterone which then rose again to their previous high levels as patients came back into sodium balance; there was then no evidence of further sodium retention despite the high levels of renin and aldosterone (Brown *et al.*, 1985). The temporary fall in plasma renin activity and plasma aldosterone is probably due to the fact that during the natriuresis, distal tubular sodium and chloride concentration rises markedly and this, through the macula densa, inhibits renin release (Davis & Freeman, 1976). These results support the increasing evidence that, in patients with nephrotic syndrome, although the renin-angiotensin-aldosterone system can be stimulated by a low blood volume, it does not contribute towards the sodium retention.

What, then, does cause the sodium retention? It is most likely to be some intrarenal mechanism. By infusing puromycin aminonucleoside into the renal artery of one kidney while simultaneously venting the renal venous effluent, it is possible to induce heavy proteinuria from only that one kidney. Using this rat model, both Chandra *et al.* (1981) and Ichikawa *et al.* (1983) found that urinary sodium excretion was decreased in the perfused but not in the control kidney; there was no change in plasma albumin concentration.

Evidence for an intrarenal mechanism causing sodium retention in patients with nephrotic syndrome is more circumstantial. The evidence from studies of patients during steroid-induced remission does suggest that some intrarenal defect causing the sodium retention is corrected resulting in a large natriuresis. There is also indirect evidence of renal haemodynamic disturbances in patients with nephrotic syndrome

since, as discussed by Searle *et al.* (1985) in this journal, renal failure can occur in the absence of hypotension and unexplained by pathological findings.

The actual nephron site of the increased sodium reabsorption is also not fully established. Studies of water clearance in patients with nephrotic syndrome suggest that proximal tubular sodium reabsorption is increased (Gur *et al.*, 1976; Dorhout Mees *et al.*, 1981) while other studies suggest that proximal reabsorption is decreased and that it is distal tubular reabsorption which is increased (Grausz *et al.*, 1972, Bohlin & Berg, 1984). Micropuncture studies of experimentally-induced nephrotic syndrome are equally confusing (Bernard *et al.*, 1978; Kuroda *et al.*, 1979), though it does appear that in the unilateral aminonucleoside perfused kidney model of Ichikawa *et al.* (1983), comparison of the perfused and normal kidney suggests that the site of the increased sodium reabsorption is in the late distal tubule and/or collecting duct.

If an intrarenal mechanism is the overriding cause of sodium retention in nephrotic syndrome, why is the renin-angiotensin-aldosterone system stimulated in some patients and not in others? Meltzer *et al.* (1979) suggested that this occurs in the presence of a low blood volume and in his series all such patients had minimal change glomerulonephritis. This correlation with the histological diagnosis is not supported by the data of Dorhout Mees *et al.* (1979) or by our own data (Brown *et al.*, 1982a). It is likely that the renin-angiotensin-aldosterone system is stimulated in those patients with a greater loss of albumin from the kidney resulting in more severe hypoalbuminaemia and hence low blood volume which then stimulates renin release. This theory appears to be substantiated by finding a significant inverse correlation between plasma renin activity and plasma albumin (Brown *et al.*, 1982a). In normal man, a diminution of blood volume and stimulation of the renin system is a potent mechanism causing sodium retention by the kidney. In nephrotic syndrome, however, there appears to be an overriding mechanism, probably intrarenal, causing sodium retention independent of the renin system. The nature of this postulated intrarenal defect is as yet unknown.

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