CLUBBING

The selective bulbous enlargement of the distal segments of the fingers and toes due to proliferation of connective tissue, particularly on the dorsal surface, is termed *clubbing*; there is also increased sponginess of the soft tissue at the base of the clubbed nail. Clubbing may be hereditary, idiopathic, or acquired and associated with a variety of disorders, including cyanotic congenital heart disease (see above), infective endocarditis, and a variety of pulmonary conditions (among them primary and metastatic lung cancer, bronchiectasis, asbestosis, sarcoidosis, lung abscess, cystic fibrosis, tuberculosis, and mesothelioma), as well as with some gastrointestinal diseases (including inflammatory bowel disease and hepatic cirrhosis). In some instances, it is occupational, e.g., in jackhammer operators.

Clubbing in patients with primary and metastatic lung cancer, mesothelioma, bronchiectasis, or hepatic cirrhosis may be associated with *hypertrophic osteoarthropathy*. In this condition, the subperiosteal formation of new bone in the distal diaphyses of the long bones of the extremities causes pain and symmetric arthritis-like changes in the shoulders, knees, ankles, wrists, and elbows. The diagnosis of hypertrophic osteoarthropathy may be confirmed by bone radiograph or magnetic resonance imaging (MRI). Although the mechanism of clubbing is unclear, it appears to be secondary to humoral substances that cause dilation of the vessels of the distal digits as well as growth factors released from platelet precursors in the digital circulation. In certain circumstances, clubbing is reversible, such as following lung transplantation for cystic fibrosis.

50 Edema

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STARLING FORCES AND FLUID EXCHANGE

About one-third of total-body water is confined to the extracellular space. Approximately 75% of the latter is interstitial fluid, and the remainder is the plasma. The forces that regulate the disposition of fluid between these two components of the extracellular compartment frequently are referred to as the *Starling forces*. The hydrostatic pressure within the capillaries and the colloid oncotic pressure in the interstitial fluid tend to promote movement of fluid from the vascular to the extravascular space. By contrast, the colloid oncotic pressure contributed by plasma proteins and the hydrostatic pressure within the interstitial fluid promote the movement of fluid into the vascular compartment. As a consequence, there is movement of water and diffusible solutes from the vascular space at the arteriolar end of the capillaries. Fluid is returned from the interstitial space into the vascular system at the venous end of the capillaries and by way of the lymphatics. These movements are usually balanced so that there is a steady state in the sizes of the intravascular and interstitial compartments, yet a large exchange between them occurs. However, if either the capillary hydrostatic pressure is increased and/or the oncotic pressure is reduced, a further net movement of fluid from intravascular to the interstitial spaces will take place.

Edema is defined as a clinically apparent increase in the interstitial fluid volume, which develops when Starling forces are altered so that there is increased flow of fluid from the vascular system into the interstitium. Edema due to an increase in capillary pressure may result from an elevation of venous pressure caused by obstruction to venous and/or lymphatic drainage. An increase in capillary pressure may be generalized, as occurs in heart failure, or it may be localized to one extremity when venous pressure is elevated due to unilateral thrombophlebitis (see below). The Starling forces also may be imbalanced when the colloid oncotic pressure of the plasma is reduced owing to any factor that may induce hypoalbuminemia, as when large quantities of protein are lost in the urine such as in the nephrotic syndrome (see below), or when synthesis is reduced in a severe catabolic state.

CAPILLARY DAMAGE

Edema may also result from damage to the capillary endothelium, which increases its permeability and permits the transfer of proteins into the interstitial compartment. Injury to the capillary wall can result from drugs (see below), viral or bacterial agents, and thermal or mechanical trauma. Increased capillary permeability also may be a consequence of a hypersensitivity reaction and of immune injury. Damage to the capillary endothelium is presumably responsible for inflammatory edema, which is usually nonpitting, localized, and accompanied by other signs of inflammation—i.e., erythema, heat, and tenderness.

REDUCTION OF EFFECTIVE ARTERIAL VOLUME

In many forms of edema, despite the increase in extracellular fluid volume, the effective arterial blood volume, a parameter that represents the filling of the arterial tree and that effectively perfuses the tissues, is reduced. Underfilling of the arterial tree may be caused by a reduction of cardiac output and/or systemic vascular resistance, by pooling of blood in the splanchnic veins (as in cirrhosis), and by hypoalbuminemia (Fig. 50-1*A*). As a consequence of underfilling, a series of physiologic responses designed to restore the effective arterial volume to normal are set into motion. A key element of these responses is the renal retention of sodium and, therefore, water, thereby restoring effective arterial volume, but sometimes also leading to or intensifying edema.

RENAL FACTORS AND THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The diminished renal blood flow characteristic of states in which the effective arterial blood volume is reduced is translated by the renal juxtaglomerular cells (specialized myoepithelial cells surrounding the afferent arteriole) into a signal for increased renin release. Renin is an enzyme with a molecular mass of about 40,000 Da that acts on its substrate, angiotensinogen, an α_2-globulin synthesized by the liver, to release angiotensin I, a decapeptide, which in turn is converted to angiotensin II (AII), an octapeptide. AII has generalized vasoconstrictor properties, particularly on the renal efferent arterioles. This action reduces the hydrostatic pressure in the peritubular capillaries, whereas the increased filtration fraction raises the colloid osmotic pressure in these vessels, thereby enhancing salt and water reabsorption in the proximal tubule as well as in the ascending limb of the loop of Henle.

The renin-angiotensin-aldosterone system (RAAS) operates as both a hormonal and paracrine system. Its activation causes sodium and water retention and thereby contributes to edema formation. Blockade of the conversion of angiotensin I to AII and blockade of the AII receptor enhance sodium and water excretion and reduce many forms of edema. AII that enters the systemic circulation stimulates the production of aldosterone by the zona glomerulosa of the adrenal cortex. Aldosterone in turn enhances sodium reabsorption (and potassium excretion) by the collecting tubule, further favoring edema formation. In patients with heart failure, not only is aldosterone secretion elevated but the biologic half-life of the hormone is prolonged secondary to the depression of hepatic blood flow, which reduces its hepatic catabolism and increases further the plasma level of the hormone. Blockade of the action of aldosterone by spironolactone or eplerenone (aldosterone antagonists) or by amiloride (a blocker of epithelial sodium channels) often induces a moderate diuresis in edematous states.

ARGININE VASOPRESSIN

(See also Chap. 404) The secretion of arginine vasopressin (AVP) occurs in response to increased intracellular osmolar concentration, and, by stimulating V_2 receptors, AVP increases the reabsorption of free water in the distal tubules and collecting ducts of the kidneys, thereby increasing total-body water. Circulating AVP is elevated in many patients with heart failure secondary to a nonosmotic stimulus associated with decreased effective arterial volume and reduced compliance of the left atrium. Such patients fail to show the normal reduction of AVP with a reduction of osmolality, contributing to edema formation and hyponatremia.