CHAPTER 21

From Ancient Seas to Modern Disease

Evolution and Congestive Heart Failure

E. Jennifer Weil

As do several other contributors to this volume, Weil makes the simple point that it is highly unlikely that our ancestors died from heart disease, and in particular, congestive heart failure (CHF).Her presentation delves far deeper into how and why both ultimate (i.e., evolutionary) factors can help, together with proximate ones, to understand why heart disease and CHF have become so prevalent for people living in Western, industrialized contexts. She explores how the vertebrate circulatory system first evolved, describing how functional anatomical homologues for distributing oxygen around an animal's body led eventually to the four-chambered heart characteristic of terrestrial mammals. She also describes the neural and hormonal modulators of the heart and circulatory system that evolved to handle gravity (e.g., the blood pressures associated with bipedalism), along with huge metabolic demands imposed by thermal regulation. The origins of what is referred to in the medical textbooks as the sympathetic nervous system, the renin–angiotensin–aldosterone system (RAAS) along with vasopressin from the brain, as Weil describes, provides the platform from which the human heart and circulatory system eventually came to sustain the needs of the most energy-needy creature of all: the human being. It is in the integrative aspect of her discussion where evolution and twenty-first century Western lifestyles meet that we understand how and why this ancient system can find itself at odds with a cultural system favoring a life style that makes this ancient otherwise effective system, dangerous, in some contexts.

INTRODUCTION

Congestive heart failure (CHF) is a life-threatening clinical syndrome that affects approximately 5 million patients in the United States and is increasing in prevalence

both in the United States and worldwide. In order to understand CHF from an evolutionary perspective, one must first understand how neural and hormonal modulators of the cardiovascular system evolved. The sympathetic nervous system (SNS), the renin–angiotensin–aldosterone system (RAAS) and the vasopressin system evolved as critical adaptations for vertebrates, particularly in terrestrial environments. These neural and hormonal regulatory systems evolved to ensure the adequacy of circulation to vital organs when blood pressure or blood volume is compromised, and they remain adaptive today. However, these adaptations may also become maladaptations for modern humans living in postagricultural, postindustrial societies wherein heart disease is epidemic. Activation of neural and hormonal regulatory systems in CHF leads to substantial morbidity and mortality. An evolutionary understanding of CHF suggests prevention and treatment strategies that are strongly supported by clinical studies.

A MISMATCH BETWEEN OUR GENES AND OUR ENVIRONMENT

Darwin demonstrated long ago how heritable variations in anatomy and physiology are naturally selected, but medicine has been slow to recognize how successive adaptations have shaped the human body (Day, 1999). When Williams and Nesse applied the Darwinian paradigm to human health, they found that many adaptations, beneficial in our ancestral environment, have become maladaptations in our modern environment (Nesse & Williams, 1996; Williams & Nesse, 1991). Many human diseases result from or are worsened by anatomical and physiological adaptations to an environment that was markedly different from the one in which we now live.

CHF is a major public health problem that may result from any disease that impairs the heart's ability to circulate sufficient blood to the organs of the body. The most common cause of CHF is cardiac damage resulting from atherosclerotic coronary artery disease (CAD). Konner and Eaton explored concepts of Darwinian medicine as they relate to the epidemic of CAD (Eaton & Konner, 1985; Eaton, Eaton, & Konner, 1999). They identified modern nutrition as the primary reason why cardiovascular disease is the leading cause of death in the developed world and is increasing throughout the developing world. This paper will *not* re-examine CAD, but instead will explore concepts of Darwinian medicine as they relate to CHF (Harris 1983a, b, c, 1985; Nesse & Williams, 1996; Weil, 1993). To see how Darwinian medicine applies to CHF, I will (1) review how the heart and its neural and hormonal control systems evolved and how they were adaptive under ancestral conditions, and (2) how neural and hormonal modulators of the heart and circulation have become maladaptive in modern environments in which heart disease is epidemic.

EVOLUTION OF THE VERTEBRATE CIRCULATORY SYSTEM

The human circulatory system, including the heart, blood vessels, and blood, originated with the first vertebrates—jawless fish—nearly 500 million years ago (Figure 21-1). As marine fish gave rise to freshwater fish, which in turn gave rise to amphibians, reptiles,

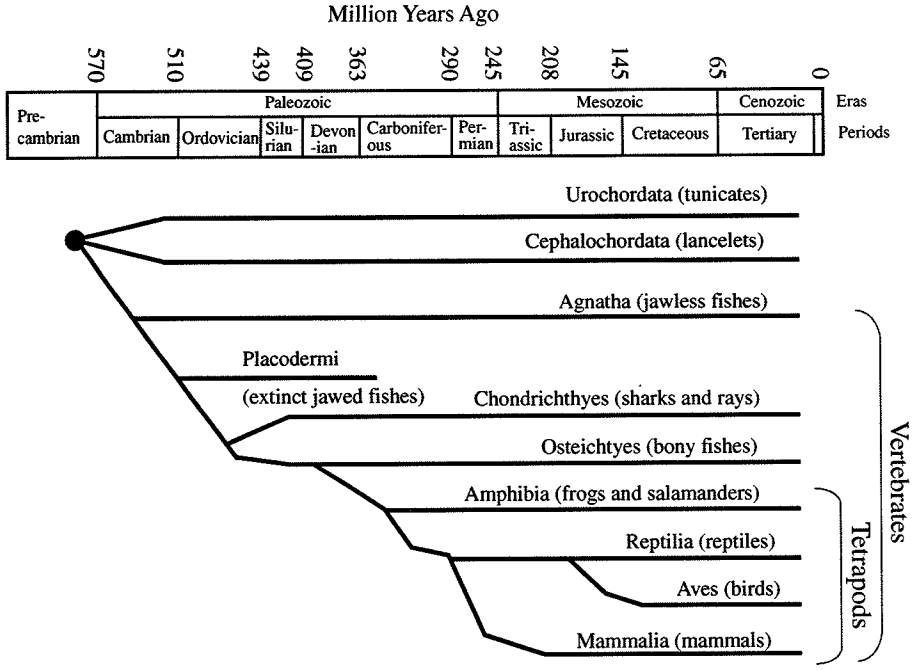

FIGURE 21-1 Evolution of vertebrates.

and ultimately to mammals, the vertebrate circulatory system also evolved. As each vertebrate class explored and conquered new environments, significant changes to the vertebrate circulatory system and the mechanisms that regulate it were required to meet new environmental demands.

The purpose of the heart is to perfuse organs, i.e., to drive blood through increasingly small blood vessels to capillaries, where nutrients and oxygen are transferred to tissues. Blood is composed mainly of water, sodium, and other minerals, including chloride, calcium, and potassium, and other chemicals along with the blood cells. The first vertebrates evolved in a marine environment where most of the components of blood are readily available and where circulation does not require much complexity. The fishes have single-circuit circulatory systems in which a low-pressure, two-chambered heart pumps blood first through the gills for oxygenation, and then through arteries to the internal organs. After delivery of nutrients and oxygen to organs and tissues, veins return blood to the heart. In comparison, the circulatory system of amphibians is more complex and is characterized by a three-chambered heart and partially divided circulation (Bishopric, 2005). Divided circulation, with one low-pressure circuit going from the heart to the lungs and a second high-pressure circuit going from the heart to the organs of the body, is an important adaptation to life on land. High pressures in the systemic circulation allow the force of the heart to overcome the effect of gravity on the blood volume as occurs in terrestrial environments (Farrell, 1991; Lillywhite, 1995). Most reptiles also have three-chambered hearts, and mammals have four-chambered hearts, thought to have evolved in part to meet the increasing metabolic demands imposed by physiological regulation of body temperature (Bennett, 1991).

Even more important than the evolution of cardiac anatomy, however, is the evolution of the neural and hormonal systems, which regulate the heart and blood vessels. Three physiological systems that first evolved in the seas became critical for life on land: the SNS, the RAAS, and the vasopressin system.

EVOLUTION AND PHYSIOLOGY OF THE SYMPATHETIC NERVOUS SYSTEM

The autonomic nervous system reflexively controls circulation by modulating the heart and the blood vessels over short periods of time—on the order of seconds—to exert fine control over the circulation. The autonomic nervous system has two different anatomical and physiological components that balance one another. The parasympathetic nervous system (PNS) is the source of nerves that decrease heart rate, thereby decreasing cardiac output (measured in liters of blood per minute) and lowering blood pressure. The SNS is the source of nerves that increase heart rate, increase the contractile force of the heart, and constrict arteries thereby raising blood pressure (Guyton, 1986). The SNS increases secretion of sympathetic mediators including epinephrine from the adrenal medulla and norepinephrine from sympathetic nerve endings on target organs and blood vessels (Guyton, 1986).

Sensory receptors that detect pressure or stretch (baroreceptors) in the large arteries and in the heart provide information to the brain about blood volume and blood pressure, both within the heart, as it fills between each contraction, and within the blood vessels. If blood decreases in volume, either as a result of blood loss or pooling within the veins, blood pressure drops. Baroreceptors send information to the brain that excites sympathetic nerves that, in turn, constrict blood vessels and increase the rate and force of contraction of the heart. These responses restore arterial pressure towards normal despite decreased blood volume and ensure adequate delivery of nutrients and oxygen to organs and tissues (Guyton, 1986). By returning blood pressure and organ perfusion towards normal the PNS and SNS maintain homeostasis in the circulation, i.e., a constant internal state necessary for life.

Depending on the environment or the physiological demands on an organism, blood pressure may vary considerably. The gravitational effect on blood circulation is completely different in water and on land. Because the effect of gravity on blood volume is offset by buoyancy in an aquatic environment, the distribution of blood volume is not changed when an aquatic organism changes position, and blood remains fairly well distributed over the entire circulatory system. On land, however, the density of water and air are markedly different, so blood has a tendency to pool in dependent regions of a terrestrial organism's body. If blood, under the influence of gravity, does not return to the heart, it decreases amount of blood the heart can pump, and cardiac output (defined above) declines. Over the course of vertebrate evolution, the SNS evolved as a significant countermeasure to gravitational stress on terrestrial vertebrates (Lillywhite, 1995). Physiological stresses have also shaped the evolution of the SNS. Organisms that run or fly have complex organ perfusion needs. The SNS allows all vertebrate organisms to

increase blood flow to exercising muscle while decreasing flow to the digestive tract and other organs (Morris & Nilsson, 1994).

The most archaic of living vertebrates, the hagfish, has no anatomical evidence of sympathetic nerves (Augustinsson, Fange, Johnels, & Ostlund, 1956). Other primitive fishes, including cyclostomes (e.g., lampreys), cartilaginous fish (e.g., sharks and rays) and dipnoans (e.g., lungfish), have sympathetic nerves, but they do not have nerve endings that reach the heart. Instead, they have specialized (chromaffin) cells located within or near the heart, which release norepinephrine, thereby promoting cardiac excitation (Morris & Nilsson, 1994). The evolutionarily more recent teleosts (bony fish, e.g., salmon) have sympathetic nerves that modify both the heart and the blood vessels in response to stimuli such as oxygen deprivation and exercise (Morris & Nilsson, 1994). The SNS of amphibians, reptiles, and mammals generally follow the anatomical pattern evolved in the teleost fishes (Morris & Nilsson, 1994).

Because vertebrates are extraordinarily diverse and live in marine, freshwater, and terrestrial environments, the SNS and the mechanisms that regulate it have evolved among the different classes of vertebrates and even among species to meet specific ecological or environmental demands. The SNS has unique properties among species that are subject to particular gravitational stresses, like tree snakes (Lillywhite, 1996), giraffes (Hargens, Millard, Pettersson, & Johansen, 1987), and perhaps humans, because of our upright posture (Mathias, 2002; Pawelczyk & Levine, 2002). In general, SNS evolution is characterized by increasing sympathetic innervation of the heart and veins over time (Morris & Nilsson, 1994), increasing the flexibility of organisms to respond to diverse environmental challenges (Gibbins, 1994).

As in other vertebrates, appropriate activation of the SNS allows our circulatory systems to function effectively under a wide array of circumstances. If we change position from supine to standing, blood volume is redistributed as gravity draws blood toward our feet and less blood returns to the heart. Baroreceptors sense decreased filling of the heart and large blood vessels and activate the SNS to preserve perfusion of vital organs by increasing the rate and force of contraction of the heart and constricting arteries to increase blood pressure. Similarly, if blood volume is reduced as a result of actual blood loss (hemorrhage), baroreceptors signal the SNS, which modulates the heart and blood vessels so that organs continue to receive nutrients and oxygen. There are many other ways in which blood volume and blood pressure may become diminished, including loss of fluids from the body (as a result of vomiting, diarrhea, or profuse sweating) or impaired access to sodium (a key component of blood plasma) and water. In sum, the SNS is a critical adaptation that helps humans and other vertebrates whenever blood volume or blood pressure drops.

EVOLUTION AND PHYSIOLOGY OF THE RAAS

Present in the blood vessels of the kidneys are nonneural receptors that differ from baroreceptors described above. These receptors are present on juxtaglomerular (JG) cells and measure the stretch and pressure within the kidneys' blood vessels to assess blood volume. Instead of sending nervous impulses to the brain, however, they regulate a hormonal system known as the RAAS (Guyton, 1986). The RAAS is also modulated by

chloride-sensing cells in the kidney (the so-called macula densa), which measure the rate of urine production, and by the SNS directly (Guyton, 1986). In concert with the SNS, the RAAS helps vertebrates survive loss of blood pressure and blood volume by restoring perfusion of vital organs.

The RAAS has several component proteins (Figure 21-2). Renin is an enzyme secreted by JG cells in the blood vessels of the kidneys, which cleaves off a portion of the circulating protein angiotensinogen to create angiotensin I. Angiotensin I (ATI) is then cleaved by another enzyme, angiotensin-converting enzyme (ACE), to create angiotensin II (ATII). ATII has many powerful effects on the circulation. When it binds to AT1 receptors located within arteries, blood vessels constrict and dramatically increase blood pressure. When ATII binds to AT2 receptors in the brain, it increases thirst, thereby increasing blood volume. ATII also acts in the brain by increasing SNS activity. Finally, ATII stimulates the adrenal gland to synthesize and release aldosterone, a steroid hormone that acts in the kidneys to increase the return of sodium from urine to blood. The effects of ATII are rapid, taking place in the order of minutes, whereas stimulation of aldosterone takes more time (Guyton, 1986). Thus the RAAS complements the rapid action of the SNS—which acts in the order of seconds—with actions that increase blood volume and blood pressure over minutes, hours, and days.

Perfusion of the kidneys is normally under the tight control of both the SNS and the RAAS to ensure adequate glomerular filtration (glomerular filtration rate [GFR] is the rate of filtration of the blood plasma by the filters in the kidneys). The SNS and RAAS also regulate the two most important components of blood volume—sodium and water retained—as they are filtered by the kidneys when they make urine. The RAAS is activated whenever the blood volume or blood pressure drops. When the RAAS is activated, the kidneys reabsorb sodium and water from the urine and raise the volume of the liquid component of blood, i.e., the plasma. By returning blood volume, blood pressure, and GFR towards their normal levels, the RAAS serves a homeostatic function (Guyton, 1986).

The RAAS probably first evolved to help fish navigate waters of variable salinity. The proteins of the RAAS are found in one primitive fish, the lamprey (Brown, Cobb, Frankling, & Rankin, 2005), in sharks and rays (Hazon, Tierney, & Takei, 1999), and in teleost fishes (Nishimura, 1980, 2001). These animals survive in both salt and freshwater. As they transition from a high-sodium to a low-sodium environment, activation of the RAAS allows them to retain sodium (Galli & Phillips, 1996). The RAAS is not present in the most archaic of living vertebrates, the hagfish (Cobb et al., 2004). This suggests that evolutionary pressure for sodium conservation occurred later in the history of

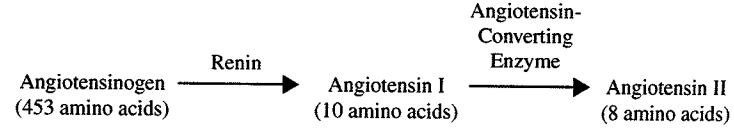

FIGURE 21-2 The enzyme renin cleaves angiotensinogen into angiotensin I. The angiotensin-converting enzyme cleaves angiotensin I into angiotensin II. Angiotensin II has powerful vasoconstrictive effects and increases blood volume via stimulation of sodium and water reabsorption in the kidneys.

fishes, probably as an adaptation to life in freshwater, where sodium, a key component of blood, is scarce.

Proteins of the RAAS are also present in all tetrapod vertebrates (Nishimura, 1980, 2001), reflecting the scarcity of sodium and water in the terrestrial environment and the threat thereby posed to blood volume and blood pressure. In addition, ATII has species-specific effects that appear to correlate with unique environmental pressures placed upon the organisms. Toads, for example, respond to decreasing blood volume with increasing concentrations of ATII (Konno, Hyodo, Takei, Matsuda, & Uchiyama, 2005), which stimulates water absorption through their skins (Goldstein, Hoff, & Hillyard, 2003). In mammals, ATII regulates blood volume independent of sodium and water concentrations individually.

The adrenal glands of most species respond to ATII by increasing production of steroid hormones (Nishimura, 1980). In lower vertebrates, steroid hormones are variable and have multiple effects, including sodium reabsorption in the kidneys. In mammals, however, the steroid hormone activated by the RAAS is exclusively aldosterone, and it has only one function, sodium conservation. Nishimura (1980) has speculated that aldosterone represents a more recent adaptation in vertebrate evolution that occurred when mammals explored environments characterized by scarcity of sodium.

In all vertebrate species, the RAAS reacts to reductions in blood volume and low blood pressure (Nishimura, 1980). Another response to RAAS activation common to all vertebrates is increased GFR (Nishimura & Bailey, 1982). More filtration by the kidneys allows removal of unnecessary minerals and waste blood even as sodium and water are returned from the urine to the blood. While the RAAS evolved to help fish manage sodium concentrations, it has become a key homeostatic system for maintenance of blood volume and blood pressure in terrestrial vertebrates.

EVOLUTION AND PHYSIOLOGY OF VASOPRESSIN

Another hormone with important effects on the circulation is vasopressin, a short peptide synthesized in the hypothalamus and secreted by the posterior part of the pituitary gland. Secretion of vasopressin occurs when specialized receptors in the brain determine that the blood is lacking sufficient water and has become too concentrated (Guyton, 1986). Another stimulus for vasopressin release is decreased blood volume, as sensed by baroreceptors in the large arteries of the neck and heart (Guyton, 1986). Vasopressin has two major effects in the body mediated by two different receptors. First, vasopressin raises blood pressure via V1a receptors in the smooth muscles of arteries (Koshimizu et al., 2006). Second, vasopressin increases blood volume by increasing water reabsorption from urine, an effect mediated by V2 receptors, in the kidneys (Hayashi et al., 1994).

The origin of vasopressin dates back a billion years to the evolution of coelenterates (jellyfish) (Grimmelikhuijzen, Dierickx, & Boer, 1982). Peptides similar to vasopressin are found among various invertebrate species including annelids (worms), mollusks (shellfish), and arthropods (crustaceans, insects) (Mizuno & Takeda, 1988). In fish species, the molecular ancestor of vasopressin is called vasotocin and is a critical adaptation for those fish that tolerate waters of variable salinity. Vasotocin and its receptor increase only the water component of plasma, not the sodium, a useful adaptation in

waters of high sodium concentration. This effect would be particularly useful to fish such as salmon, which migrate from freshwater to saltwater as they mature (anadromy). Vasotocin is also found in amphibians (Konno et al., 2005) and in reptiles (Bradshaw & Bradshaw, 2002), where it regulates blood pressure and blood concentration via water reabsorption in the kidney. Vasopressin itself is found only in mammals, along with several different receptors (Mohr, Meyerhof, & Richter, 1995). Despite the amino acid substitutions between vasotocin and vasopressin, however, the effect of these peptides on their receptors is to increase blood pressure and water within the body.

Whether its release is triggered by osmoreceptors in the brain or by baroreceptors in arteries of the chest, neck, and heart, vasopressin serves a homeostatic function by raising blood pressure and increasing plasma volume when an organism becomes dehydrated. Although vasopressin and its receptors have a long evolutionary history, clearly they were critical adaptations for life on land where fresh water is scarce.

THE NATRIURETIC PEPTIDES: A COUNTERREGULATORY SYSTEM

In balance with systems that raise blood pressure and blood volume (the SNS, RAAS, and vasopressin system), natriuretic peptides and their receptors evolved to lower blood pressure and blood volume. These hormones constitute an adaptive system for the rare instances in which sodium concentration, blood pressure, or blood volume becomes excessive.

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are synthesized in and secreted by the heart, and c-type natriuretic peptide (CNP) is synthesized and secreted in the brain and other organs (Farrell & Olson, 2000). ANP and BNP are secreted in response to stretch of the cardiac muscle, a result of excessive blood volume in the circulation (McGrath & de Bold, 2005). The function of C-type natriuretic peptide remains somewhat unclear in mammals, but is active in vascular tissue (Anand-Srivastava, 2005). These hormones bind to receptors in the brain, arteries, and kidneys, where they inhibit thirst, relax blood vessels, and stimulate sodium and water excretion in the urine. These are useful adaptations in situations where the sodium concentrations are too high or blood volumes are excessive.

The natriuretic hormones and their receptors are ancient within vertebrate evolution, while closely related hormones are found in invertebrates, including mollusks (Bystrova, Parfenov & Marynova, 2002) and insects (Kim et al., 1994). The hagfish possesses a unique natriuretic peptide, and sharks and rays have only CNP (Kawakoshi, Hyodo, Yasuda, & Takei, 2003). Teleosts have four natriuretic peptides: ANP, BNP CNP, and a related hormone, ventricular natriuretic peptide (VNP) (Kawakoshi, Hyodo, Yasuda, & Takei, 2003). These play a particularly important role when a euryhaline fish (a fish that adapts to waters of variable salinity, e.g., eel) moves from freshwater to saltwater (Toop & Donald, 2004). The natriuretic peptides are released from the heart and act on the kidney to unload sodium as blood volume increases (Takei & Hirose, 2002).

The natriuretic hormones are thought to have initially evolved to regulate sodium concentration, because fish may navigate waters of variable salinity due to anadromy, catadromy, or euryhalinity (migration or tides) (Loretz & Pollina, 2000). In terrestrial

environments, however, where there are no sources for great quantities of sodium, total blood volume (i.e., sodium and water together) is more important. Consequently, the natriuretic peptides have less of an effect on sodium concentration and more of an effect on blood pressure and blood volume in amphibians, reptiles, and mammals (Takei, 2001). In the rare event that the blood pressure and blood volume becomes excessive, the natriuretic peptides decrease blood pressure and allow sodium and water to be eliminated in urine.

DEFINITION OF CONGESTIVE HEART FAILURE

CHF is a clinical syndrome that arises when the heart and blood vessels cannot effectively deliver sufficient blood to organs of the body to meet their metabolic needs. Without adequate blood flow, tissues do not function properly. Cardiomyopathies are diseases that weaken the heart, thereby initiating CHF. Some of the most common cardiomyopathies are caused by damaged cardiac valves, ischemia (decreased blood flow through coronary arteries to the muscle of the heart), hypertension, diabetes, and alcohol (Collucci, 2006a). CHF occurs when the heart's pumping function is impaired and the cardiac output declines (so-called high output heart failure will not be discussed here).

Risk factors for CHF include obesity, hypertension, hyperlipidemia (together creating "metabolic syndrome"), diabetes, and tobacco and alcohol abuse. Each of these risk factors may cause cardiomyopathy directly. More commonly, patients have multiple risk factors, especially for CAD. In CAD, atherosclerotic plaque (composed of cholesterol, calcium, and fibrous tissue) is deposited in the arteries of the heart, thereby limiting flow of blood to the muscle of the heart, resulting in impaired cardiac contraction. A myocardial infarction (heart attack) occurs when deposits of cholesterol in the arteries of the heart rupture, causing a blood clot to completely block the flow of blood through the vessel. The heart muscle that would normally receive blood through the now clotted coronary artery dies, and a scar forms in its place. A scarred heart does not contract properly and delivers too little nutrients and oxygen to the organs and tissues of the body. After CAD, the most common single cause is alcohol abuse, which has a direct toxic effect on the muscle cells of the heart. Whatever the cause, the impairment in cardiac pumping function is the common denominator of low output CHF.

Patients with any form of advanced CHF develop edema, defined as an accumulation of fluid in the tissues. When edema is present, the patient is said to have "cogestion." The site of edema in the body depends on the part of the heart that is dysfunctional (Figure 21-3). Diseases affecting the left ventricle cause pulmonary edema (fluid accumulation in the lungs), resulting in hypoxia (low oxygen tension in the blood). Patients with left heart failure feel short of breath in the extreme, and pulmonary edema is a life-threatening condition (Colucci, 2006a). Diseases affecting principally the right ventricle cause peripheral edema, or fluid accumulation in the lower extremities and torso. Patients with peripheral edema may accumulate a considerable amount of fluid, which, although not immediately life threatening, may result in discomfort and skin ulceration. Most patients with CHF eventually experience both left and right ventricular failure and therefore both pulmonary and peripheral edema.

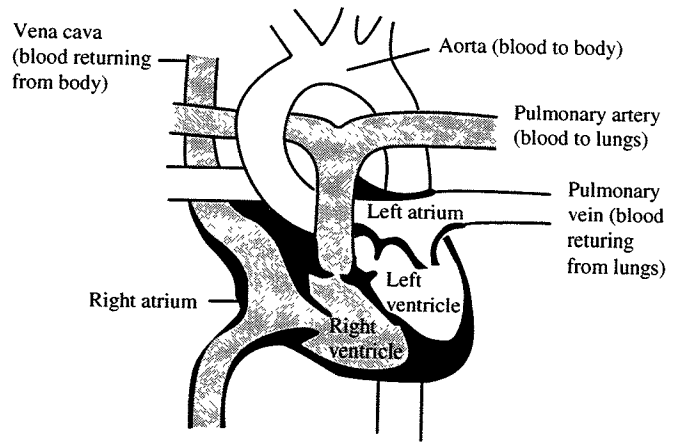

FIGURE 21-3 Left heart failure: the left side of the heart is weak and cannot pump out as much blood as it receives from the right side of the heart. As a result, blood backs up in the lungs. Right heart failure: the right side of the heart cannot pump as much blood to the lungs as it receives from the body. As a result, fluid backs up in the body tissues.

EPIDEMIOLOGY OF HEART FAILURE

CHF is a major public health problem in the United States (Levy et al., 2002), other developed nations (Cowie et al., 1997), and increasingly in South America (Cubillos-Garzon, Casas, Morillo, & Bautista, 2004), Africa (Cooper, Amoah, & Mensah, 2003), and Asia (Reddy, 2004; Sanderson, 2004). CHF affects men and women approximately equally, and its incidence increases with age (Thom et al., 2006). According to the American Heart Association 2006 update on heart disease, 4–5 million Americans are believed to have symptomatic heart failure, and many more have left ventricular dysfunction that will likely progress to CHF (Thom et al., 2006). Heart failure is the leading hospital admission diagnosis in the United States. In 2001, there were over 500,000 hospital admissions primarily for heart failure in women and over 400,000 in men (Young, 2004). This number represents about an eightfold increase from the 200,000 admissions for CHF tallied in 1970 (Young, 2004).

Nearly 15 million individuals are affected with heart failure worldwide (Wilson, 2003; Young, 2004), and that prevalence is expected to increase as populations undergo transition in their economies from agriculture to industry (Mendez, 2001). In the United States, 50% of heart failure patients are over the age of 65 years, and the prevalence increases with increasing age (Young, 2004). These statistics reflect the underlying diseases causing heart failure. It takes years for obesity, hypertension, hyperlipidemia, diabetes, tobacco abuse, and alcohol abuse to cause CHF. In the rest of the world, valvular cardiomyopathy is a more common cause of CHF, which is caused by an infection with streptococcus and affects younger patients (Mendez, 2001). However, the increasing prevalence of heart failure worldwide reflects an epidemiological transition that mirrors economic transition, with prevalence of valvular heart disease remaining stable, but prevalence of ischemic, hypertensive, diabetic, and alcoholic cardiomyopathies

increasing. The fact that CHF results from diseases more prevalent in aging is important from an evolutionary perspective and will be discussed below.

Heart failure is deadly. Data from the Framingham Heart Study demonstrate that the 5-year mortality for men diagnosed with CHF between 1990 and 1999 was 59%, an improvement over mortality in previous decades (Levy et al., 2002). Despite the decline in mortality rates secondary to better therapy, however, the increased incidence and prevalence of CHF in the United States and worldwide will still result in an increasing death toll in the years to come.

NEUROHORMONAL ACTIVATION IN CONGESTIVE HEART FAILURE

CHF develops with any disease that impairs cardiac function, but progresses because of neurohormonal activation—activation of the SNS, RAAS, and other hormones in CHF. Neurohormonal activation is paradoxical in CHF, because it results in a further increase in blood volume and vasoconstriction even though initial blood volume is already normal or increased. The severity of CHF is best judged by symptoms, such as shortness of breath, which a patient experiences as a result of neurohormonal activation (Francis et al., 1990; Swedberg, Eneroth, Kjekshus, & Wilhelmsen, 1990). Prognosis in CHF is also closely associated with the degree of neurohormonal activation.

SNS activation occurs early in the natural history of CHF and results in blood vessel constriction and faster heart rate (Grassi, Seravalle & Cattaneo, 1995; Rundqvist et al., 1997). SNS activation should also increase the force of contraction of the heart, but in CHF the heart is less capable of responding to the SNS on account of its intrinsic disease. The exact mechanisms that lead to neurohormonal activation in CHF are not well understood. Activation of the SNS is likely due, at least in part, to reduced control by baroreceptors in the heart and large arteries. These receptors normally limit SNS activity, but they seem to function abnormally in CHF, thereby removing their restraining influence.

SNS activation is, to a degree, homeostatic because it constricts arteries and maintains blood pressure. This allows the limited cardiac output to be distributed in such a way as to maintain perfusion of vital organs, i.e., the heart and brain, but often at the expense of other organs, i.e., the skin, the gut and the kidneys. However, SNS activation contributes to the worsening of CHF because of its vasoconstrictive effect on arteries. The heart must overcome the resistance load placed on it by the constriction of the vessels it is trying to fill. Over time, the extra work required to overcome this resistance further weakens the heart. Elevated levels of circulating norepinephrine and epinephrine, secreted respectively from the sympathetic nerves and from the adrenal medulla, give quantitative evidence of SNS activation in CHF (Benedict, 1996). Effects of the SNS on the cardiovascular system lead to "the vicious cycle" of CHF (Figure 21-4). The weaker the heart, the greater the activation of the SNS, which in turns weakens the heart further. The more activated the SNS (as reflected by blood concentration of norepinephrine), the worse the prognosis (Benedict, 1996).

The RAAS is also activated in CHF, and it too appears to have a homeostatic function. Although kidneys normally receive 25% of the cardiac output, renal perfusion is greatly diminished when heart function is impaired and GFR declines. Receptors in the kidneys located on JG cells and in the macula densa detect the decrease in perfusion and urinary

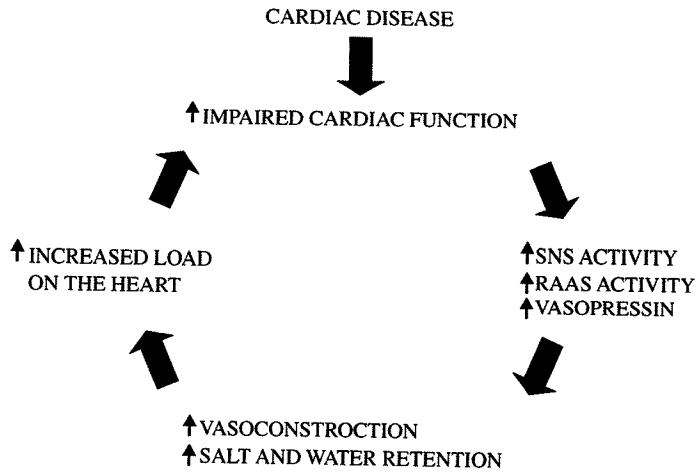

FIGURE 21-4 The vicious cycle of heart failure. Each adjustment by the nervous and hormonal systems that regulate the heart in CHF increases the load on the heart and further weakens it.

filtrate and activate both the SNS and RAAS, which together restore blood flow to the kidneys by increasing blood pressure and blood volume. The normalization of kidney function, however, comes at a great price. The RAAS contributes to the vicious cycle of CHF by expanding blood volume and increasing the load on the heart (Parmley, 1992) (Figure 21-4).

Vasopressin secretion occurs in severe CHF when baroreceptors in the heart and large arteries of the neck signal a decreased blood volume. Vasopressin levels rise, raising blood pressure and increasing water reabsorption from urinary filtrate. Consequently the blood becomes excessively dilute and concentrations of the minerals in the blood, particularly sodium, can drop to dangerously low levels (Chaterjee, 2005). Vasopressin too contributes to the vicious cycle of CHF. Elevated vasopressin and low sodium concentrations in the blood herald a very poor prognosis (Lee & Packer, 1986; Leier, Dei Cas, & Metra, 1994).

The final component of neurohormonal activation in heart failure is the natriuretic peptides. Natriuretic peptide levels, which are secreted by the heart in response to increased blood volume, rise early and progressively in heart failure (Lee, Miller, Edwards, & Burnett, 1989). Since natriuretic peptides evolved to cause arterial relaxation and a decrease in blood volume, it remains one of the central paradoxes of CHF why the kidneys respond more vigorously to the SNS and RAAS than they do to the natriuretic peptides. This may have some important implications for an evolutionary understanding of CHF, as will be addressed below.

TREATMENT OF CONGESTIVE HEART FAILURE

Therapy for CHF has advanced over the last 25 years, reflecting our increasing understanding of how neurohormonal activation drives progression of CHF. New treatments have focused on blocking neurohormonal activation, a detail that will become important in the conclusions below.

Prior to these advances, therapy for heart failure consisted mainly of digoxin, an agent thought to reverse heart muscle weakness by increasing the contractile force of the heart, and diuretics, medicines that decrease reabsorption of sodium and water from the urine. While diuretics relieve the body of volume overload, they have the additional effect of *activating* the neural and hormonal systems that lead to congestion in the first place.

In the late 1970s, drugs developed to antagonize the RAAS were first used in patients with CHF (Turini, Brunner, Gribic, Waebaer, & Gavras, 1979). Angiotensin-converting enzyme (ACE) inhibitors, agents that block the conversion of ATI to ATII, both relieve symptoms and prolong life in patients with heart failure (CONSENSUS Trial Study Group, 1987; SOLVD Investigators, 1991). In the early 1990s, angiotensin receptor blockers (ARBs), which block the binding of ATII to the AT1 receptor, were found to have effects similar to ACE inhibitors on morbidity and mortality in heart failure while avoiding some of the side effects of ACE inhibitors (Gottlieb et al., 1993; Pitt et al., 1999a).

β-Blockers (BBs) are agents that block the SNS. They were developed in the 1960s but for many years were thought to be contraindicated in CHF, since blocking the SNS was believed to decrease the contractile force of an already weakened heart. Some researchers maintained, however, that by antagonizing the SNS, BBs could block the vicious cycle of heart failure (Waagstein, Hjalmarson, Varnausakas, & Wallentin, 1975). BBs seem to improve cardiac performance over the long term by decreasing heart rate, altering the way the heart fills, and by improving muscle metabolism. As the importance of blocking the SNS became fully appreciated in the mid-1980s (Anderson et al., 1985) the rationale for avoidance of BBs was abandoned and BBs emerged as critical drugs for the treatment of heart failure. The COPERNICUS study of carvedilol (Packer et al., 1996, 2002) and the MERIT-HF study of metoprolol (Hjalmarson & Fagerberg, 2000) confirmed that BBs relieve symptoms and reduce mortality in patients with CHF.

Because ATII is the major stimulus for aldosterone secretion from the adrenal gland, it was believed for many years that RAAS inhibition with ACE inhibitors or ARBs would be sufficient for blocking aldosterone release and therefore sodium reabsorption in the kidney. There are, however, several other stimuli for aldosterone release, and aldosterone concentrations may actually rise after initiation of therapy with RAAS inhibitors, a phenomenon known as "aldosterone escape" (Struthers, 1996). Spironolactone, a selective blocker of aldosterone, was found to add benefits in CHF beyond blockade of the RAAS with ACE inhibitors and ARBs in the RALES trial (Pitt et al., 1999b). Blocking aldosterone removes a major stimulus to sodium retention in the body in heart failure, so blood volume does not increase.

Although the kidneys fail to excrete sodium and water in response to elevated levels of BNP released by the heart in CHF, it was found that high doses of synthetic BNP can overwhelm the kidneys' reluctance. Nesiritide, a recombinant BNP given by intravenous administration, is used to treat CHF in patients with severe edema. It has both vasodilator and sodium-excreting (natriuretic) effects.

The newest agents for potential treatment of CHF are the vasopressin antagonists called vaptans. These drugs have not yet undergone extensive clinical testing and are not yet approved by the U.S. Food and Drug Administration for the therapy of CHF. One large multicenter, randomized, double-blind, placebo-controlled study is underway to determine if tolvaptan is efficacious and if it will reduce mortality of patients with CHF (Gheorghiade et al., 2005).

Finally, it is worth mentioning that digitalis, a drug originally derived from the foxglove plant and used for centuries in the treatment of CHF, was thought to act by improving the force of contraction of the heart. It now appears that digitalis and its derivatives may act mainly by decreasing SNS activity, thereby decreasing neurohormonal activation and blocking the vicious cycle of heart failure (Teruya, 1997).

Patients with CHF do not receive all of these drugs simultaneously. Rather, they are usually started first on a diuretic and an ACE inhibitor or an ARB, and then a BB or an aldosterone antagonist completes the regimen. Additional medicines are added as needed. A "cocktail" of medication works best, since multiple physiological systems are activated in CHF. In addition to drugs, recommendations for the treatment of CHF include treatment of underlying heart disease and lifestyle modification. Reduction of salt intake and cessation of alcohol are critically important in the treatment of heart failure (Colucci, 2006b).

GENETIC AND ENVIRONMENTAL MISMATCH: CHF IN THE MODERN WORLD

The adaptations we inherited from our vertebrate ancestors when we became human, approximately 100,000 years ago, protect us from threats posed by our environment and have served us well for the better part of our history as a species. Since the emergence of *Homo sapiens* in the late Paleolithic period, we have spent the majority of our time making our living by hunting and gathering. Foraging for food presents many challenges: running, climbing, pursuing game into hostile environments, and encountering savage predators. Imagine one of your ancestors who, while foraging, encounters a bear. The bear attacks and wounds your relative, but then ambles off. Now your ancestor must make his or her way back to camp, perhaps a long distance away, sweating and bleeding. Adaptations to upright posture, hard exercise, and an environment with an unpredictable supply of sodium and fresh water are crucial for your ancestor's survival. Despite the bleeding, your ancestor's blood pressure is maintained because three physiological systems—the SNS, RAAS, and vasopressin—are all activated in this situation. In addition, the SNS keeps your relative upright so he or she can walk, the RAAS preserves kidney function and restores plasma volume lost through bleeding, and vasopressin conserves water. Your ancestor returns safely to camp, eats, drinks and restores the lost volume of blood. His or her blood pressure rises, and the three systems return to baseline levels of activity. Although life in the Paleolithic period was accompanied by many hardships, we survived because our bodies were well adapted to the challenges of that environment.

It is highly unlikely your ancestor died of CHF. Epidemic heart disease was certainly not commonplace in the evolutionary history of the vertebrates or in our past as a species. The reason our ancestors did not develop CHF is that the modern risk factors for heart diseases were all but absent in our ancestral environment. The Paleolithic diet was high in protein, fiber, and unrefined carbohydrates from fruits and vegetables and low in fat, simple sugars, and sodium. It included no milk after weaning and no alcohol (Eaton & Konner, 1985; Eaton, Eaton, & Konner, 1999). Our Paleolithic ancestors did not smoke tobacco. Moreover, our ancestors expended a lot of energy to obtain food, and when prey became scarce, they trekked long distances in search of better hunting (Eaton, 2003). Our ancestral dietary and exercise patterns were protective against heart disease.

While there are no Paleolithic humans available for physiological measurements, hunter-gatherers still living in remote parts of the world are our best available surrogates for determining our ancestors' health (Eaton, Eaton, & Konner, 1999). Many of the risk factors for heart disease are not present in hunter-gatherers. Among the !Kung San hunter-gatherers of Botswana, for example, there is no obesity. The mean body mass index (BMI, a measure of obesity) for women is 19.1 kg/m^2 and for men, 19.4 kg/m^2. According to World Health Organization standards, the !Kung San are at the low end of normal for BMI (Kirchengast, 1998). Another important risk factor for heart disease is high blood pressure. Like BMI, the mean blood pressure of modern hunter-gatherers is low and does not rise with age (Stamler, 1997). The ingestion of sodium in these societies is very low. The cholesterol levels of hunter-gatherers are likewise low, and hunter-gatherers exhibit very low risk for type 2 diabetes, a disease in which many of the risk factors for CHF are clustered together (Joffe et al., 1971; Merimee et al., 1972). Members of these communities do not drink alcohol or smoke tobacco unless they are brought in by colonizers or by trade with the outside world. Hunter-gatherers die of many different causes (mainly infectious), but not heart disease (Eaton, Eaton, & Konner, 1999).

In the last 10,000 years (a blink of an eye in the history of human evolution) our species has experienced both the agricultural and industrial revolutions. We have, through our cultural attainments, shaped our environment so rapidly that our genome has not kept up. Our modern environment, complete with industrial agriculture, burdens our bodies in ways never expected based on our evolutionary history. We are adapted to a meager diet and strenuous activity, and now we eat excessively and exercise too little. We are adapted to a low-salt environment, and yet we now eat excessive amounts of salt. We are adapted to eating lean game, and instead fatten our domesticated animals and then fry our food in yet more fat. We are adapted to eating high fiber and no simple sugars, and yet now we eat processed foods loaded with high-fructose corn syrup. We are not adapted to drinking alcohol, and yet many of us drink to excess. We have easy access to cheap tobacco, and many of us smoke it. A consequence of becoming fat, hypertensive, diabetic, hypercholesterolemic drinkers and smokers is the epidemic of heart disease we now face (Figure 21-5).

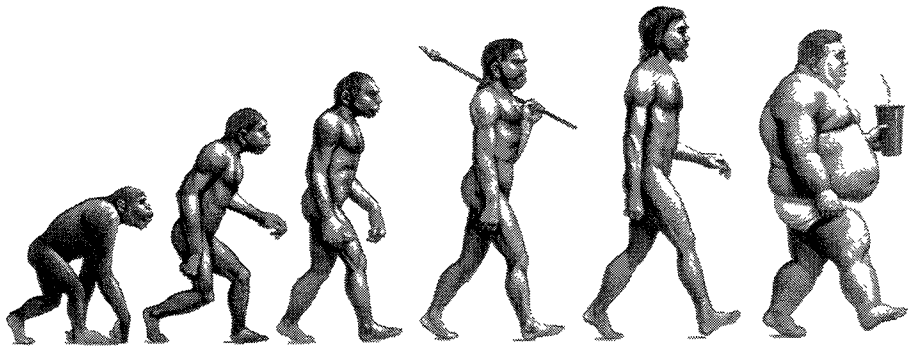

FIGURE 21-5 Human evolution in postagricultural, postindustrial societies. (Reprinted with permission from www.jonberkeley.com)

CONCLUSIONS

Now, having abandoned our ancestral ways of life, we face epidemics of both heart disease and CHF. The CHF epidemic has come about because of a convergence of two factors: (1) increasing amounts of heart disease and (2) ancestral adaptations to gravity and a low sodium and water environment. The hypothesis presented in this chapter is that the SNS, RAAS, and vasopressin evolved early in our vertebrate history in response to threats upon the blood volume, particularly in terrestrial environments. Neurohormonal activation as a result of hemorrhage, vomiting, diarrhea, or profuse sweating is homeostatic and returns circulatory function towards normal. Neurohormonal activation in CHF, however, is pathological, increasing both the load on the heart as well as the blood volume, and driving the vicious cycle of heart failure.

Why do the natriuretic peptides fail to reverse or even significantly modify the clinical state of heart failure, even when levels of these hormones are increased 100-fold above normal in CHF? In contrast to the seas from which vertebrates originally came, the terrestrial environment is sodium poor. The need to reduce sodium in the blood has therefore been unusual throughout most of the history of the tetrapods. Similarly, our species has suffered from limited access to sodium for most of our history (Kurlansky, 2002; Laszlo, 2001; Pliny the Elder). Therefore, evolutionary pressure to develop robust systems to promote sodium excretion has not existed throughout vertebrate history, whereas pressure for development of systems that ensure sodium retention has been intense. Now that salt is commonly available, however, it plays a significant role in human disease (Law, 2000). Accordingly in CHF, when the SNS, RAAS, vasopressin, and the natriuretic peptides are *all* activated, the natriuretic peptides are overwhelmed by the other more robust neurohormonal systems, reflecting the far greater importance of the SNS, the RAAS, and vasopressin to our survival throughout most of our evolutionary history.

Because CHF occurs too late in our individual life histories to affect our success at reproduction, we will never evolve a way to turn off the 500-million-year-old adaptations that help us survive episodes of decreased blood pressure and blood volume. Instead, we must use an evolutionary understanding CHF to enlighten our clinical approach to the prevention and treatment of heart failure. To reverse the epidemic of heart disease and CHF, an evolutionary perspective suggests that we should mimic, if not recreate, ancestral conditions. As Eaton, Konner, and Shostak recommend in their book, *The Paleolithic Prescription* (1989), we can eat and exercise more like our ancestors did, despite living in a postagricultural and postindustrial society. Indeed, the American Heart Association (AHA) also recommends changes in diet and exercise as primary prevention for heart disease (American Heart Association, 2006; Thom et al., 2006). The AHA does not use an evolutionary rationale for its guidelines, but relies on studies of many thousands of patients to show that reduction of key risk factors associated with our postagricultural, postindustrial lifestyle—obesity, hypertension, hyperlipidemia, and diabetes, tobacco abuse and alcohol abuse—reduces the risk of cardiovascular disease and CHF. For patients who *do* develop CHF, an evolutionary perspective suggests that the best way to alleviate suffering and prolong life is to block the ancient adaptations, which lead to neurohormonal activation and the vicious cycle of CHF, using medications. Studies of drugs developed to treat heart failure, outlined above, validate precisely such an approach.