Edema in childhood

SATOSHI HISANO, SEUNGHOON HAHN, NANCY B. KUEMMERLE, JAMES C.M. CHAN,
and NATALE G. DESANTO

Pediatric Nephrology Division, Virginia Commonwealth University's Medical College of Virginia, Richmond, Virginia, USA, and Divisione di Nefrologia dell' Adulto e del Bambino, Seconda Universita'degli Studi di Napoli, Naples, Italy

Edema in childhood. There are two types of edema: localized edema and generalized edema. The causes of generalized edema in childhood are diverse. Formation of generalized edema involves retention of sodium and water in the kidney. The treatment of generalized edema depends on the primary etiology. Supportive nutritional and medical therapies are needed to prevent further edema. These and related features of edema in childhood are discussed in this review.

Edema can be defined as the presence of excess fluid in the interstitial space of the body. Edema is divided into two types, localized edema and generalized edema. The formation of edema is associated with renal sodium retention. However, localized edema does not reflect a sustained impairment in the ability to maintain normal sodium balance. Generalized edema can arise via two different processes: (1) a reduced intravascular volume leading to sodium and water retention, that is, an "underfilling edema," or (2) sodium and water retention secondary to expanded plasma and intracellular tissue fluid volume accompanied by a lack of natriuresis, that is, an "overfilling edema" [1]. The generalized edema occurs in the presence of parenchymal renal damage (nephrotic syndrome, acute and chronic glomerulonephritis and renal failure) or in the absence of structural renal disease (heart failure, liver cirrhosis). Idiopathic edema affects women in the menstrual period or in the immediate premenstrual period, who manifest generalized edema secondary to water and sodium retention [2]. Idiopathic edema is uncommon in the pediatric age group. Toxemia of pregnancy is characterized by generalized edema and hypertension [1]. The severity of renal involvement is correlated to the degree of proteinuria.

A less easily classified type of edema is the edema of sequestration {third space}, which is associated with contracted extracellular volume for which the treatment is distinctly different, requiring infusion of extracellular-like osmotic colloids [3].

The mechanism of "underfilling edema" is initiated with an increased glomerular permeability to albumin, that is, albuminuria. The subsequent hypoalbuminemia leads to decreased plasma oncotic pressure accompanied by movement of water from intravascular space to the interstitium. The intravascular contracted volume in turn stimulates the following neuroendocrinological factors, resulting in sodium and water retention: (1) an increased renin-angiotensin-aldosterone (RAA) activity; (2) an increased

sympathetic nervous system (SNS) activity; and (3) antidiuretic hormone (ADH) release [4–6]. These forces and perhaps as yet unidentified factors give rise to the consequential water and sodium retention, which promotes the development of edema. The sodium and water retention leads to further decreased plasma oncotic pressure, setting up a vicious cycle perpetuating the edema formation. The movement of water from intracellular space to interstitial space by itself also contributes to the development of edema formation [1, 3].

In contrast, the mechanism of "overfilling edema" is expanded extracellular volume that results from primary renal sodium retention, possibly secondary to the renal damage. The RAA system, SNS system and ADH secretion are depressed in the "overfilling edema" [4–6].

This review deals with the pathophysiology of generalized edema and describes its treatment.

Causes of edema

An approach to delineating the causes of edema in childhood can be summarized in Table 1, according to the following physiological changes: (1) reduced oncotic pressure, (2) increased blood volume, and (3) increased capillary permeability.

Reduced oncotic pressure

Edema in nephrotic syndrome. Traditionally, the mechanism of edema formation in nephrotic syndrome has been considered to be due to plasma volume contraction (underfilling edema) [5, 7]. Hypoalbuminemia that results from albuminuria causes reduced oncotic pressure, leading to transcapillary fluid in the interstitial space [5, 7–9]. The resulting decrease in plasma volume affects sodium and water retention in the kidney through stimulating the activity of RAA and SNS and ADH secretions [7–9]. As long as the disequilibrium of the capillary fluid exchange remains, the retained fluid will continue to accumulate in the interstitial space resulting in further edema formation [7–9]. In a majority of the patients with nephrotic syndrome, edema formation can be explained by this mechanism. However, there are observations arguing against reduced plasma and blood volume in the nephrotic syndrome [8, 10–13]. Some patients with nephrotic syndrome show increased plasma volume (overfilling), hypertension and edema [13]. In the patients with steroid-induced remission of minimal change nephrotic syndrome, diuresis and natriuresis usually begin before hypoalbuminemia is reversed [7, 8]. Patients with nephrotic syndrome have high plasma renin activity and increased plasma aldosterone concentration, especially in minimal

Table 1. Causes of childhood edema

(1) Reduced oncotic pressure
 Hypoproteinemic diseases
  Nephrotic syndrome
  Liver cirrhosis
  Malnutrition
  Protein losing nephropathy
  Severe burns
(2) Increased blood volume
 Cardiovascular diseases
  Heart failure: low-output (congestive heart failure); high-output
   heart failure (hyperthyroidism, anemia, beriberi)
  Arteriovenous fistula
 Renal diseases
  Acute glomerulonephritis
  Acute and chronic renal failure
 Idiopathic diseases
  Familial idiopathic edema
  Non-familial idiopathic edema
  Pregnancy
(3) Increased capillary permeability
 Allergic diseases (angioneurotic edema, aeroallergens, food allergy)
 Vasculitis (anaphylactoid purpura, systemic lupus erythematosus,
  dermatomyositis, polyarteritis nodosa, scleroderma, Kawasaki
  disease)

change nephrotic syndrome with low plasma oncotic pressure [13]. However, plasma aldosterone concentrations are usually normal in children with minimal change nephrotic syndrome [8, 14]. Shapiro et al [15] reported that a negative sodium balance was induced in the nephrotic patients by administration of the aldosterone antagonist, spironolactone. However, Brown et al [16] showed that angiotensin converting-enzyme (ACE) inhibitor could not induce natriuresis in nephrotic patients. It was suggested that several other factors must play a role in increased sodium retention [15, 16].

The reduction in plasma volume presumably suppresses atrial natriuretic peptide (ANP) secretion, which inhibits sodium resorption in the inner medullary collecting duct [17]. Studies in experimental animals with nephrotic syndrome have shown resistance to the renal effects of ANP [18, 19]. In nephrotic patients, the response to exogenous ANP varies between a normal response and a blunted natriuretic response [20, 21]. However, volume-expanded nephrotic patients increased plasma ANP levels in the presence of a blunted natriuretic response [12, 22]. These findings suggest ANP resistance in nephrotic syndrome.

It is likely that intrarenal mechanisms are responsible for sodium retention in nephrotic syndrome rather than systemic mechanisms, and sodium-handling disturbances in the distal nephron should be further investigated.

Edema in liver cirrhosis. Edema and ascites are major clinical findings in patients with liver cirrhosis. The pathophysiology of edema and ascites in liver cirrhosis is related to portal hypertension, primary or secondary renal sodium retention, and hemodynamic changes [6, 23]. Three pathophysiological theories have been proposed to account for the ascites formation and sodium retention in liver cirrhosis [6]. According to the traditional, classic "underfilling theory," the initial event in renal sodium retention is disruption of the Starling equilibrium within the hepatic sinusoids and splanchnic capillaries owing to the increased resistance to portal flow, which leads to increased filtration of fluid into the

interstitial space, that is, peritoneal cavity [6]. Intravascular fluid movement to the interstitial space leads to reduced plasma volume, resulting in increased activity of RAA and SNS and increased ADH secretion [6]. The RAA actvity is stimulated in the patients with decompensated cirrhosis and more so in the patients with hepatorenal syndrome [24, 25]. If this theory were correct, blood volume and cardiac output would be reduced. However, it is well established that plasma volume and cardiac output are markedly increased, and peripheral vascular resistance is markedly reduced in patients with cirrhosis and ascites [24]. This "underfilling" theory does not correlate with the systemic hemodynamic abnormalities related to portal hypertension.

The "overflow theory" was proposed in an attempt to explain the relationship between portal hypertension and hyperdynamic circulation in the edema formation [6, 23]. The initial event is a primary renal sodium retention, and not secondary to a reduction in intravascular volume [6, 23]. The renal sodium and water retention would result in expanded plasma volume and increased cardiac output. The existence of portal hypertension and circulating hypervolemia would accelerate ascites formation. However, this theory does not explain the reduced resistance of peripheral arteries and arterial hypotension. In addition, this theory cannot explain the results of events leading to the development of hepatorenal syndrome.

The third theory, the "peripheral arteriolar vasodilation hypothesis" is that sodium retention in cirrhosis is a secondary event related to an arterial vascular underfilling [6]. However, in contrast to the classic "underfilling" theory, the vascular underfilling is not the result of reduced intravascular volume but rather due to a decrease in intravascular volume against a disproportionate enlargement of the arterial vascular compartment secondary to arteriolar vasodilation [6]. Portal hypertension and resultant splanchnic arteriolar vasodilation lead to underfilling of the arterial vascular compartment. The baroreceptors sense this arterial underfilling and stimulate the activity of RAA and SNS and increase ADH secretion. Renal sodium and water retention leads to the increase in plasma volume [6]. In the status of compensated cirrhosis, normalization of circulatory homeostasis suppresses the activity of neuroendocrinological system and renal sodium and water retention is normalized. However, in decompensated cirrhosis, splanchnic arteriolar vasodilation further increases and then a more intense arterial vascular underfilling ensues [6]. At this time, the increased intravascular volume is not enough to maintain circulatory homeostasis. Arterial pressure is maintained by the persistent stimulation of the RAA, SNS and ADH and the activation of these systems perpetuates sodium and water retention, resulting in accumulation of ascites [6].

What dilates the peripheral artery is not known. Several potential mediators, such as nitric oxide, glucagon, prostacyclin, potassium channels, endotoxin and cytokines are considered vasodilators [25]. Nitric oxide synthesis by up-regulation of gene expression is likely induced in response to shear stress of the vascular wall concomitant with portal hypertension and increased flow [26–28], and nitric oxide causes vasodilation [29]. However, recent studies do not consistently support this hypothesis. Plasma glucagon concentration is high in cirrhotic patients and glucagon causes vasodilation in pharmacological doses [30]; glucagon likely enhances nitric oxide production in cirrhosis [25]. Prostacyclin is elevated in cirrhosis. Prostacyclin is a systemic vasodilator and its secretion is stimulated by shear stress of the splanchnic arterioles

[27, 28]. ATP-sensitive potassium channels can cause vasodilation due to hyperpolarization of vascular smooth muscle cells. Moreau et al [31] found that vasodilation in cirrhotic rats is dependent on potassium channels.

Edema in severe malnutrition. Undernutrition, marasmus (caloric deficiency), or marasmus with kwashiorkor (severe-protein malnutrition) can occur in the same patient. The development of edema formation in this pathophysiology is due to "underfilling mechanism" [5].

Edema in protein-losing enteropathy. The hypoalbuminemia resulting from chronic protein loss gives rise to a contraction of extracellular volume, allowing the development of edema due to the "underfilling mechanism" [5].

Edema in severe burns. In burned tissues, plasma fluid shifts into the interstitial space by the burn-induced increase in vascular permeability and the consequent extravasation of protein, and water and protein accumulate in the interstitial space. Hypoproteinemia leads to a reduction in oncotic pressure in severe burns, and edema formation develops progressively through the underfilling mechanism [5].

Edema formation due to increased blood volume

The edema formation secondary to increase in blood volume results from heart failure, acute glomerulonephritis, acute and chronic renal failure and toxemia of pregnancy. The activity of RAA and SNS and ADH secretion are suppressed in increased blood volume.

Edema in heart failure. The relation between cardiac output and peripheral arterial vascular resistance, both of which are primary determinants of the "fullness" of the arterial vascular system, defines the volume-control system [23, 32]. Basically, heart failure is characterized by increased blood volume and increased venous pressure. There are two types of heart failure, such as low-output heart failure (congestive heart failure) and high-output heart failure (hyperthyroidism, anemia, beriberi or an ateriovenous fistula) [6]. Hormonal and baroreceptor response to both types of heart failure is quite similar. The low-output heart failure is characterized by reduced cardiac output and increasing filling pressures in one or both ventricles. Arterial pressure is maintained because of an increase in systemic peripheral vascular resistance. The hemodynamic characteristics of high-output heart failure are increased cardiac output, low systemic vascular resistance, arterial hypotension and increased central venous pressure.

In the development of edema from heart failure, the initial event is reduced effective arterial blood volume, in both low-output heart failure and high-output heart failure. This event stimulates arterial and ventricular baroreceptor, resulting in activation of SNS and RAA and release of ADH (nonosmotic secretion) [6, 23]. The low renal perfusion also stimulates secretion of renin from the juxtaglomerular apparatus. Increased sodium and water retention leads to edema formation [6, 23].

Prostaglandins are important for maintaining the systemic hemodynamics in heart failure and increased production of prostaglandins in the kidney is important in maintaining renal hemodynamics. In congestive heart failure, plasma prostaglandin E_2 and prostaglandin I_2 concentrations are increased [6]. The circulating level of ANP is constantly increased in heart failure. The enhanced ANP release is a physiological response to counteract the expanded extracellular volume and reduce the increased afterload of heart failure as a natriuretic factor and a

vasodilator [6]. However, high level of circulating ANP is not capable of exerting natriuresis because of a resistance to the renal effects of endogenous ANP in heart failure [6]. The plasma concentration of human brain natriuretic peptide is also increased in patients with heart failure [6].

Edema in acute glomerulonephritis. In acute glomerulonephritis, glomerular filtration is reduced by the glomerular capillary obstruction caused by the immunological injury. The reduced glomerular filtration results in a fall in the filtered load of sodium and water, leading to expanded extracellular volume. The hemodynamic characteristics of this disease are increased blood volume, hypertension and normal or increased cardiac output [5, 6]. Blood volume expansion increases peripheral capillary filtration by increasing arterial and venous pressures [5, 6]. The return of filtered fluid into venules and via lymphatics is impaired by the high venous pressure [5, 6]. The primary event of edema formation in acute glomerulonephritis is the increased blood volume.

Edema in acute and chronic renal failure. The decline of glomerular filtration is primarily attributable to edema formation in acute and chronic renal failure. An abrupt fall in glomerular filtration in acute renal failure causes an accumulation of sodium and water, resulting in an increased blood volume, hypertension and edema formation. There is also a diffuse increase in peripheral capillary permeability caused by massive tissue injury [33]. In the early stages of chronic renal failure, polyuria and polydypsia are evident. The ability to dilute the urine is well preserved and urine output does not dminish [34]. Thus, water depletion and sodium wasting may ensure in the inadvertent restriction of water and sodium intake during the early stages of chronic renal failure. Edema formation is uncommon in early chronic renal failure [34]. However, with the progressive loss of nephrons, the fall in the glomerular filtration of water and sodium becomes evident. Blood volume is increased, leading to edema formation and hypertension, especially after an abrupt increase of salt intake [35].

Increased capillary permeability

Increased capillary permeability usually leads to localized edema, less commonly to generalized edema. This pathological event often occurs in association with inflammation, allergic causes and vasculitis (anaphylactoid purpura, systemic lupus erythematosus, dermatomyositis, polyarteritis nodosa, scleroderma, Kawasaki disease) and is less commonly accompanied by increased sodium and water retention [35]. In childhood, anaphylactoid purpura is one of the major diseases related to increased capillary permeability caused by vasculitis. Edema is usually localized around joints. However, generalized edema develops in conjunction with low albumin concentration with severe protein-losing enteropathy and nephrotic syndrome.

Approach to the diagnosis of edema

The identification of primary diseases as a cause of edema is most important. Symptoms and signs should be quickly evaluated. Dyspnea, fatigue and a history of cardiac disease are suggestive of heart failure. Gallop rhythm, heart murmur, facial edema with enlarged jugular veins, pulmonary rales and hepatomegaly are the characteristic findings of congestive heart failure.

Jaundice, ascites, vascular spiders, enlarged vein of the abdomen and abnormalities of liver function with or without hepatosplenomegaly are suggestive of severe liver disease.

Pallor, macrohematuria, proteinuria and hypoalbuminemia are indicative of acute glomerulonephritis or nephrotic syndrome.

Other causes of generalized edema, such as protein-losing enteropathy, vasculities, vascular or lymphatic obstruction and allergic origins, can be differentiated by the characteristic clinical findings and laboratory findings of these diseases.

Management of edema

The presence of edema is not always an indication for vigorous treatment. Mild edema without symptoms does not need special treatment. Edema which gives the edematous patients discomfort or the consequential complications induced by edema should be ameliorated. The special therapy should be designed in accordance with the pathophysiological characteristics of the primary disease.

Supportive management

Bed rest is of limited value in the treatment of edematous states, but is helpful in preventing accumulation of edema and decreasing sodium and water retention [35]. Bed rest results in an augmentation of blood volume in the central circulation by decreasing the peripheral venous pooling and leads to an increase in cardiac output, renal and hepatic perfusion and sodium diuresis [6].

Sodium restriction is usually indicated in the edematous state. Restricting salt intake to about 1 to 1.5 mEq/kg/day is generally sufficient [35]. This degree of restriction may be achieved by avoiding salty foods. In the severe edematous state, adequate water restriction is effective in preventing further edema formation. The daily water intake equal to the amount of the urine and the insensible water loss is sufficient. To maintain water balance, when diuresis occurs water restriction should be avoided. Hyponatremia, which often occurs as a consequence of salt restriction and diuretics administration, should be avoided.

Medical therapy of edema

The first principle of therapy in childhood edema is reversing the primary diseases. The second principle is to restore the hemodynamics and cardiac output, which will lead to improvement of hepatic or renal perfusion.

In edema of renal diseases, such as nephrotic syndrome or acute glomerulonephritis, only the supportive treatment, such as bed rest and restriction of salt intake and water, may be helpful in mobilizing edema. The majority of childhood nephrotic syndrome is minimal change nephrotic syndrome [9]. Prednisone treatment (2 mg/kg/day for 6 weeks followed by 2 mg/kg every other day for 6 weeks) provides a good response to childhood minimal change nephrotic syndrome and with the response of this agent, edema soon dissipates [9]. When respiratory distress from diaphragmatic excursion owing to extensive ascites or the shock caused by hypovolemia is evident in patients with nephrotic syndrome, the infusion of intravenous sodium-poor albumin to 0.5 to 1 g per kilogram body wt slowly over three hours, followed by furosemide 1 to 2 mg per kg intravenous injection, is helpful in removing ascites and preventing hypovolemic shock [9]. The albumin infusion should be at this slow rate to prevent precipitating pulmonary edema. In minimal change nephrotic syndrome constant diuretics administration is not needed. In the nephrotic syndrome with poor response to prednisone, that is, focal segmental glomerulosclerosis, diuretics administration (hydrochlorothiazide 0.5 to 2

mg/kg/day p.o.) may induce some diuresis. Hypokalemia is a known side effect of diuretic administration and serum potassium should be monitored. In acute glomerulonephritis, hypervolemia with pulmonary edema or congestive heart failure or acute severe hypertension require treatment with intravenous furosemide (0.5 to 2 mg/kg) and oral or intravenous antihypertensive drugs, such as nifedipine (0.25 to 0.5 mg/kg p.o., t.i.d. or q.i.d.) or diazoxide (1 to 3 mg/kg/dose i.v.) [35, 36]. In hypervolemia accompanied by acute renal failure, dialysis is required in the absence of early return of renal function. In chronic renal failure, severe edema is rare until uremia is far advanced. However, an abrupt increase of salt intake induces volume expansion and edema formation. Diuretics (furosemide, 0.5 to 2 mg/kg/day p.o.) and restriction of salt intake lead to diuresis and prevent further edema formation [35]. In the state of end-stage renal failure, these adaptive responses to change in salt intake become exhausted, and dialysis is required.

In edema of liver cirrhosis, the initial diuretic therapy is spironolactone (1 to 3 mg/kg/day p.o.) or triamterene (2 mg/kg/day p.o.) because of hyperaldosteronism usually associated with cirrhotic edema [6]. The effective dose should be determined by monitoring urine sodium and potassium concentrations. When renal insufficiency secondary to hypovolemia (diuretics or gastrointestinal bleeding) is present, intravenous albumin infusion (1 g/kg given over 3 hr) is required and nephrotoxic drugs should be avoided [25].

In congestive heart failure, relief of edema is associated with a contraction of blood volume and improvement in cardiac hemodynamics [35]. Constant diuretic therapy accompanied by salt intake and water restriction is necessary for preventing further edema formation. Dopamine agonists improve cardiac hemodynamics and renal perfusion, and therefore, the concomitant therapy of dopamine agonists and diuretics induces natriuresis in refractory cases with congestive heart failure.

Future therapy

The gene encoding the water channel protein, aquaporin has been cloned and the action of this protein has been delineated. Aquaporin 2 is considered to be a new class of specific inhibitors of these water channels [37]. It is, therefore, conceivable that in the not too distant future, orally administered aquaporin nonapeptide may be available to regulate vasopressin V2 receptor and open a new era of treatment of edema using water channel inhibition.

References

1. EPSTEIN M, PEREZ GO: Pathophysiology of edema-forming states, in *Clinical Disorders Fluid Electrolyte Metabolism* (4th ed), edited by MAXWELL MH, KLEEMAN CR, NARIS RG, New York, McGraw Hill Book Co, 1987, pp 409–427
2. KLEEMAN CR, SZATALOWICZ VL: Idiopathic edema, in *Testbook of Nephrology* (3rd ed), edited by MASSRY SG, GLASSOCK RJ, Baltimore, Williams & Wilkins, 1995, pp 508–512

3. BARTTER FC, DELEA CS: Disorders of water metabolism, in *Kidney Electrolyte Disorders*, edited by CHAN JCM, GILL JR JR, New York, Churchill-Livingston, 1990, pp 107–135

4. GINES P, SCHRIER RW: Sodium hemostasis and edema, in *Textbook of Nephrology* (3rd ed), edited by MASSRY SG, GLASSOCK RJ, Baltimore, Williams & Wilkins, 1995, pp 694–695

5. REINECK HJ, STEIN JH: Disorders of sodium metabolism, in *Kidney Electrolyte Disorders*, edited by CHAN JCM, GILL JR JR, New York, Churchill-Livingston, 1990, pp 59–105

6. GINES P, HUMPHREYS MH, SCHRIER RW: Edema, in *Textbook of Nephrology* (3rd ed), edited by MASSRY SG, GLASSOCK RJ, Baltimore, Williams & Wilkins, 1995, pp 582–599

7. RABELINK TJ, JOLES JA, KOOMANS HA: Edema formation in the nephrotic syndrome: An update. *Kidney* 3:260–263, 1994

8. HUMPHREYS MH: Mechanisms and management of nephrotic syndrome. *Kidney Int* 45:266–281, 1994

9. SALCEDO JR, THABET MA, LATTA K, CHAN JCM: Nephrosis in childhood. *Nephron* 71:373–385, 1995

10. GEERS AB, KOOMANS HA, ROOS JC, DORHOUT MEES EJ: Preservation of blood volume during edema removal in nephrotic subjects. *Kidney Int* 28:652–657, 1985

11. KOOMANS HA, BRAAM B, GEERS AB, ROOS JC, DORHOUT MEES EJ: The importance of plasma protein for blood volume and blood pressure homeostasis. *Kidney Int* 30:730–735, 1986

12. RABELINK TJ, BIJLSMA JA, KOOMANS HA: Iso-oncotic expansion in the nephrotic syndrome. *Clin Sci* 84:627–632, 1993

13. MELTZER JI, KEIM HJ, LARAGH JH, SEALY JE, KUNGMING J, CHIEN S: Nephrotic syndrome: Vasoconstriction and hypervolemic types indicated by renin-sodium profiling. *Ann Intern Med* 91:688–696, 1979

14. NEUHANS TJ, BARRAT TM: Minimal change disease, in *Textbook of Nephrology* (3rd ed), edited by MASSRY SG, GLASSOCK RJ, Baltimore, Williams & Wilkins, 1995, pp 710–719

15. SHAPIRO MD, NICHOLLS KM, GROVES BM, SCHRIER RW: Role of glomerular filtration rate in impaired sodium and water excretion of patients with the nephrotic syndrome. *Am J Kidney Dis* 8:81–87, 1986

16. BROWN EA, MARKANDU ND, SAGNELLA GA, SQUIRES M, JONES BE, MACGREGOR GA: Evidence that some mechanism other than the renin system causes sodium retention in the nephrotic syndrome. *Lancet* ii:1237–1240, 1982

17. VAN DE STOLPE A, JAMISON JL: Micropuncture study of the effect of ANP on the papillary collecting duct in the rat. *Am J Physiol* 254:F477–F483, 1988

18. KOEPKE JP, DIBONA GF: Blunted natriuresis to atrial natriuretic peptide in chronic sodium retaining disorders. *Am J Physiol* 252:F865–F871, 1987

19. HILDEBRANDT DA, BANKS RO: Effects of atrial natriuretic factor on renal function in rats with nephrotic syndrome. *Am J Physiol* 254:F210–F216, 1988

20. WOOLF AS, LYON TL, HOFFBRAND BI, COHEN SL, MOULT PJA: Effects of physiological infusion of atrial natriuretic factor on healthy subjects and patients with the nephrotic syndrome. *Nephron* 52:244–250, 1989

21. HISANAGA S, YAMAMOTO Y, KIDA O, KATO J, FUJIMOTO S, TANAKA K: Plasma concentration and renal effect of human atrial natriuretic peptide in nephrotic syndrome. *Nippon Jinzo Gakkai Shi* 31:661–669, 1989

22. PETERSON C, MADSEN B, PERLMAN A, CHAN AYM, MYERS BD: Atrial natriuretic peptide and the renal response to hypervolemia in nephrotic humans. *Kidney Int* 34:825–831, 1988

23. SCHRIER RW: Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, cirrhosis, and pregnancy. *N Engl J Med* 319:1065–1072, 1127–1134, 1988

24. SCHRIER RW, ARROYO V, BERNARDI M, EPSTEIN M, HENRIKSEN J, RODES J: Peripheral vasodilation hypothesis. A proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 8:1151–1157, 1988

25. ROEY GV, MOORE K: The hepatorenal syndrome. *Pediatr Nephrol* 10:100–107, 1996

26. STARK ME, SZURSZEWSKI JH: Role of nitric oxide in gastrointestinal and hepatic function and disease. *Gastroenterology* 103:1928–1949, 1992

27. HECKER M, MULSCH A, BASSENGE E, BUSSE R: Vasoconstriction and increased flow: Two principle mechanisms of shear stress-dependent endothelial autacoid release. *Am J Physiol* 265:H828–H833, 1993

28. BOMZON A, BLENDIS LM: The nitric oxide hypothesis and the hyperdynamic circulation in cirrhosis. *Hepatology* 20:1343–1350, 1994

29. VALLANCE P, MONCADA S: Hyperdynamic circulation in cirrhosis: A role for nitric oxide? *Lancet* ii:776–778, 1991

30. PAK JM, LEE SS: Review: Glucagon in portal hypertension. *J Hepatol* 20:825–832, 1994

31. MOREAU R, KOMEICHI H, KIRSTETTER P, OHSUGA M, CAILMAIL S, LEBREC D: Altered control of vascular tone by adenosine triphosphate sensitive potassium channels in rats with cirrhosis. *Gastroenterology* 106:1016–1023, 1994

32. SCHRIER RW: Body fluid volume regulation in health and disease: A unifying hypothesis. *Ann Intern Med* 113:155–159, 1990

33. HAYCOCK G: Clinical disorders of sodium, chloride, and water, in *Pediatric Nephrology* (2nd ed), edited by HOLLIDAY MA, BARRATT TM, VERNIER RL, Baltimore, Williams & Wilkins, 1987, pp 95–113

34. HANNA JD, FOREMAN JW, CHAN JCM: Chronic renal insufficiency in infants and children. *Clin Pediatr* 30:365–384, 1991

35. GAUTHIER B, EDELMAN CM JR, BARNETT HL: Management of edema, in *Nephrology and Urology for the Pediatricians*, edited by GAUTHIER B, EDELMAN CM JR, BARNETT HL, Boston, Little Brown and Company, 1982, pp 213–218

36. HANNA JD, CHAN JCM, GILL JR JR: Hypertension and the kidney. *J Pediatr* 118:327–340, 1991

37. SASAKI S, FUSHIMI K, SAITO H: Cloning, characterization and chromosomal mapping of human aquaporin of collecting duct. *J Clin Invest* 93:1250–1256, 1994