TABLE 50-1 PRINCIPAL CAUSES OF GENERALIZED EDEMA: HISTORY, PHYSICAL EXAMINATION, AND LABORATORY FINDINGS

Organ System	History	Physical Examination	Laboratory Findings
Cardiac	Dyspnea with exertion prominent—often associated with orthopnea—or paroxysmal nocturnal dyspnea	Elevated jugular venous pressure, ventricular (S_3) gallop; occasionally with displaced or dyskinetic apical pulse; peripheral cyanosis, cool extremities, small pulse pressure when severe	Elevated urea nitrogen-to-creatinine ratio common; serum sodium often diminished; elevated natriuretic peptides
Hepatic	Dyspnea uncommon, except if associated with significant degree of ascites; most often a history of ethanol abuse	Frequently associated with ascites; jugular venous pressure normal or low; blood pressure lower than in renal or cardiac disease; one or more additional signs of chronic liver disease (jaundice, palmar erythema, Dupuytren's contracture, spider angiomata, male gynecomastia; asterixis and other signs of encephalopathy) may be present	If severe, reductions in serum albumin, cholesterol, other hepatic proteins (transferrin, fibrinogen); liver enzymes elevated, depending on the cause and acuity of liver injury; tendency toward hypokalemia, respiratory alkalosis; macrocytosis from folate deficiency
Renal (CRF)	Usually chronic: may be associated with uremic signs and symptoms, including decreased appetite, altered (metallic or fishy) taste, altered sleep pattern, difficulty concentrating, restless legs, or myoclonus; dyspnea can be present, but generally less prominent than in heart failure	Elevated blood pressure; hypertensive retinopathy; nitrogenous fetor; pericardial friction rub in advanced cases with uremia	Elevation of serum creatinine and cystatin C; albuminuria; hyperkalemia, metabolic acidosis, hyperphosphatemia, hypocalcemia, anemia (usually normocytic)
Renal (NS)	Childhood diabetes mellitus; plasma cell dyscrasias	Periorbital edema; hypertension	Proteinuria (≥3.5 g/d); hypoalbuminemia; hypercholesterolemia; microscopic hematuria

Abbreviations: CRF, chronic renal failure; NS, nephrotic syndrome.

Source: Modified from GM Chertow: Approach to the patient with edema, in *Primary Cardiology*, 2nd ed, E Braunwald, L Goldman (eds). Philadelphia, Saunders, 2003, pp 117–128.

effective arterial volume through the operation of Starling's law of the heart, in which an increase in ventricular diastolic volume promotes a more forceful contraction and may thereby maintain the cardiac output. However, if the cardiac disorder is more severe, sodium and water retention continue, and the increment in blood volume accumulates in the venous circulation, raising venous pressure and causing edema (Fig. 50-1).

The presence of heart disease, as manifested by cardiac enlargement and/or ventricular hypertrophy, together with evidence of cardiac failure, such as dyspnea, basilar rales, venous distention, and hepatomegaly, usually indicates that edema results from heart failure. Noninvasive tests such as echocardiography may be helpful in establishing the diagnosis of heart disease. The edema of heart failure typically occurs in the dependent portions of the body.

Edema of Renal Disease (See also Chap. 338) The edema that occurs during the acute phase of glomerulonephritis is characteristically associated with hematuria, proteinuria, and hypertension. Although some evidence supports the view that the fluid retention is due to increased capillary permeability, in most instances, the edema results from primary retention of sodium and water by the kidneys owing to renal insufficiency. This state differs from most forms of heart failure in that it is characterized by a normal (or sometimes even increased) cardiac output. Patients with edema due to acute renal failure commonly have arterial hypertension as well as pulmonary congestion on chest roentgenogram, often without considerable cardiac enlargement, but they may not develop orthopnea. Patients with *chronic* renal failure may also develop edema due to primary renal retention of sodium and water.

Nephrotic Syndrome and other Hypoalbuminemic States The primary alteration in the nephrotic syndrome is a diminished colloid oncotic pressure due to losses of large quantities (≥3.5 g/d) of protein into the urine. With severe hypoalbuminemia (<35 g/L) and the consequent reduced colloid osmotic pressure, the sodium and water that are retained cannot be restrained within the vascular compartment, and total and effective arterial blood volumes decline. This process initiates the edema-forming sequence of events described above, including activation of the RAAS. The nephrotic syndrome may occur during the course of a variety of kidney diseases, which include glomerulonephritis, diabetic glomerulosclerosis, and hypersensitivity reactions. The edema is diffuse, symmetric, and most prominent in the dependent areas; as a consequence, periorbital edema is most prominent in the morning.

Hepatic Cirrhosis (See also Chap. 365) This condition is characterized in part by hepatic venous outflow blockade, which in turn expands the splanchnic blood volume and increases hepatic lymph formation. Intrahepatic hypertension acts as a stimulus for renal sodium retention and causes a reduction of effective arterial blood volume. These alterations are frequently complicated by hypoalbuminemia secondary to reduced hepatic synthesis of albumin, as well as peripheral arterial vasodilation. These effects reduce the effective arterial blood volume further, leading to activation of the RAAS and renal sympathetic nerves and to release of AVP, endothelin, and other sodium- and water-retaining mechanisms (Fig. 50-1*B*). The concentration of circulating aldosterone often is elevated by the failure of the liver to metabolize this hormone. Initially, the excess interstitial fluid is localized preferentially proximal (upstream) to the congested portal venous system and obstructed hepatic lymphatics, i.e., in the peritoneal cavity (causing ascites, Chap. 59). In later stages, particularly when there is severe hypoalbuminemia, peripheral edema may develop. A sizable accumulation of ascitic fluid may increase intraabdominal pressure and impede venous return from the lower extremities and contribute to the accumulation of edema of the lower extremities.

The excess production of prostaglandins (PGE_2 and PGI_2) in cirrhosis attenuates renal sodium retention. When the synthesis of these substances is inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs), renal function may deteriorate, and this may increase sodium retention further.

Drug-Induced Edema A large number of widely used drugs can cause edema (Table 50-2). Mechanisms include renal vasoconstriction (NSAIDs and cyclosporine), arteriolar dilation (vasodilators), augmented renal sodium reabsorption (steroid hormones), and capillary damage.

Edema of Nutritional Origin A diet grossly deficient in protein over a prolonged period may produce hypoproteinemia and edema. The latter may be intensified by the development of beriberi heart disease, which also is of nutritional origin, in which multiple peripheral arteriovenous fistulae result in reduced effective systemic perfusion and effective arterial blood volume, thereby enhancing edema formation (Chap. 96e) (Fig. 50-1*B*). Edema may actually become intensified