

## **THE CENTRAL NERVOUS SYSTEM: BRIDGE BETWEEN THE EXTERNAL MILIEU AND THE CARDIOVASCULAR SYSTEM**

### **THE ENVIRONMENT-BRAIN-HEART CONNECTION: ECONEUROCARDIOLOGY** *by Stewart Wolf, MD*

The concept of neurocardiology emerged in the medical literature for the first time in an editorial by this author in the February, 1967 issue of the Oklahoma State Medical Journal.<sup>62</sup> The editorial introduced the manuscripts of 12 investigators collaborating on a project supported by the National Heart Institute (NHI) of the National Institutes of Health. Six years later, this neurocardiology research program culminated in a report at an international colloquium in Lindau on Bodensee, West Germany—*The Artery And The Process of Arteriosclerosis: Measurement and Modification*.<sup>55</sup>

"Eco" was added to the term neurocardiology to acknowledge the fact that the brain's activities are largely governed by life experience and environment, as proposed by John Locke in the early 16th century.<sup>30</sup> "Eco" derives from a Greek word meaning house, and ecology implies an interdependent relationship between the inner and outer aspects of a system, our ecosystem. Many aspects of our environment are capable of activating neuroregulatory mechanisms to develop, enhance, enrich, adapt, protect, or challenge our capacity for fulfillment on this planet. Most commonly the environmental forces at work are people. The emotionally significant events that take place in our relationships with parents, siblings, colleagues, mates, and children may set off almost any type of cardiovascular (CV) effect through their impact on the forebrain mechanisms.

Among the first to discover the importance of the forebrain in CV regulation was René Leriche, a pioneer in peripheral neurosurgery.<sup>27,28</sup> His demonstration that stimuli from higher neural centers are required to achieve fatal arrhythmia has been confirmed by several subsequent investigators.<sup>1,9,29,33,34,51,61,65</sup>

In 1985, Natelson published a comprehensive paper on neurocardiology.<sup>37</sup> Within the next 10 years, as if in response to a call, two books appeared under the title "Neurocardiology."<sup>1,26</sup> Despite the massive body of evidence published over the past 67 years that documents the importance of forebrain discharges in causing fatal cardiac arrhythmia, the findings have been neglected by the most recent and widely quoted cardiovascular textbooks.

It has taken a long time to dispel the many popular dogmas that have emerged in relation to the disorder generally labeled "heart attack." Evidence that established

the role of the brain in CV control, including internal vascular changes involved in atherosclerosis<sup>56</sup> and the process of MI,<sup>55</sup> has been widely ignored. Early recognition of the importance of the nervous system to CV development and disease was slow coming to confirmation, but the data have been supplemented recently with direct evidence that higher neural forebrain mechanisms affect all aspects of cardiovascular function.<sup>23</sup> Although it has been well established that intracranial neural mechanisms may support or impair multiplex CV functions, there needs to be further inquiry into the molecular sequences whereby a life experience communication with intracranial axon cones enables the axons to trace long distances throughout the forebrain cortex. We owe the discovery of this extraordinary and indispensable communicative process to the work of Santiago Ramon y Cajal nearly a century ago.<sup>44</sup>

Failure to appreciate the most relevant regulatory forces governing cardiac function and dysfunction may have emerged from the unfortunate pedagogic error of medical schools to subdivide medical teaching of residents and fellows into clinical specialties. That narrow focus has been carried over into the leading CV specialty textbooks,<sup>54</sup> which fail altogether to deal with neuroregulatory mechanisms, except for a few autonomic reflexes.

Among the most important and frequently involved forebrain areas is the site on the ophthalmic branch of the fifth cranial nerve that connects to autonomic efferents producing the O<sub>2</sub>-conserving dive reflex, which affects the sinoatrial node.<sup>23</sup> These regulatory efferents may be activated during the brain's interpretation of emotionally laden life experience, and thereby may influence all aspects of cardiac function and vulnerability. In 1962, recognizing the importance of higher neural mechanisms to most cardiovascular functions, the NIH established a special program in neurocardiology at the University of Oklahoma School of Medicine. The program supported a 10-year prospective study of 79 subjects who had experienced MI in the past, matched with an equal number of subjects who had been free of CV disorders.

Among the studies that emerged from that program was the first report on the relationship of reduced RR variability to sudden arrhythmic death.<sup>45</sup> The prospective findings were so novel that the paper was turned down for publication by two of the leading heart journals. The work was later presented at the cardiovascular conference in Lindau, West Germany in 1971.<sup>45</sup>

Thereafter, the data from the entire 10-year prospective study were re-examined, fully analyzed, and published.<sup>61</sup> The findings that emerged established a validity of reduced RR variability being predictive of subsequent sudden cardiac death. Not all of the fatal heart attacks were associated with a fresh MI, or even other evidence of occlusive disease of the coronary arteries. Some were fatal arrhythmias.

In the 1950s and 1960s a great deal was learned about the autonomic nervous system, but inattention to brain mechanisms that governed autonomic functions still prevailed. The voices that implicated the intermediate forebrain in cardiac disorders were not heard until the 1970s and 1980s, when reports linked forebrain influences to control of autonomic reflexes as well as more direct neural pathways to the heart. Such channels were found to derive from numerous forebrain sites, including the insular cortex, hypothalamus, medial frontal cortex, septum, thalamus, zona incerta, amygdala, and bed nucleus of the stria terminalis.<sup>1</sup>

These and other data led to an investigation of a possible involvement of forebrain functions with sudden arrhythmic death independent of MI or other cardiac injury. A search of the literature provided considerable support for this view, and a series of experiments with Paul Houk provided strong confirmation.<sup>23</sup>

The claim that environmental forces may arouse physiological and pathological manifestations does not usually refer to some change in the *physical* environment, but more likely to the *social* environment, especially the phenomenon that Horsley Gantt called **the effect of person**.<sup>17</sup> Our social interactions may powerfully affect the heart and influence its performance in many ways. It appears that the CV systems contain structures most susceptible to the influence of person. Vivid examples range from the facial blush in response to an embarrassing comment, to sudden death, including angina pectoris, hypertension, and MI. The mechanisms responsible for such effects have been brought to light by recent experiments exploring sites rostral to autonomic nerve origins in forebrain areas that elicit and control autonomic responses. The activities of these forebrain structures are, of course, activated by sensory signals that may originate from the environment in the form of a word or a threat from a person. They may be relayed by the afferent fibers of the ophthalmic branch of the trigeminal nerve, as in the diving reflex that is important in inducing fatal ventricular fibrillation. Other examples include cardiac stand-still during drowning; during intubation of the trachea under anesthesia; from trauma to the pleura or to the surface of the heart itself, as may happen during cardiac catheterization; or even from the fright that sometimes is associated with this latter procedure.

Anecdotes abound concerning the "infliction" of sudden death throughout history. For example, it was described among certain New England women in relation to the sociological treatment known as "shunning." Among the ancient Greeks, sudden death to the person being socially excluded was inflicted by ostracism, by simply writing the victim's name on an oyster shell and throwing it out to sea. Comparable techniques have been described in other civilizations, such as voodoo in Central America or pouri-pouri in the Pacific Islands. We cannot exclude the possibility that these techniques activated the victim's forebrain mechanisms to turn off the heart with a fatal arrhythmia. As Ben Natelson expresses it, "The brain adapting the heart to the circumstances of its surroundings is econeurocardiology."<sup>37</sup> Some of the most convincing data that support the "eco" aspect of econeurocardiology have emerged from human experiments in which cardiac arrhythmias, anginal pain, blood pressure elevations, and angina pectoris have been induced by the technique of stress interviews.<sup>63</sup>

### **THE FOREBRAIN: CENTRAL STRESS MECHANISMS AND CARDIOVASCULAR RESPONSES** by Karen Belkić, MD, PhD

The concept of econeurocardiology renders plausible the various theoretical constructs of work stress as they relate to CVD. It also offers a framework in which the reader can integratively grasp how these stress mechanisms give rise to various cardiovascular target organ responses. The following text provides empirical grounding, focusing on animal studies in which CNS mediation of stress mechanisms, as it relates to cardiovascular responses, is specifically examined. Particular attention is paid to CNS triggering of cardiac electrical accidents. Detailed reviews of the anatomic connections between the brain and the heart and of experimental and clinical data on the role of the CNS in cardiac dysfunction can be found elsewhere.<sup>37,38</sup> These reviews point out that "links between emotional states, neural control, and cardiac function have been investigated since Cannon's classic studies in the 1920s and those from Selye in the 1930s." They not only explore "the role of the nervous system in the pathogenesis of lethal ventricular arrhythmias," but also "the role of stress in turning on the neural link that connects the environment to the heart."



drivers to cognitively-relevant visual signals has been broadly viewed in light of Skinner's model as a possible econeurocardiologic mechanism of cardiac vulnerability in this stressed occupational group.<sup>2</sup>

In contrast to the role of brain norepinephrine, elevated cerebral levels of serotonin *raise* the threshold for VF.<sup>31</sup> Other experimental findings of Lown and colleagues also illustrate the role of forebrain mechanisms in VF. In dogs, stimulation of the posterior hypothalamus in the face of experimentally-induced myocardial ischemia proves to be the critical factor in inducing VF.<sup>32</sup>

Alerting and the defense response are elicited with stimulation of the posterior hypothalamus.<sup>22</sup> Stimulation of the "defense area" of the hypothalamus in conscious rabbits gives rise to furious running such as would be expected in escape behavior. The cardiovascular-respiratory responses are consistent with a flight-or-fight pattern: tachycardia, hyperventilation, and augmented blood pressure (BP) with blood flow directed to the skeletal muscles at the expense of the viscera.

Other brain structures involved in the defense response are the amygdala and periaqueductal gray matter of the midbrain.<sup>3</sup> Neural traffic from the amygdala contributes to the risk of life-threatening ventricular tachyarrhythmias in the face of myocardial ischemia. Electrical stimulation of the midbrain reticular formation also lowers the threshold for VF.<sup>35</sup>

#### THE DIVE REFLEX AND CARDIAC ASYSTOLE

The ophthalmic branch of the fifth cranial nerve connects to autonomic efferents producing the oxygen-conserving dive reflex. Activation of this reflex can trigger sudden asystolic cardiac death. The dive reflex is a complex patterned reaction mediated by the reticular-activating system. Along with vasoconstriction and vagally-mediated bradycardia and cardiac conduction abnormalities, metabolic changes consistent with hypoventilation are found.<sup>24,60,62</sup> In addition to noxious agents and hypoxia, this reflex can be evoked by threatening symbolic stimuli. The dive reflex is basically a conservative reflex, but it may be inappropriately activated under circumstances of hopelessness, extreme fear, or exhaustion.

Besides the defense response, another CNS integration of CV and behavioral stress responses has been identified by McCabe and colleagues.<sup>36</sup> Quite reminiscent of the dive reflex, stimulation of the medial part of the lateral hypothalamus and the ventrolateral periaqueductal grey area of the midbrain in conscious rabbits elicits the **vigilance response**, with behavioral immobilization and a cardiovascular-respiratory pattern of vagally mediated bradycardia, bradypnea (to the point of inspiratory apnea), and elevated BP but with diminished blood flow to skeletal muscle *and* to the viscera.<sup>8,36</sup>

The insular cortex has been identified as a site that mediates stress-induced ventricular asystole. As described by Cechetto, this site receives an "organized representation of visceral information," as well as "highly processed association cortex information. The insular cortex is also highly interconnected with many subcortical limbic and autonomic regions. This combination of sensory input and limbic/autonomic connectivity would be necessary to permit the insular cortex to be a critical site for the integration of emotional and autonomic responses."<sup>7</sup> Prolonged phasic stimulation of the posterior insular cortex has been shown in rats to lead to progressive degrees of heart block, together with increased plasma norepinephrine and myocardial damage, and finally to asystolic death.<sup>40</sup>

The fight-or-flight defense response pattern may occur in rapid alternation with the vigilance response. This alternation may represent yet another centrally-mediated mechanism leading to cardiac electrical accidents.

### PROFOUND CONFLICT: RAPID ALTERNATION OF FIGHT-OR-FLIGHT AND PLAYING DEAD

It has been proposed that rapid alternation between these two mechanisms leads to forebrain-mediated cardiac electrical accidents. Buell and Eliot observed the behavioral backdrop typical of sudden cardiac death in animals as a combination of arousal and enforced helplessness, plus profound conflict.<sup>5</sup> They suggested that this combination may lead to a "breakdown of reciprocity between the flight-or-flight reaction and the playing-dead reaction."<sup>5</sup> Under overwhelming stress, both systems may activate simultaneously or in rapid alternation with each other, constituting the basis of the behavioral disorganization "typically exhibited by animals under extreme stress. The dog that startles, crouches, trembles, moves about aimlessly, barks, whines, salivates, urinates, defecates, pants, piloerects, and sometimes momentarily dozes. All these activities indicate simultaneous or rapidly alternating sympathetic and parasympathetic activation."<sup>5</sup>

The retrospective, content-analytical study by Engel of 170 victims of sudden cardiac death provides some anecdotal corroboration.<sup>13</sup> The following patterns were repeatedly observed among these victims: (1) the individual faces overwhelming excitement, (2) there is a personal dilemma or conflict about a course of action, (3) the situation is overwhelming, and the individual attempts to cope or he/she gives up completely, and (4) the events that occur cannot be ignored by the individual.

While these observations require neurophysiologic support, they are coherent with the dual regulation of increased vulnerability of the heart as elaborated by Skinner.<sup>49</sup> He proposes that combined high sympathetic and parasympathetic tone lead to a state of electrical instability. Wolf considers that autonomic control requires an autonomic nervous system inhibitory network; this can be disturbed in overwhelming, unavoidable, conflicting situations, resulting in a loss of regulatory inhibition.<sup>57</sup> These findings are conceptually reminiscent of Pavlov's formulation of conflict as the "difficult meeting of excitation and inhibition" in the brain.<sup>43</sup>

### Stress-Mediated Forebrain Mechanisms and Control of Blood Pressure and Heartbeat Dynamics

#### BLOOD PRESSURE

Repeated elicitation of the defense response appears to play a critical role in the development of primary hypertension.<sup>14</sup> Henry states: "Chronic arousal of the defense response with catecholamine and renin release provides a physiological mechanism giving rise to sustained hypertension."<sup>19</sup> Loss of control/giving-up as a consequence of prolonged exposure to overwhelming stress is also implicated as an important mechanism of primary hypertension.<sup>14</sup> Experimental studies reveal that strong control over animals' behavior elicits hypertensive responses.<sup>3,16</sup> Signaled and un signaled avoidance conditioning in dogs and monkeys is associated with an increase in BP, as well as heart rate. When exposure to this type of paradigm is sustained over several months, the animals become hypertensive.<sup>46</sup> In general, induction of hypertension in experimental animals requires several months of repeated exposure to stressful situations.<sup>15,16</sup> Henry also has found that long-term stressful life conditions in crowded cages leads to permanent hypertension among rats.<sup>21</sup>

Stimulation of the lateral hypothalamus in rabbits evokes a defeat-type pattern with motoric immobilization, *generalized* vasoconstriction, and vagally mediated bradycardia.<sup>8,36</sup> Short-lived but repeated stimulation of the lateral hypothalamus for several days to weeks in rats is found to lead to a progressive, sustained rise in arterial BP.<sup>18</sup>

Microstimulation of the rostral portion of the posterior insular cortex evokes arterial pressor responses in rats.<sup>64</sup> Szilagy and colleagues have demonstrated, in rats with experimental hypertension, that synaptic cryoblockade of the ventromedial region of the frontal cortex leads to a significant fall in arterial BP.<sup>53</sup> This frontal cortical site projects via the anteroventral hypothalamus to brainstem cardio regulatory loci. Other forebrain loci that have been identified as important in blood pressure regulation include the amygdala, the septal nuclei, and the cingulate cortex. Oparil and colleagues state: "Since these areas are involved in learning, emotional responses (especially the defense reaction), and the integration of information from higher centers, they are likely to be most important in the pathogenesis of hypertension that is related to environmental stress."<sup>39</sup> These authors provide a detailed review of neuroanatomic and neurochemical pathways as they relate to the development of hypertension.

#### HEARTBEAT DYNAMICS

Heart rate variability (HRV) has been noted to provide one important mechanistic link between exposure to mental stress and risk of cardiac events. Using a deterministic measure of HRV that tracks non-stationarities,<sup>52</sup> injection of intracerebral l-propranolol in pigs has been found to increase HRV.<sup>50</sup> This landmark finding illustrates the role of central noradrenergic mechanisms in control of HRV.

#### Econeurocardiology and Clinical Outcomes

The econeurocardiologic model of Skinner<sup>49</sup> can be expanded to the realm of human psychosocial experience, for which symbolic stimuli often play a particularly important role:

*Bodily responses triggered by a thought or by a perception of one's surroundings are attributable, of course, to symbolic as contrasted with tangible stimuli. The bodily changes observed constitute a part of the behavior of a person, behavior that is governed by the significance of the situation to the implicated individual. There is, indeed, a vast repertoire of behaviors that adapt the individual to life experiences of all sorts. Each involves discrete patterned responses that are activated and coordinated by the nervous system, and may involve voluntary as well as involuntary behavior.*<sup>59</sup>

The impact of these mechanisms on clinical CV events has been appreciated since early times. One particularly important sociological example has been called the "Roseto effect," in which a consistently lower mortality rate from myocardial infarction was observed over 30 years in a homogeneous Italian-American community, compared to adjacent towns with greater acculturation and lower social cohesion. Further followup revealed that with erosion of social networks in Roseto, a dramatic rise in deaths from MI occurred, most notably among the young of both genders and older women.<sup>10,57</sup> These findings are highly consistent with the burgeoning literature on social isolation as a potential risk factor for clinical CV events.<sup>4,41</sup>

#### HYPERFUNCTIONAL OVERDRIVE: ACQUIRED CARDIOVASCULAR DISORDERS

In 1974, R.S. Eliot introduced the concept of "acquired cardiovascular disorders." These include: acute MI, angina pectoris, arterial hypertension, and sudden cardiac death. The common feature of these disorders may be a stress-related component mediated by the CNS, resulting from "hyperfunctional overdrive," i.e., overstimulation by the catecholamine system (see Chapter 5). Eliot broadly outlined the

environmental backdrop for CNS-mediated overactivity of the sympathetic nervous system, noting "the social inpropriety" of the flight-or-fight reaction in modern day life, such that most stressors are chronically present and cannot be resolved in a physical way.<sup>12</sup> The consequence is a "chronic alarm reaction" in which there is a "constant state of visceral-vascular readiness" whereby the heart and blood vessels are activated irrespective of the actual metabolic needs of the organism.

The acquired CV disorder formulation could be expanded to include loss of control—a defeat or "giving-up" dimension—which also is associated with untoward CV outcomes. Henry presents a model in which the deleterious effects of the latter are highlighted.<sup>20</sup> In working life, a particularly cardioxious combination is arousal plus low control or defeat, i.e., job strain, which would imply the activation of both branches of Henry's model.<sup>25</sup>

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