REVIEW

Peripheral Edema

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Peripheral edema often poses a dilemma for the clinician because it is a nonspecific finding common to a host of diseases ranging from the benign to the potentially life threatening. A rational and systematic approach to the patient with edema allows for prompt and cost-effective diagnosis and treatment. This article reviews the pathophysiologic basis of edema formation as a foundation for understanding the mechanisms of edema formation in specific disease states, as well as the implications for treatment. Specific etiologies are reviewed to compare the diseases that manifest this common physical sign. Finally, we review the clinical approach to diagnosis and treatment strategies. **Am J Med. 2002;113:580–586.** ©2002 by Excerpta Medica, Inc.

PATHOPHYSIOLOGY

Total body water is divided between the intracellular and extracellular spaces. The extracellular space, which comprises about one third of total body water, is composed of the intravascular plasma volume (25%) and the extravascular interstitial space (75%) (1). Starling defined the physiologic forces involved in maintaining the balance of water between these two compartments (2,3), which include the gradient between intravascular and extravascular hydrostatic pressures, differences in oncotic pressures within the interstitial space and plasma, and the hydraulic permeability of the blood vessel wall (4). The lymphatic system collects fluid and filtered proteins from the interstitial space and returns them to the vascular compartment (Figure). Major perturbations in this delicate homeostasis that favors net filtration out of the vascular space, or impaired return of fluid by lymphatics from the interstitial space, will result in edema.

Starling Forces

Increased venous pressures due to central or regional venous obstruction or to an expansion in plasma volume are transmitted to the capillary bed, thereby increasing hydrostatic pressure and predisposing to edema (Figure). Conversely, local autoregulation by smooth muscle sphincters on the precapillary (or arterial) side protect the capillary bed from increases in systemic arterial pressure, which explains why hypertensive patients do not have edema despite elevated blood pressure (5,6).

The major contributors to interstitial oncotic pressure are mucopolysaccharides, filtered proteins such as albumin, capillary wall protein permeability, and the rate of lymphatic clearance (5,6). Changes in capillary wall permeability are mediated by cytokines such as tumor necrosis factor, interleukin 1, and interleukin 10, as well as by circulating vasodilatory prostaglandins and nitric oxide (7). Increased vascular permeability is central to edema resulting from local inflammation (e.g., insect bites), allergic reactions, and burns.

Renal and Neurohumoral Factors

Because the tissues constituting the interstitium easily accommodate several liters of fluid, a patient's weight may increase nearly 10% before pitting edema is evident. The source of this expansion of interstitial fluid is the blood plasma. Because normal blood plasma is only about 3 L, the diffusion of large amounts of water and electrolytes into the interstitial space necessitates the renal retention of sodium and water to maintain hemodynamic stability (6). Hence, blood volume and normal osmolality are maintained despite movement of large amounts of fluid into the extravascular space.

"Effective" intravascular volume depletion, which occurs in chronic heart failure and cirrhosis, initiates a neurohumoral cascade that attempts to maintain effective circulating volume. This cascade reduces glomerular filtration rate via renal vasoconstriction, increases sodium reabsorption proximally mediated by angiotensin II and norepinephrine, and increases sodium and water reabsorption in the collecting tubules mediated by aldosterone and antidiuretic hormone. Additionally, endothelium-derived factors such as nitric oxide and prostaglandins are increasingly recognized as being important in regulating homeostasis (8,9). Collectively, they limit sodium and water excretion, thereby promoting edema development (5). Over time, these responses become mal-

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Manuscript submitted March 13, 2002, and accepted in revised form August 5, 2002.

0002-9343/02/$–see front matter
PII S0002-9343(02)01322-0

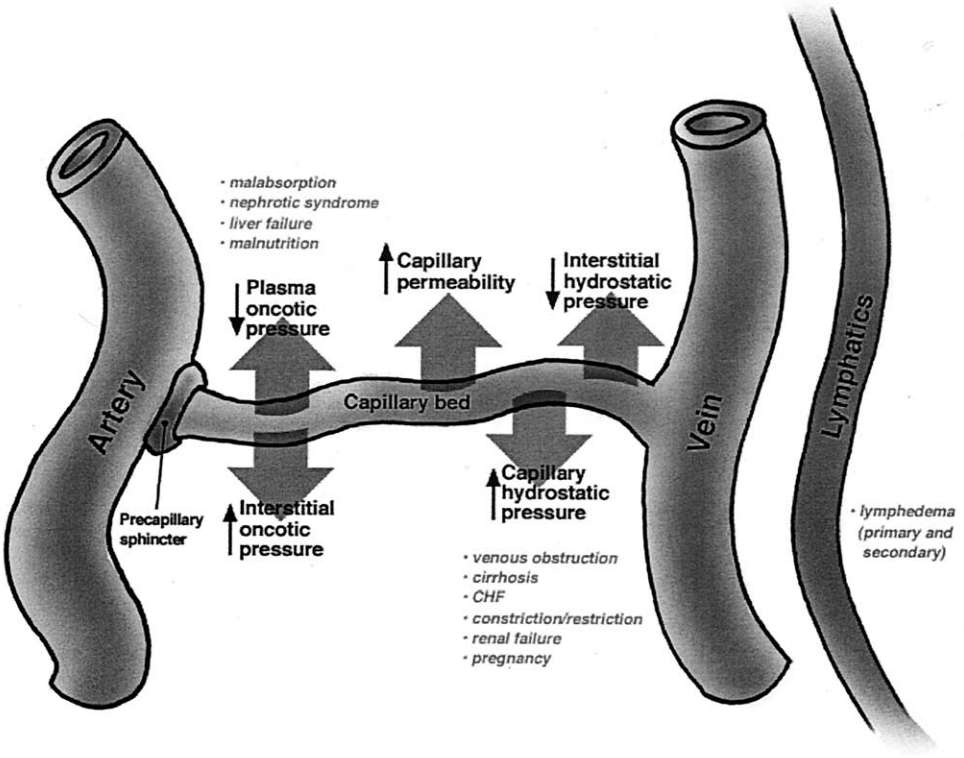

Figure. Factors involved in the formation of edema include the hydrostatic pressures of the interstitial and intravascular spaces, and the oncotic pressures of the plasma and interstitium. Capillary membrane permeability determines the movement of osmotically active particles between the intravascular and extravascular spaces. The lymphatic channels parallel the venous bed and return protein-rich lymph to the circulation. The precapillary arterial sphincter allows the capillary bed to autoregulate, thereby protecting it from large fluctuations in arterial pressure. CHF = heart failure

adaptive, leading to a cycle of further sodium and water retention.

In contrast, natriuretic peptides, which are released into the circulation in response to cardiac chamber distention or sodium load, enhance excretion of sodium and water by the kidneys. They augment glomerular filtration, inhibit sodium reabsorption in the proximal tubule, inhibit release of renin and aldosterone, and result in arteriolar and venous dilatation. Unfortunately, abnormal end-organ resistance to natriuretic peptides inevitably occurs in chronic edematous states, which explains the sodium retention in these conditions despite high circulating levels of atrial natriuretic peptide (9,10).

ETIOLOGIES

Heart Failure

In heart failure, an elevation in venous pressure caused by ventricular systolic or diastolic dysfunction increases capillary hydrostatic pressure (Table 1). The resulting low-output state activates the aforementioned neurohumoral mechanisms that maintain arterial perfusion. If the resulting extravasation of fluid outpaces the ability of the lymphatic system to return this fluid to the vascular space, edema will result. With left ventricular failure, this manifests as pulmonary edema; whereas with right ventricular failure, this leads to peripheral edema (6). The severity of the edema may be disproportionate to the degree of central venous pressure elevation depending on factors such as immobility, posture, and venous insufficiency.

Constrictive Pericarditis/Restrictive Cardiomyopathy

The signs of both constrictive pericarditis and restrictive cardiomyopathy are similar to those of right heart failure, namely elevated jugular venous pressure, hepatic congestion, ascites, and peripheral edema (Table 1), and their onset may be insidious. Patients with elevated neck veins often receive a misdiagnosis of primary hepatic cirrhosis (11). A possible diagnosis of constriction or restriction should be considered in a patient presenting with unexplained edema, elevated jugular venous pressure, and relatively preserved systolic function. Although echocardiography may provide indirect evidence, more invasive

Table 1. Causes of Peripheral Edema

Increased capillary hydrostatic pressure
Regional venous hypertension (often unilateral)
Inferior vena caval/iliac compression
Deep venous thrombosis
Chronic venous insufficiency
Compartment syndrome
Systemic venous hypertension
Heart failure
Constrictive pericarditis
Restrictive cardiomyopathy
Tricuspid valvular disease
Cirrhosis/liver failure
Increased plasma volume
Heart failure
Renal failure (acute, chronic)
Drugs
Pregnancy
Premenstrual edema
Decreased plasma oncotic pressure
Protein loss
Malabsorption
Preeclampsia
Nephrotic syndrome
Reduced protein synthesis
Cirrhosis/liver failure
Malnutrition (e.g., kwashiorkor)
Malabsorption
Beriberi
Increased capillary permeability (usually clinically obvious)
Allergic reactions: histamine release (hives), serum sickness, angioedema
Burns
Inflammation/local infections
Interleukin 2 therapy
Lymphatic obstruction or increased interstitial oncotic pressure
Lymphedema (primary or secondary [nodal enlargement due to malignancy, postsurgical/radiation, filariasis])
Other
Idiopathic
Myxedema

studies such as right heart catheterization or tissue biopsy are often necessary to make a conclusive diagnosis.

Nephrotic Syndrome

The nephrotic syndrome comprises a group of disorders that are characterized by severe proteinuria, hypoalbuminemia, hyperlipidemia, and edema. Nephrotic proteinuria is often caused by diabetic nephropathy, although it may result from primary glomerular disease or less common conditions (12). Although the syndrome has been long recognized, the mechanism of edema formation is still debated. The long-held "underfill" theory postulates that edema results from reduced colloid oncotic pressure due to massive protein loss by the kidneys, which leads to translocation of water into the interstitial space (Table 1). The reduction in effective circulating volume then triggers the efferent mechanisms that perpetuate the cycle of edema formation. Although this may occur in children with acute nephrosis, it is not the likely mechanism in most adults. In fact, most patients with nephrotic syndrome have increased neurohumoral hormone levels (13–15) . These findings suggest that primary salt retention by the kidneys has substantial effects in most patients (16). The low plasma oncotic pressure increases the amount of edema that is observed for any increase in plasma volume and central venous pressure. Therefore, estimation of the central venous pressure is very important as a guide to diuretic therapy. If the plasma volume is reduced very rapidly with diuretics, patients can develop acute renal failure while having substantial edema.

Hypoproteinemia

Hypoproteinemia can occur in several conditions other than nephrotic syndrome, although the mechanism of edema formation may be similar. These etiologies include severe nutritional deficiency (e.g., kwashiorkor), protein-losing enteropathies, and severe liver disease where hepatic synthetic function is impaired (Table 1). Albumin is important for maintaining plasma oncotic pressure, and a level below 2 g/dL of plasma often results in edema.

Cirrhosis

End-stage liver disease results in profound salt and water retention. Although most of this fluid retention manifests in the peritoneal cavity as ascites, peripheral edema may become prominent in later stages, particularly when there is severe hypoalbuminemia. As in heart failure, decreased "effective" circulating volume initiates a neurohumoral cascade of events leading to increased sodium and water reabsorption by the kidneys (Table 1). This decrease is, in part, the result of splanchnic vasodilatation and arteriovenous fistula formation throughout the body that reduce vascular resistance. Unlike heart failure, cardiac output is normal or elevated in this form of high-output failure (5,17).

Drugs

Medications may cause, or exacerbate, peripheral edema (Tables 1 and 2). Antihypertensive drugs such as calcium channel blockers and direct vasodilators are most frequently implicated. Of the calcium channel blockers, the dihydropyridines are more likely to induce peripheral edema than are the phenylalkylamine or benzothiazepine classes, purportedly because of more selective arteriolar vasodilatation (18–20). The direct vasodilators such as minoxidil and diazoxide enhance renal sodium reabsorption through their blood pressure effect and activation of the renin-angiotensin-aldosterone system (21,22). Angiotensin-converting enzyme inhibitors, in contrast,

Table 2. Drugs that Cause Peripheral Edema

Antidepressants
Monoamine oxidase inhibitors
Antihypertensive medications
Calcium channel blockers: dihydropyridines (e.g., nifedipine, amlodipine, felodipine), phenylalkylamines (e.g., verapamil), benzothiazepines (e.g., diltiazem)
Direct vasodilators: hydralazine, minoxidil, diazoxide
Beta-blockers
Centrally acting agents: clonidine, methyldopa
Antisympathetics: reserpine, guanethidine
Hormones
Corticosteroids
Estrogens/progesterones
Testosterone
Nonsteroidal anti-inflammatory agents
Nonselective cyclooxygenase inhibitors
Selective cyclooxygenase-2 inhibitors
Others
Troglitazone, rosiglitazone, pioglitazone
Phenylbutazone

rarely cause dependent edema, suggesting that in other vasodilators angiotensin may play a central role in edema formation.

Troglitazone, rosiglitazone, and pioglitazone have been associated with peripheral and pulmonary edema, and are generally contraindicated in patients with New York Heart Association class III or IV heart failure. The edema is partly attributed to the 6% to 8% increase in plasma volume associated with use of these drugs. The mechanism of edema formation, however, is not known. Hence, use of these drugs in patients with milder forms of heart failure must be weighed against the potential risk of worsening volume overload. Such patients should be monitored for changes in weight and fluid status (23,24).

Pregnancy

Peripheral edema is evident in 80% of normal pregnancies, half of which involve the lower extremities. The majority of this weight gain occurs during the second trimester (25). Several factors conducive to edema formation are present in the gravid patient, such as increased plasma volume and sodium retention (Table 1), decreased plasma protein concentration, increased capillary hydrostatic pressure late in pregnancy because of mechanical compression of the internal vena cava and iliac veins, increased antinatriuretic hormones such as aldosterone and desoxycorticosterone, and activation of the renin-angiotensin-aldosterone system (26).

Chronic Venous Insufficiency

Chronic venous insufficiency often results from long-standing venous valvular incompetence that leads to venous hypertension (Table 1). The most common cause of valvular incompetence is the sequela of prior clinical or occult deep venous thromboses. As the thrombosis heals, valves are destroyed, leading to incompetency and venous wall distortion (27).

The edema may be unilateral or bilateral, although it is often asymmetric. Early in its course, it is soft and pitting, whereas in the later stages, chronic venous and dermal changes such as varicosities, induration, fibrosis, and pigmentation develop. Symptoms may be exacerbated by heat or prolonged sitting or standing. The extremities are susceptible to secondary complications such as dermatitis, cellulitis, and stasis ulceration. Venous stasis ulcers typically occur around the medial malleoli (28).

Lymphedema

Lymphedema results from impaired lymphatic transport leading to the pathologic accumulation of protein-rich lymphatic fluid in the interstitium, most commonly in the extremities (Table 1). Secondary lymphadema is the most common form. In the United States, edema of the upper extremity after axillary lymph node dissection is the most common cause of acquired lymphadema, whereas filariasis is the most common cause worldwide, affecting more than 90 million people (29,30).

With long-standing lymph stasis, cutaneous and subcutaneous fibrosis develops into the classic, indurated *peau d'orange* appearance of the skin. There is preferential swelling of the dorsum of the foot, with a characteristic "squared-off" appearance to the toes. This swelling results in the inability to tent the skin on the dorsum of the digits of the affected extremity, also known as Stemmer's sign (31). Depending on the etiology, the edema may be unilateral or bilateral. Even when bilateral, it is common for the lymphedema to be asymmetric in severity.

Lipedema is commonly mistaken for peripheral edema or lymphedema. In this condition, the leg swelling is due to abnormal accumulation of fatty substances in the subcutaneous tissues, characteristically sparing the feet, and found almost exclusively in young women. The onset is usually insidious and often becomes apparent shortly after puberty. The lack of involvement of the feet and the absence of Stemmer's sign help to distinguish lipedema from lymphedema (31).

Myxedema

Peripheral edema may occur in the setting of hyperthyroidism or hypothyroidism, although it is more common with thyroid hormone deficiency, occurring in about half of all patients with myxedema (Table 1). Localized edema of the eyelids, face, and dorsum of the hand are noted more frequently. There are numerous direct and indirect biochemical responses to hypothyroidism that affect nearly all organ systems, and the mechanism of myxedema is not fully understood. At the capillary level, there is increased permeability resulting in the accumulation of proteins and mucopolysaccharides in the interstitium,

followed by sodium and water. There is a concomitant expansion in total body water and sodium (32–37).

Idiopathic Edema

"Idiopathic edema" describes a poorly understood syndrome of abnormal fluid retention that primarily affects premenopausal women (Table 1). In attempts to describe its primary features, the condition has also been termed cyclical edema, periodic edema, fluid retention syndrome, or orthostatic edema (38). The key features are periodic episodes of edema in women who have weight changes that are not clearly related to the menstrual cycle. Symptoms are usually described as swelling of the hands, legs, or face, or abdominal bloating, which may be real, or perceived by the patient. By definition, its diagnosis is made after excluding other organic causes of water retention. It is most common in the third and fourth decades of life. Psychologic and emotional disturbances are common comorbid conditions. Concomitant misuse of diuretics or laxatives is also common in patients with this disorder (39,40).

CLINICAL APPROACH

Initial efforts in the work-up should focus on excluding major organ system failure as the underlying cause. However, given the ubiquity and often benign causes of peripheral edema, a rational approach is necessary to minimize patients' exposure to unnecessary tests and to contain costs. A thorough history and physical examination are critical. Examination of the lower extremities should document more than the presence or absence of pitting. Comparisons of one foot and leg with those on the other side should note any asymmetry, epidermal and dermal changes, discoloration, tenderness, cords, and prominence of veins. The character and location of any ulcers should be noted. The severity of edema, from slight to very marked, is traditionally reported on a four-point scale (41). Because this scale is subjective, noting the height of the edema may provide more practical and reproducible information. Simple diagnostic tests can be ordered as part of the initial evaluation. These may include a chemistry panel and urinalysis to evaluate renal function, liver function tests to detect hepatic disease, measurement of albumin levels to assess nutritional status, and measurement of thyroid-stimulating hormone levels to rule out hypothyroidism. An electrocardiogram and chest radiograph may be useful in assessing cardiopulmonary disease. Additional studies such as serum and urine protein electropheresis, full thyroid function studies, 24-hour urine collection, imaging studies (e.g., computed tomography, echocardiography), and invasive studies (e.g., right heart catheterization, biopsies) are more invasive and costly, and should only be ordered when preliminary findings raise enough clinical suspicion to warrant them.

Developing a less expensive means of screening for heart failure as the cause of edema has been addressed (42–47), focusing on electrocardiography and the measurement of plasma hormone levels such as atrial natriuretic peptide or brain natriuretic peptide (48,49). Results from the recent study by Dao et al. (49) suggest that measurement of B-type natriuretic peptide blood concentration may be a sensitive and specific test to diagnose heart failure in urgent care settings.

Treatment

Treatment requires the recognition and management of underlying conditions that predispose to the formation of edema. Only by correcting the disruptions in Starling forces that lead to the cascade of water retention can the cycle be halted and the process reversed. In many cases, the elimination of edema is not possible, whereas in some it is not desirable. A combination of patient education, sodium restriction, and, when appropriate, the use of diuretics are often required.

To reduce extracellular fluid volume, a negative sodium balance must be achieved by reducing sodium intake, increasing excretion of sodium, or both. If sodium intake remains high, increasing sodium excretion may not be sufficient to decrease extracellular volume. Reducing sodium intake is often not sufficient, and diuretics such as loop diuretics, thiazide diuretics, and potassium-sparing diuretics may be needed. These classes of diuretics act within the tubular lumen to inhibit sodium reabsorption within the nephron.

Diuretics

Loop diuretics are usually the most effective for diuresis. Because their plasma half-lives are short (e.g., 1 hour for bumetanide, 1.5 to 2 hours for furosemide, 3 to 4 hours for torsemide) (50), several doses are required per day to maintain natriuresis. The maximal response to each loop diuretic is patient specific; hence, a threshold level of the drug at the site of action must be attained for maximal response. Exceeding this threshold dose will not result in greater diuresis. Similarly, if an adequate dose fails to achieve a response, changing to a different loop diuretic will not be efficacious because the mechanisms of action are the same (51).

The bioavailability of loop diuretics is the same in patients with renal insufficiency and in normal patients, but a larger dose may be necessary to attain the threshold amount of drug in the tubular fluid (51). Reducing sodium reabsorption in the distal nephron by adding thiazide or potassium-sparing diuretics may improve diuresis in patients who are refractory to loop diuretics alone. Sodium retention in patients with nephrotic syndrome is high. Therefore, higher doses of loop diuretics are often

required to achieve effective sodium excretion, and the addition of a thiazide diuretic is often necessary (52).

Patients with cirrhosis often have secondary hyperaldosteronism, and for them spironolactone is a common first choice for diuretic therapy. The initial dose is usually 50 mg/d, and its long half-life allows for once-daily dosing. The maximum dose is 400 mg/d. In patients in whom spironolactone is inadequate, a thiazide or loop diuretic may be added. If needed, large-volume paracenteses can be performed to reduce the need for higher doses of diuretics. Rapid diuresis should be avoided in cirrhotic patients, especially in those without much peripheral edema in whom the extravascular fluid is primarily localized as ascites. In these patients, only the peritoneal capillaries are available to mobilize the fluid. Overly aggressive diuresis may then outpace the ability to replenish the plasma volume, precipitating the hepatorenal syndrome or hemodynamic collapse. A daily rate of diuresis of about 500 cc is recommended (6).

CONCLUSION

Peripheral edema is a common manifestation of many disease states. Its proper diagnosis and management mandates an understanding of the physiologic principles governing its formation. By directing specific therapy at correcting the underlying capillary hemodynamic disturbance, development of edema may be halted or reversed. Lifestyle and dietary modification in conjunction with pharmacotherapy are also useful in long-term management.

ACKNOWLEDGMENT

We are indebted to Drs. Paul Heidenreich, Victor Froelicher, and Timothy Meyer for their thoughtful review of this manuscript. We also thank Ms. Belinda Byrne for assistance with the artwork.

REFERENCES

1. Braunwald E. Edema. In: Isselbacher KJ, Braunwald E, Wilson JD, et al., eds. *Harrison's Principles of Internal Medicine.* 13th ed. New York: McGraw-Hill; 1994:183–187.
2. Starling EH. Physiologic forces involved in the causation of dropsy. *Lancet.* 1896;I:1267–1270.
3. Little RC, Ginsburg JM. The physiologic basis for clinical edema. *Arch Intern Med.* 1984;144:1661–1664.
4. Rose BD, Post TW. *Clinical Physiology of Acid-Base and Electrolyte Disorders.* New York: McGraw-Hill; 2001.
5. Andreoli TE. Edematous states: an overview. *Kidney Int.* 1997; 51(suppl):S2–S10.
6. Rose BD. *Renal Pathophysiology: The Essentials.* Baltimore: Williams & Wilkins; 1994.
7. Diskin CJ, Stokes TJ, Dansby LM, et al. Towards an understanding of oedema. *BMJ.* 1999;318:1610–1613.
8. Townsend JN, Doran J, Lote CJ, Davies MK. Peripheral hemodynamic effect of inhibition of prostaglandins synthesis in congestive heart failure and interactions with captopril. *Br Heart J.* 1995;73: 434–441.
9. Martin PY, Schrier RW. Sodium and water retention in heart failure: pathogenesis and treatment. *Kidney Int.* 1997;51(suppl): S57–S61.
10. Anand IS, Ferrari R, Gurcharan SK, et al. Edema of cardiac origin: studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive failure. *Circulation.* 1989;80:299–305.
11. Anand IS, Ferrari R, Kalra GS, et al. Pathogenesis of edema in constrictive pericarditis. *Circulation.* 1991;83:1880–1887.
12. Ritz E, Stefanski A. Diabetic nephropathy in type II diabetes. *Am J Kidney Dis.* 1996;27:167–194.
13. Dorhout Mees EJ, Geers AB, Koomans HA. Blood volume and sodium retention in the nephrotic syndrome: a controversial pathophysiological concept. *Nephron.* 1984;36:201–211.
14. Eisenberg S. Blood volume in persons with the nephrotic syndrome. *Am J Med Sci.* 1968;255:320–326.
15. Chonko AM, Bay WH, Stein J, et al. The role of renin and aldosterone in the salt retention of edema. *Am J Med.* 1977;63:881–889.
16. Palmer BF, Alpern RJ. Pathogenesis of edema formation in the nephrotic syndrome. *Kidney Int.* 1997;51(suppl):S21–S27.
17. Martin PY, Schrier RW. Pathogenesis of water and sodium retention in cirrhosis. *Kidney Int.* 1997;51(suppl):S43–S49.
18. Halperin AK, Cubeddu LX. The role of calcium channel blockers in the treatment of hypertension. *Am Heart J.* 1986;111:363–382.
19. Andresdottir MB, van Hamersvelt HW, van Helden MJ, et al. Ankle edema formation during treatment with the calcium channel blockers lacidipine and amlodipine: a single-centre study. *J Card Pharm.* 2000;35(suppl):S25–S30.
20. Valentin JP, Ribstein J, Halimi JM, Mimran A. Effect of different calcium antagonists on transcapillary fluid shift. *Am J Hypertens.* 1990;3:491–495.
21. Markham RV Jr, Gilmore A, Pettinger WA, et al. Central and regional hemodynamic effects and neurohumoral consequences of minoxidil in severe congestive heart failure and comparison to hydralazine and nitroprusside. *Am J Cardiol.* 1983;52:774–781.
22. Mroczek WJ, Lee WR. Diazoxide therapy: use and risks. *Ann Intern Med.* 1976;85:529.
23. Gorson DM. Significant weight gain with Rezulin therapy. *Arch Intern Med.* 1999;159:99.
24. Thomas ML, Lloyd SJ. Pulmonary edema associated with rosiglitazone and troglitazone. *Ann Pharmacother.* 2001;35:123–124.
25. Davison JM. Edema in pregnancy. *Kidney Int.* 1997;51(suppl):S90–S96.
26. Valenzuela GJ. Is a decrease in plasma oncotic pressure enough to explain the edema in pregnancy? *Am J Obstet Gynecol.* 1989;161: 1624–1627.
27. Young JR. The swollen leg: clinical significance and differential diagnosis. *Cardiol Clin.* 1991;9:443–456.
28. Schirger A. DDx and management of leg edema in the elderly. *Geriatrics.* 1982;37:26–32.
29. Lymphatic filariasis—tropical medicine's origin will not go away [editorial]. *Lancet.* 1987;1:1409–1410.
30. Szuba A, Rockson S. Lymphedema: anatomy, physiology and pathogenesis. *Vasc Med.* 1997;2:321–326.
31. Rockson S. Lymphedema. *Am J Med.* 2001;110:288–295.
32. Hierholzer K, Finke R. Myxedema. *Kidney Int.* 1997;51(suppl): S82–S89.
33. Goldberg M, Reivich M. Studies on the mechanism of hyponatremia and impaired water excretion in myxedema. *Ann Intern Med.* 1962;56:120–130.

34. Pettinger WA, Talner L, Ferris TF. Inappropriate secretion of antidiuretic hormone due to myxedema. *N Engl J Med.* 1965;272:362–364.
35. Chinitz A, Turner FL. The association of primary hypothyroidism and inappropriate secretion of antidiuretic hormone. *Arch Intern Med.* 1965;116:871–874.
36. DeRubertis FR, Michelis MF, Bloom ME, et al. Impaired water excretion in myxedema. *Am J Med.* 1971;51:41–53.
37. Iwasaki Y, Oiso Y, Yamauchi K, et al. Osmoregulation of plasma vasopressin in myxedema. *J Clin Endocrinol Metab.* 1990;70:534–539.
38. Kay A, Davis CL. Idiopathic edema. *Am J Kidney Dis.* 1999;34:405–423.
39. Thorn G. Approach to the patient with "idiopathic edema" or "periodic swelling." *JAMA.* 1968;206:333–338.
40. McKendry JB. Idiopathic edema. *Can Nurse.* 1973;69:41–43.
41. Bates B. *Examination and History Taking.* Philadelphia: J.B. Lippincott; 1991.
42. Blankfield RP, Finkelhor RS, Alexander JJ, et al. Etiology and diagnosis of bilateral leg edema in primary care. *Am J Med.* 1998;105:192–197.
43. Davie AP, Love MP, McMurray JJ. Value of ECGs in identifying heart failure due to left systolic dysfunction. *BMJ.* 1996;313:300–301.
44. Davidson C. Can heart failure be diagnosed in primary care. Chest radiography is still useful. *BMJ.* 2000;321:1414–1415.
45. McDonagh TA, Robb SD, Murdoch DR, et al. Biochemical detection of left-ventricular dysfunction. *Lancet.* 1998;351:9–13.
46. Talwar S, Squire IB, Davies JE, et al. Plasma N-terminal pro-brain natriuretic peptide and the ECG in the assessment of left ventricular systolic dysfunction in a high risk population. *Eur Heart J.* 1999;20:1736–1744.
47. McClure SJ, Caruana L, Davie AP, et al. Cohort study of plasma natriuretic peptides for identifying left ventricular systolic dysfunction in primary care. *BMJ.* 1998;317:516–519.
48. Nielsen OW, Hansen JF, Hilden J, et al. Risk assessment of left ventricular systolic dysfunction in primary care: cross sectional study evaluating a range of diagnostic tests. *BMJ.* 2000;320:220–224.
49. Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. *J Am Coll Cardiol.* 2001;37:379–385.
50. Vargo DL, Kramer WG, Black PK, et al. Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. *Clin Pharmacol Ther.* 1995;57:601–609.
51. Brater DC. Diuretic therapy. *N Engl J Med.* 1998;339:387–395.
52. Voelker JR, Cartwright-Brown D, Anderson S, et al. Comparison of loop diuretics in patients with chronic renal insufficiency. *Kidney Int.* 1987;32:572–578.