

# 27 BRAIN FAILURE AND BRAIN DEATH

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He seems to be completely unreceptive  
The tests I gave him show no sense at all  
His eyes react to light; the dials detect it  
He hears but cannot answer to your call  
"Go to the Mirror Boy" (from *Tommy*, The Who, 1969)

## Brain Failure

### BRAIN FAILURE AND IMPAIRMENT OF CONSCIOUSNESS

As a type of organ system failure, brain failure invariably affects consciousness. Consciousness is structurally produced in the cerebral hemispheres, including the pons and the medulla.<sup>1</sup> These structures are all interconnected by the reticular formation, which begins in the medulla and extends to the midbrain, where it forms the reticular activating system. This pathway modulates the perception of events and controls integrated responses.<sup>2</sup>

Clinical evaluation of consciousness states is heavily dependent on the findings from physical examination. When the physical examination yields visual and palpable clues to the integrity of consciousness, impairment thereof may be classified into one of the following categories<sup>3</sup>:

1. Cloudy consciousness. This state is defined as a mild deficit in the speed of information processing by the brain, resulting from disruption of cell-to-cell connectivity at the histologic level. Cloudy consciousness may be noted after mild to moderate head trauma and may persist for several months. Memory of recent events is often diminished, but long-term memory typically remains intact.
2. Lethargy. This state is defined as a decrease in alertness, resulting in impaired ability to perform tasks that are normally accomplished without effort. Patients rouse briefly in response to stimuli, then settle back into inactivity when left alone. They retain awareness of their immediate environment.
3. Obtundation. This state is defined as a decrease in awareness and alertness, in which patients rouse briefly in response to stimuli and follow simple commands but are unaware of their immediate surroundings. When stimulation ceases, they settle back into inactivity.
4. Stupor. In this state, patients cannot communicate clearly but can be aroused by continued painful stimulation. Arousal may be manifested only as withdrawal from painful stimuli. As soon as stimuli are removed, patients settle back into inactivity.
5. Coma. In this state, patients do not respond to even the most vigorous stimuli.
6. Brain death. This state is equivalent to functional decapitation and is characterized by irreversible cessation of whole brain function and function of the hemispheres and the brain stem.

It should be kept in mind that the efficacy of the physical examination in the evaluation of consciousness diminishes when visual clues disappear (e.g., during heavy sedation or therapeutic musculoskeletal paralysis). In such situations, monitoring of cerebral function is helpful in assessing the effect of therapy on neuronal function.

### RELATION OF CARDIAC ARREST TO BRAIN FAILURE

In a substantial proportion of unconscious patients admitted to the intensive care unit, the brain failure resulted from metabolic and hemodynamic deteriorations that followed cardiac arrest.<sup>4</sup> There is a great difference between surviving cardiopulmonary resuscitation (CPR) and walking out of the hospital unaided after such an event. It is relatively easy to restart the heart with traditional CPR; it is considerably harder to restart the brain.<sup>5</sup> After several minutes of cardiac arrest, CPR will occasionally restore cardiac activity, but it will not necessarily restore useful brain function. Brain metabolism requires a constant high flow of oxygenated blood and nutrients. During cardiac resuscitation, cerebral perfusion decreases sufficiently to promote hypoxia and tissue edema. A number of mechanisms have been shown to underlie deteriorating and failed reflow. Hyperviscosity from hemoconcentration of plasma proteins and formed elements contributes to initial poor reperfusion at the capillary level. Endothelial cell swelling and edema of the pericapillary astrocytes also greatly inhibit reperfusion by reducing capillary diameter to less than 5  $\mu\text{m}$ .

During reperfusion, abnormally high amounts of superoxide convert almost all available nitric oxide to peroxynitrite, which is regarded as the agent that causes most of the damage to brain capillary endothelial cells.<sup>6</sup> As noted (see above), damage to the endothelium not only increases edema (tissue swelling resulting from leakiness) but also causes endothelial protrusions (blebs) that can block capillaries. Calcium-mediated vasospasm also plays a role. L-type calcium channel blockers, given before the insult, have been shown to prevent the no-reflow phenomenon in dogs and to result in an 80% survival rate (compared with an 86% mortality in the control group).<sup>7</sup>

During CPR, cerebral perfusion tends to decrease dramatically over time if adequate flow is not quickly reestablished.<sup>8</sup> Maintaining a small amount of blood flow to the brain with CPR is not necessarily beneficial. Incomplete brain ischemia, which is created when only a small amount of blood is allowed into the brain after an anoxic insult (as in CPR), appears to result in more detrimental alterations in brain metabolism than does the complete anoxia resulting from the absence of any flow.<sup>9</sup> When a small amount of blood is allowed to flow into an actively distorted and stressed metabolic system, the resulting cellular activity generates more toxic products of metabolism than complete anoxia would have produced.<sup>10</sup> In other words, more brain damage seems to occur with prolonged CPR states than with no-flow states<sup>11</sup>—especially if there is an increased level of glucose in the small quantities of blood supplied by CPR.<sup>12</sup> To date, this phenomenon has not been completely explained. Acidosis, in and of itself, is unlikely to be the only damaging factor, because severe respiratory acidosis does not damage the brain.<sup>13</sup>

### PATHOPHYSIOLOGY OF BRAIN FAILURE

In vitro, central nervous system neurons can tolerate between 20 and 60 minutes of complete ischemic anoxia without irreversible injury.<sup>14</sup> In vivo, however, injury occurs after a much shorter time

and is much more severe. Immediately after the cessation of circulation to the brain, the cerebral vessels dilate in response to the local environmental factors and to increased arterial carbon dioxide tension ( $P_a\text{CO}_2$ ). Because the brain has no stores of glucose, cellular metabolism quickly ceases. Absence of nutrients and hypoxia cause the most sensitive structures to lose their cellular integrity. This loss results in capillary leakage, edema, and cellular disruption and leads to the release of proteases and other damaging compounds into the surrounding tissues.<sup>15</sup>

These events, in turn, result in clogged microcirculation, stasis, and a vicious circle of worsening damage that backs up into the macrocirculation. If this process is allowed to continue for a substantial period and blood flow is then reestablished, the increased pressure gradient in the damaged area tends to disrupt the fragile architecture, much as the sudden bursting of a dam might do to downstream communities. The result is a progressive postresuscitative hypoperfusion state in which blood flow falls to less than 20% of normal within 90 minutes after reperfusion and remains at this low level for as long as 18 hours.<sup>16,17</sup>

Two explanations for these phenomena have been proposed. The first is that massive overloading of the cells with calcium ions ( $\text{Ca}^{2+}$ ) may be the initial stage of irreversible damage.<sup>18</sup> Normally, the extracellular level of  $\text{Ca}^{2+}$  is high and the intracellular level is low. The damage to the cell membrane caused by hypoxia and loss of nutrient flow alters the gradient and allows  $\text{Ca}^{2+}$  to enter the cell, causing interference with enzymes, DNA, RNA, mitochondria, and energy production cycles. Infusion of high levels of  $\text{Ca}^{2+}$  into precapillary arterioles causes vasospasm and a vicious circle characterized by decreased flow and further depletion of oxygen and nutrients. The second theory is that during ischemia, abnormal metabolism may result in the creation of reactive oxygen metabolites, which attack DNA, RNA, and mitochondria, causing irreversible damage.<sup>19</sup>

## Brain Death

### DIAGNOSIS OF BRAIN DEATH

Brain death protocols have evolved to become highly specific and sensitive.<sup>20</sup> Brain death is a diagnosis of what is, not what might be. Initially, for an accurate diagnosis of brain death, there must be clear evidence of an acute, catastrophic, irreversible brain injury, and any reversible conditions that may obfuscate the clinical assessment (e.g., drug intoxication, hypothermia, and metabolic abnormalities) must be excluded.<sup>21</sup> Subsequently, the physical examination must show coma, absent motor responses, absent brain stem reflexes, and apnea. Some protocols call for a second examination, performed after a variable interval.<sup>22</sup> Further confirmatory studies (e.g., electroencephalography [EEG] or cerebral blood flow studies) may be ordered if there is any ambiguity in the clinical evaluation.<sup>23</sup>

A typical brain death protocol may be summarized as follows:

1. Confirm that the patient is in a coma.
2. Evaluate the patient for seizure activity and decerebrate or decorticate movements.
3. Test for motor response to painful stimulation.
4. Test for pupillary response to light.
5. Test for the corneal reflex.
6. Test for the oculocephalographic reflex (the doll's head reflex).
7. Test for the vestibulo-ocular reflex (the caloric test).
8. Test for upper and lower airway stimulation (e.g., pharyngeal and endotracheal suction).

9. Test for the gag reflex.
10. Perform the apnea test. This test should be the last test and should be conducted after two clinical examinations (separated by the mandatory observation period) have confirmed the absence of brain stem functions. The patient is disconnected from the ventilator while oxygenation of the lungs is continued passively. On the basis of calculation (whereby  $P_a\text{CO}_2$  is assumed to rise 4 mm Hg in the first minute and 3 mm Hg every minute thereafter), the patient is allowed to build up to a  $P_a\text{CO}_2$  of 60 mm Hg or more without becoming hypoxic. If there is no respiratory effort, the apnea test is considered confirmatory.<sup>24</sup>
11. Consider ordering an EEG. The EEG should show electrocerebral silence for at least 30 minutes and must conform to established criteria for brain death.<sup>25</sup>
12. If the cause of death cannot be determined with absolute accuracy, consider cerebral angiography. The absence of intracranial arterial circulation, as demonstrated by four-vessel angiography, confirms brain death.<sup>26</sup>

### DEFINITION OF DEATH

In earlier times, it could be said that a person was dead when the heart and lungs ceased functioning. Today, however, this view no longer suffices, because with the advent of critical care techniques such as mechanical ventilation, selected organ systems can be artificially supported.<sup>27,28</sup> In this era of critical care, death is more a process than an event. Lack of blood flow to the brain leads to loss of consciousness within seconds, but other functions of the brain may persist for much longer.<sup>29</sup> Other somatic organs may take hours to stop functioning, and connective tissues can take days to die.<sup>30</sup>

The evolution of life support systems capable of prolonging death indefinitely necessitated a more eclectic definition of death, which arrived in 1968 with the formulation of the Harvard criteria.<sup>31</sup> In essence, these criteria considered the irreversible loss of certain organ functions, rather than whole body metabolic cessation, to be indicative of death. When the Harvard criteria were met, death was inevitable, even with continuing treatment. A 1970 study found that a population of patients meeting the Harvard criteria all eventually died while undergoing continued medical treatment.<sup>32</sup> The Harvard criteria objectified the progression of disease, thereby making it possible for clinicians to predict death.

These early studies only predicted with a reasonable certainty that patients meeting particular criteria would eventually die. A prognosis of death, however, cannot serve as a diagnosis. In 1981, the President's Commission broke with the past and established brain death as a criterion for determining death, not simply for predicting the inevitability of death.<sup>33</sup> The Uniform Determination of Death Act (UDDA) made brain death and cardiopulmonary collapse criteria for death in 44 states<sup>34</sup>:

An individual who has sustained either: (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead.

Under the UDDA, death is pronounced at the time the criteria are met, and families may not demand continuing mechanical ventilation or other forms of ICU life support (except in the states of New York and New Jersey, both of which have conscience clauses).<sup>35</sup>

### *Is Brain Death Equivalent to Death?*

Physicians and ethicists continue to disagree on the question of whether whole brain death (WBD) is equivalent to death.<sup>36</sup> It

is generally asserted that there is only one real definition of death—irreversible cessation of the integrated functioning of the organism as a whole—but as noted (see above), the determination of death can have either a cardiovascular or a neurologic basis. The connections between cardiovascular and neurologic criteria are tenuous, and the criteria mean different things to different people at different times. For example, the criterion of irreversible cessation of all circulatory and respiratory function does not imply the cessation of brain function.<sup>37</sup> Conversely, the criterion of irreversible cessation of all brain function does not imply the cessation of circulation and respiration.<sup>38</sup> It appears, then, that the definition of death does not require the permanent cessation of the functioning of the organism as a whole but, rather, cessation of only certain functions.<sup>39</sup>

Ethicists maintain that the criteria used to fulfill the definition of death should be both necessary and sufficient.<sup>30</sup> This is not an easy standard to meet. For example, loss of consciousness is necessary for death, but it is not sufficient. Although the UDDA endorses two criteria for death—cardiac death and WBD—only WBD is both a necessary and a sufficient criterion, because a declaration of death can be made without the heart having stopped beating. Therefore, the UDDA does not ensure that each of the two criteria is an instantiation of the other.<sup>40</sup> Loss of heartbeat and breathing is sufficient for death, but it is not necessary if WBD is present. Moreover, the UDDA does not require that every brain cell be dead for brain death to be declared—only those cells that contribute to the integration of the organism as a whole.<sup>41</sup> Accordingly, the UDDA suggests that death occurs when “critical” parts of the brain responsible for integrated functioning of the rest of the body cease functioning, in that, according to this argument, it is the brain that integrates the entire organism.

It is commonly postulated that when the brain dies, the body must die with it. However, there is a problem with the idea of the brain as the fundamental orchestrator of all body functions. It has been pointed out that many organ functions are, for variable periods, not obligately linked to the brain as an integrating controller.<sup>30</sup> In fact, the rest of the body can be viably sustained for some time in the absence of brain function simply by maintaining protection, ventilation, circulation, and nutrition. Some WBD patients actual-

ly require less support than other patients who are clearly alive but gravely ill.<sup>42</sup> It can easily be shown that the brain will continue to function for a time after cessation of cardiopulmonary function.

#### *Brain Death and Artificial Organ Support*

Acceptance of WBD as essentially defining death involves the assumption that artificially maintained respiration and circulation are irrelevant because they are controlled by mechanical intervention rather than by the brain.<sup>43</sup> This assumption is based on the further assumption that because body functions are being manipulated externally, they cannot be functioning in any integrated manner. However, death cannot be predicated on the use of life-sustaining treatment, for two reasons. First, the availability of life-sustaining treatment ought not to determine who is alive and who is dead. Second, if the definition of death were to be contingent on the need for an artificial intervention, patients who require life-sustaining treatment to recover from an illness would have to be considered resurrected from the dead.<sup>44</sup> Furthermore, the definition of death does not require irreversible cessation of “spontaneous” organism functions, because spontaneous function is not necessary for life, as evidenced by the many patients who require life-sustaining treatment but who are very much alive.<sup>45</sup>

#### IMPLICATIONS FOR FUTURE DEFINITIONS OF DEATH

There are disturbing differences between a corpse in a morgue and a brain-dead patient. If the WBD patient is a corpse, he or she is certainly a corpse with some unusual properties—one that breathes, circulates blood, digests food, filters wastes, and is capable of carrying a pregnancy to term.<sup>46</sup> These considerations raise the issue of whether there is a practical or ethical difference between being dead, being almost dead, or being in the process of dying, and they show that the precise moment when death occurs cannot be accurately pinpointed. It is clear that a WBD patient can be maintained on life-sustaining treatment for much longer than was once thought and still retain definite characteristics of a living being. The organism as a whole, though disabled, is not yet dead and should not be represented as such—a fact that may have important consequences for our future conceptions of death and of life in death.

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