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Determination of Death: A Scientific Perspective on Biological Integration

Maureen L. Condic*

Abstract

Human life is operationally defined by the onset and cessation of organismal function. At postnatal stages of life, organismal integration critically and uniquely requires a functioning brain. In this article, a distinction is drawn between integrated and coordinated biologic activities. While communication between cells can provide a coordinated biologic response to specific signals, it does not support the integrated function that is characteristic of a living human being. Determining the loss of integrated function can be complicated by medical interventions (i.e., "life support") that uncouple elements of the natural biologic hierarchy underlying our intuitive understanding of death. Such medical interventions can allow living human beings who are no longer able to function in an integrated manner to be maintained in a living state. In contrast, medical intervention can also allow the cells and tissues of an individual who has died to be maintained in a living state. To distinguish between a living human being and living human cells, two criteria are proposed: either the persistence of any form of brain function or the persistence of autonomous integration of vital functions. Either of these criteria is sufficient to determine a human being is alive.

Keywords: *brain death*, *capacity for rationality*, *determination of death*, *organismal function*, *persistent vegetative state*

I. INTRODUCTION

Determining when a human has died is scientifically challenging. Unlike the beginning of human life, an event that can be accurately localized to a period of less than a second (Condic, 2008, 2014b), precisely when death occurs is far less clear. In part, this may reflect the great variety of ways in which death occurs. Yet even when death occurs as the consequence of a relatively common event (e.g., heart failure), the transition from a living human being to a collection of human cells and tissues (i.e., a corpse)[1] cannot be directly observed. Consequently, the physical criteria used for determination of death are not intended to pinpoint the moment of death, but rather to identify a point at which we can state with confidence that death has already occurred.

Yet what are the valid criteria for making this determination? The simplest criterion for death is total cellular death; that is, the transition from a living organism to a collection of non-living organic matter with no viable cells present. Yet cellular life persists in the body for hours or even days after an individual has been declared dead by current medical standards (National Conference of Commissioners on Uniform State Laws, 1980, Uniform Determination of Death Act); live cells have been recovered from human skin, dura (Bliss et al., 2012), and retina (Carter, 2007) up to 48h after death, with cells remaining viable in the human cornea for up to a week (Slettedal et al., 2008). This period can be extended considerably when artificial intervention (i.e., “life support”) is used to provide oxygen or blood circulation to the body. Even without artificial intervention, all of the sophisticated structures associated with tissues, organs, and organ systems remain intact following death, degenerating only slowly in the process of decomposition. Moreover, given that human cells and tissues are not the same as human *beings*, requiring total cellular death is too stringent a criterion for human death. If the total cessation of body-wide metabolic processes is the only admissible criterion for death, then nearly every human being who ever lived was either killed by the mortician who terminated cellular life in the embalming processes, or was buried or burnt alive. A more reasonable criterion must allow for the persistence of living cellular structures and functional cell metabolism following death of the human being.

These preliminary considerations are important for contextualizing the debate regarding whether or not total brain death is a valid criterion for human death, and especially for evaluating the significance of the evidence indicating that (with the help of artificial interventions) many complex functions can persist in the body after death of the brain (table 1).[2] This evidence has led many to question the validity of the claim that brain death marks the death of a human being, or at least to question the standard rationale—i.e., that the brain is necessary to maintain organismal integration (Bernat, Culver, and Gert, 1981)—for considering brain death to be death.[3] Yet all of the functions listed in table 1 are either seen in isolated cells and tissues maintained in culture or are known to be due to chemical signals that could easily be reproduced in the laboratory. The fact that these activities are also seen in human cells/tissues *ex vivo* indicates that they are not sufficient for determining whether or not a human is still alive—i.e., whether or not what remains after brain death is still a human organism as a whole, rather than an aggregation of unintegrated cells and tissues that used to be part of the unified human organism.

Table 1.

Coordinated functions persisting after determination of death by current medical standards

Functions	Seen in cells or tissues *ex vivo*?	Preserved after death?
Homeostasis	Yes	Impaired
Elimination/detoxification	Yes organ culture	Impaired
Energy balance	Yes	Impaired
Temperature regulation	Yes components	Minimal
Wound healing	Yes	Yes
Immune defense	Yes components	Impaired
Fever	Yes components	Minimal
Stress response	Yes organ culture	Impaired
Gestation-maternal side[a]	Yes components	Impaired
Sexual maturation[b]	Yes components	Minimal
Proportional growth	Yes organ culture	Impaired

[a]A fetus is manifestly a living organism, and is responsible for many gestational functions.

[b]Components of sexual maturation have been observed in two individuals after brain death (see Shewmon, 1998). "Baby A" abnormally developed pubic hair (Tanner stage II) at 1 year of age following brain death; BES, a 13-year-old male who survived 65 days following a diagnosis of brain death, developed minimal pubic hair in this period.

Given that cells and tissues are known to persist and perform an impressive and complex array of activities *ex vivo,* it is entirely reasonable to claim that the same situation could occur in a body that is no longer a living human being. Yet this leaves open the disturbing question of precisely what level of biologic function can persist in a purportedly dead human body, without giving us reason to question our judgment that the body is in fact dead. What signs can we rely on to indicate with sufficient certainty that a human being has died?[4]

The challenge of determining when death occurs is therefore the challenge of discerning when the human *being* has ceased to be, leaving behind a collection of human cells that continue to exhibit some of the natural properties they had during life. The aim of this article is precisely to offer an analysis, from a biological perspective,[5] of what differentiates a human being from a mere aggregation of human cells. Both are alive and genetically "human." Both exhibit complex behavior. Yet human beings are organisms,[6] and their function categorically requires a level of organization above that seen in cells, tissues, and organs (fig. 1). As argued below, the difference between tissue or cell-level organization and human organismal organization is not just a difference in degree, but rather a difference in kind—the difference between coordination and integration. While cells, tissues, organs, and organ systems engage in extremely complex coordinated activities, in nature they are not in themselves organisms because they are integrated into, at the service of, and globally regulated by the organism of which they are part and by which they were formed. In isolation from the whole, these parts lack the autonomous capacity to sustain their own functions, and can remain alive only with the aid of artificial interventions, such as culture medium or, in the case of organs, the perfusion of oxygenated blood. In contrast, all of the activities of an organism are *globally* and *autonomously* integrated to promote the continued life, health, and maturation of the organism as a whole. Thus, what differentiates genuine organismal integration from the coordination which occurs at the cell and tissue levels is that organismal integration is both global and autonomous. It is global in the sense that the activities of all the vital parts are regulated and organized to promote the health and survival of the whole (rather than just the survival of the parts themselves). It is autonomous in the sense that this regulation and organization is carried out by the organism itself.

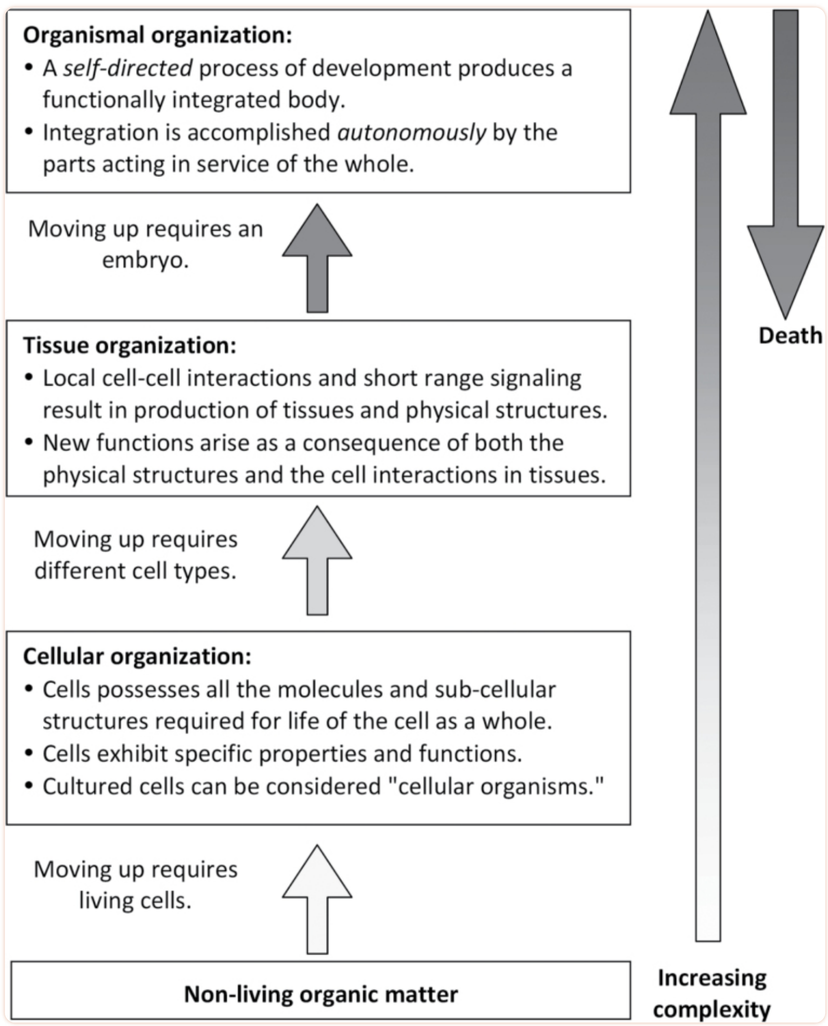

Fig. 1.

Levels of organization in living entities. In nature, only organisms (single cell and multicell) autonomously exist. With artificial support, cells and tissues that are naturally parts of a multicellular organism can exist independently of that organism. Each level of organization depends on the levels below. The transition between tissue organization and organismal organization reflects the difference between coordination and integration. Adapted from Condic (2011).

The remainder of this article elaborates on and provides further evidence for the above claims, drawing on them to propose reasonable criteria for the determination of death that are stringent enough to avoid classifying the living as dead (even when artificial interventions are necessary to sustain life), but not so stringent that they require us to wait until every cell has died before declaring death.

II. THE ORGANISMAL CRITERION FOR BOTH THE BEGINNING AND THE END OF NATURAL LIFE

Living human beings are fundamentally different from human cells, based on the level at which integration occurs (fig. 1). Cells integrate the activity of molecules, molecular complexes, and subcellular organelles to promote the life and health of the cell as a whole. Different kinds of cells have different properties, but in all cases, cells are the fundamental unit of life, whether existing independently or as a part of a larger living thing. In the absence of some additional organizing principle, cells display no intrinsic drive to a higher level of organization. When left to their own devices, cells only produce more cells. In the artificial environment of a laboratory dish, a cell will survive and function according to its intrinsic characteristics, without reference to or requirement for anything beyond itself.[7] In light of this, an individual human cell in the laboratory can be considered an organism in its own right, albeit an artificial one. Artificial, because its isolation and sustenance depend on human actions; that is, it does not exist in nature. In the natural environment of the body, cells function as a *part* of an organism, not as independent organisms in their own right.

Similarly, human tissues and organs can also be maintained in a living state in the laboratory. Yet, despite the higher level of complexity observed in tissues and the extensive interactions that occur between the cells that comprise them, such collections of cells cannot be considered organisms, because (unlike free-standing cellular creatures and complete, multicellular human beings) organs do not autonomously produce and regulate all of the structures and relationships required for the life of the organ as a whole. The individual cells in the organ naturally produce the structures necessary for cellular life. Yet organs and tissues are not entities organized for life independent of the body of which they are normally a part (organs are not "free-standing"). The structures which the cells of the organ can produce are not sufficient to sustain the life and health of the organ as a whole. Tissues and organs in laboratory culture are aggregates of cellular organisms, but not organisms in their own right. In the natural environment of the body, they are parts that contribute to the function and survival of the (multicellular) organism as a whole.

In contrast to human organs, a human being functions as an organism at all stages of life. From the moment of sperm–egg fusion onward, a human embryo enters into a developmental sequence that will produce the cells, tissues, organs, and relationships required for progressively more mature stages (Condic, 2008, 2014b). Thus, unlike an individual cell or group of cells, which organize at the cellular and tissue levels only (fig. 1), the embryo exhibits a clear, self-directed drive towards a higher, multicellular level of organization.[8] At all stages of life, the parts of a human organism work together to promote the life and health of the entity as a whole. Thus, a mature human body is composed of many trillions of cells, but these cells are integrated into a single functional unit that autonomously sustains its own life and health. Unlike an isolated tissue or organ, the body as a whole is a true organism.

The clear difference in the levels of organization exhibited by cells, tissues, and organisms provides an organismal definition for both the natural beginning and end of human life:

Human life commences at the onset of globally self-integrated organismal function and concludes when globally self-integrated organismal function irreversibly ceases.

This definition applies only to the natural life span of a human (i.e., to cases where there has been no intervention to sustain biologic function) since, as we will see, when artificial interventions supplement or replace biologic functions, many challenging and counterintuitive situations arise. Yet in the absence of such intervention, organismal function provides a clear and unambiguous criterion for both the beginning and end of human life.

III. ORGANS REQUIRED FOR LIFE CHANGE OVER LIFE SPAN

Application of this definition to all stages of human development is complicated by the fact that the vital organs required for organismal integration change over the life span. In the early embryo, a complex molecular "program" produces and organizes cells with specific properties that will build up the more mature tissues and systems of the body.[9] The embryo is more than a mass of tissue since the cells do more than simply make more cells or produce isolated organs; the cells of the embryo produce the organization of the entire body. In later embryos and fetuses, the heart and the placenta are the most critically required organs for continued life, growth, and coordination of body systems. In postnatal stages, the brain, the lungs, and the heart are all required organs, and the brain provides crucial integration of the three by regulating the other vital organs so that they function in the service of the whole.

Importantly, this does not mean that a human being is nothing more than a molecular program, the placenta, the heart, the lungs, or the brain. It means that at different stages of the life span, specific organs are required for a human being to autonomously perform the globally integrated functions necessary to remain alive. It also means that the function of specific organs cannot *universally* distinguish between the living and the dead: irreversible cessation of placental function is likely to be a sufficient criteria for death at prenatal stages of life, but the fact that I do not currently have a functioning placenta does not mean that I am dead. Similarly, the lack of a functioning heart at early embryonic stages does not indicate an embryo is not alive or not a human being. It indicates that, similar to the brain and the lungs, the heart is not a required organ for early stages of human prenatal life. What is critical at *all stages* of human life is the continued, global, and autonomous integration of function that is characteristic of an organism and that distinguishes a living human being from an aggregation of human cells.

IV. DISTINGUISHING A HUMAN PART FROM A HUMAN WHOLE

Discriminating between the living and the dead is further complicated by the fact that many biologic functions that are naturally required for human life can currently be replaced (perfectly or imperfectly) by artificial interventions. Thus, in the past, irreversible cessation of cardiopulmonary function was adequate to conclude that the capacity of a human to function as an organism had been irreversibly lost, and therefore the human being had died. Yet today there are many medical interventions that can bypass such "irreversible" cardiac arrest and restore to full function individuals who would have otherwise been declared "dead."[10]

In light of an organismal criterion for both the beginning and end of life and in light of our ability to artificially replace many vital functions of the body, what features can reliably distinguish between a living human being and a dead one? Clearly cells, tissues, and organs *ex vivo* show complex functions that can also persist in a human body following some diagnoses of death (table 1). Consequently, these functions (e.g., wound healing) reflect only the operations of *parts* and do not necessarily imply the presence of a whole human. Conversely, the fact that many parts of the body can be lost or damaged without resulting in total loss of organismal integration indicates that limited or partial function does not necessarily imply the individual is dead.

Therefore, the challenge in defining death is to determine when the activity observed in a biological system is self-regulated in the service of the "whole" and when it merely reflects the intrinsic properties of cellular parts. Stated in a somewhat different way, determination of death requires us to discern when a body has completely lost its capacity for global and autonomous self-regulation and integration, versus when a living human being is merely "blocked" from exercising its self-integrating capabilities, as when a head injury causes swelling which temporarily blocks the body's ability to regulate its own breathing.

If strictly functional criteria do not reliably distinguish parts from whole human beings (table 1), how can we tell that a human "whole" exists? Humans have been defined in many ways, but one of the simplest and most robust definitions is that humans are rational animals. This definition is independent of any specific religious tradition (it was initially put forward by the pagan philosopher Aristotle) and it acknowledges the two essential aspects of our nature: that we are living biological beings of the Kingdom *Animalia* who are capable of reason. Importantly, on the Aristotelian account, both of these essential aspects of our nature are ultimately rooted in the soul, understood as the unifying, vivifying, organizing principle of a living being.[11] This understanding of what constitutes a human being suggests two clear criteria that are each sufficient evidence for the persistence of human life in an entity that originally met the Aristotelian definition, because each is sufficient evidence for the presence of the human organizing-principle or soul:

1. Persistence of mental function, no matter how impaired, demonstrates the persistence of a living human being. Although not all humans with mental function are immediately capable of rationality,[12] the presence of any mental function in a human being gives reason to believe that the basic natural capacity for rationality, rooted in the soul, has not been completely lost. Given that the minimal neurologic structures required for mental function are not known,[13] prudence would dictate that persistence of any brain function should be considered evidence that the basic natural capacity for mental function may remain.[14]
2. Persistence of global, autonomous integration of vital functions ("animality" or organismal function), even in the absence of evident mental function, indicates that an organism of the type *Homo sapiens* (i.e., a human being) exists. This criterion is a restatement of the "organismal" criteria given above.

Applying these criteria enables a clear distinction between the living and the dead even in difficult cases. For example, individuals with severe brain damage who are in a persistent vegetative state have limited or absent mental function. However, such individuals (unless they also suffer from illness or injury affecting other vital organs[15]) also show sustained, global, autonomous integration of bodily functions. They require normal care (i.e., food and water, and alleviation of the symptoms associated with prolonged bed rest), but not ventilation or other mechanical support systems. Such individuals are in a seriously impaired state, but they are clearly functioning as a human *organism* to maintain their body as a whole and regulate their own vital functions. They exhibit both persistent brain function (criterion #1) and persistent integration (criterion #2), and are therefore still alive.

In contrast, individuals with high-level cervical spinal cord injury (hereafter, SCI) show limited or absent autonomous integration of bodily functions. They are dependent on artificial interventions (i.e., "life support") to maintain their vital activities, yet their capacity for mental function remains. Such individuals are also severely impaired and they no longer function as a biological organism,[16] but by virtue of the fact that they remain capable of mental function (criterion #1), they are also still alive.

In situations where there is *both* limited or absent autonomous control of the body (patients who are dependent on artificial medical interventions) *and* the individual is not conscious, great care must be taken to determine if any aspect of brain function persists. If so, no matter how impaired brain function may be, it remains possible that the capacity for some form of mental activity persists, and that the basic natural capacity for rationality (rooted in the soul) still remains.[17] Therefore, such individuals must be given the benefit of the doubt and seen as still alive. This does not imply a moral obligation to sustain such an individual by extraordinary means. But it does require an acknowledgement that removing life support will result in the death of a living (albeit severely impaired) human being.

In contrast, following the irreversible cessation of all brain function, including the brain stem (i.e., "brain death"), the human body exhibits *neither* of the defining characteristics of a living human being: global autonomous integration cannot be maintained (i.e., the body is no longer able to function as an organism because it has lost the capacity to regulate its own vital activities, criterion #2), and mental function is also precluded (criterion #1). Therefore, brain death is "real death" because at postnatal stages, the brain is required for both self-directed integration of bodily function above the level of cells and tissues *and* for mental function.[18]

Unlike a SCI patient where criterion #1 provides unambiguous evidence for the presence of a living human being, for a brain dead body we have no such evidence. All of the evidence that we currently have regarding the observed activities of bodies after brain death (with the help of artificial intervention) is consistent with the claim that the brain dead body is not an integrated whole, but rather an aggregate of human cells, persisting in the ordered relationships established during life and functioning under the auspices of individual cellular organizing principles. We know this because the same activities have also been observed in cells and tissues *ex vivo* (table 1), which obviously are not in themselves human organisms. While the brain dead body can exhibit coordinated activity within some of its systems or across cells in certain tissues (see below: "Objections to Brain Death as Evidence for Human Death"), it is unable to exercise either rationality or global, self-integrated organismal function, and therefore we lack sufficient evidence to show that a brain dead body is a living human organism.

Of course, this in itself does not *prove* that a brain dead body is not a living human organism. More argumentation would be needed in order to show that (1) the capacity for global, self-integrated organismal function is *necessary* for the persistence of an organism,[19] and (2) in postnatal stages of life, the brain is required for such function. Premise 1 is a philosophical one, which is beyond the scope of this paper, but is defended elsewhere,[20] and is assumed explicitly or implicitly by many participants in the brain death debate.[21] Premise 2 is a biological premise, for which evidence is offered below. But even if the reader rejects either (or both) of these premises, what has already been said shows that the evidence indicating some functions can persist in a brain dead body on a ventilator is far from providing a conclusive reason to reject the belief that brain death marks the loss of organismal integration. This is, in itself, an important conclusion.

V. HUMAN BEINGS WHO CANNOT FUNCTION AS ORGANISMS

The criteria given above to distinguish the living from the dead raise the challenging possibility that in cases of patients with SCI who are sustained by artificial intervention, a human being can persist, even when they are no longer able to function as a human organism.

In nature, there is a clear hierarchy of biological organization, with each level dependent on the one below it to remain alive, and lower levels not existing independent of their natural, higher level of organization (fig. 2, “Natural State”). Thus, living cells require organic molecules and subcellular organelles to function as cells. Without mitochondria, a human cell cannot persist, and conversely, mitochondria are never found independent of living cells. Similarly, organs cannot exist without cells and organs never naturally exist independent of an intact organism. At the highest level of biological organization, organisms are dependent on both living cells and living organs (i.e., the removal of vital organs or the death of the cells in the body will make it impossible for the organism to persist).

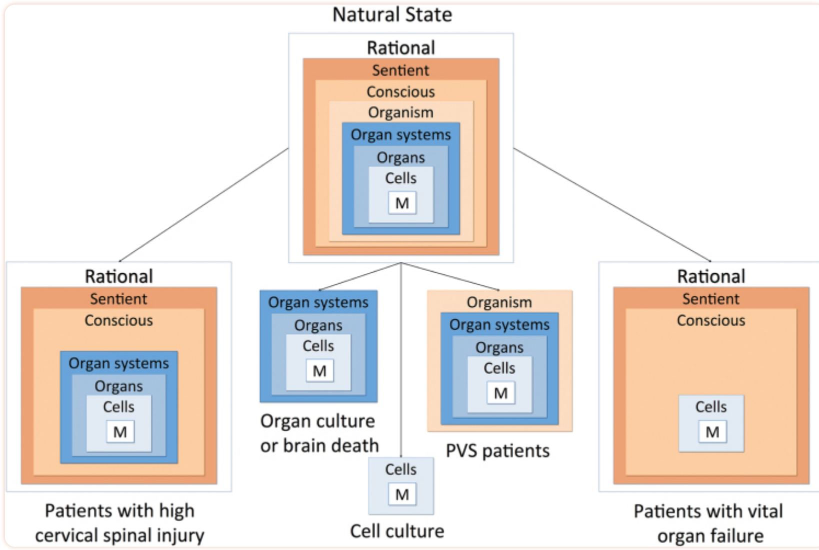

Fig. 2.

Natural hierarchies and how they are disrupted by technology. In the natural state, cells require molecules (M), organs require cells, and organ systems require organs. Together with a functioning brain, these lower levels (blue) comprise the highest biologic level of organization: an organism. Similarly, a subset of organisms is capable of consciousness, and a subset of these is capable of sentience, with humans being capable of rational thought. Technology circumvents this hierarchy in many ways. Cells and organs can be removed from the body and maintained artificially (cell culture; organ culture). Patients in a persistent vegetative state (PVS patients) continue to function as organisms, but do not exhibit higher mental functions. Patients on life support with vital organ failure no longer function as organisms and lack the functions of the affected organ system, but retain living cells and higher mental functions. Patients with spinal injury have also ceased to function as organisms, but retain all other levels of human organization.

Similar to the natural *biological* hierarchy, there is also a natural metaphysical hierarchy that orders properties of organisms in a specific sequence. Thus, not all organisms are capable of consciousness, yet the properties associated with consciousness never occur in nonorganisms, and therefore conscious entities are also organisms. In the same way, sentience requires consciousness, yet it does not occur in all conscious organisms. Finally, rational thought requires sentience, yet not all sentient organisms are rational. Thus, each successively higher function depends on lower functions for its operation.

Most arguments for what constitutes a living human being take these natural biological and metaphysical hierarchies as given. For example, in the earlier-mentioned case of total cellular death, it is assumed that if all the cells of a human body are dead, the human must also be dead. Moreover, philosophers within the Aristotelian-Thomistic tradition require that an organizing principle, or soul, is necessary for organismal function, and that this same soul is also the principle of mental functions. Thus, it is assumed that regardless of the state of the body, if a human is capable of rational thought (i.e., manifestly continues to possess an organizing principle or soul), he must also possess the capacity (rooted in the soul) for organismal integration.[22]

If man is truly a "rational animal," one and the same principle is responsible for both the integration of the body *and* rational function. Metaphysically speaking, the continued presence of *either* power in an entity previously established as human is, in the abstract, sufficient to conclude that the human organizing principle (soul) remains. And modern, technological advances have put this abstract principle to the test. It is now possible to circumvent the natural hierarchies of biological systems and thereby create a wide range of counterintuitive and intellectually challenging situations. As noted above, a human cell in laboratory culture is a living entity that does not exist in nature (fig. 2, "Cell culture").[23] How are we to think of such a cell? Clearly, it is not a human being, and yet by all reasonable scientific criteria it is both of human origin and also an organism. In this case, technological intervention has broken the natural biological hierarchy to produce an unnatural single-cell "human" organism that exists independent of the normal requirement for an intact human body as a necessary condition for the existence of human cells.

Similarly, human patients with SCI are no longer functioning as organisms by any reasonable biological definition. While limited integration persists, such patients have ceased to autonomously integrate the biologic function of parts at the level required to sustain the life of the body as a whole. If left untreated, an individual with SCI would not survive more than a few minutes. However, with appropriate mechanical interventions, such an individual can be kept alive for many years. This creates an intellectually challenging situation of a living human being who (similar to the human cell in culture) is no longer dependent on the natural hierarchy of biological organization; that is, a living human being who does not function as an organism (fig. 2, "Patients with high cervical spinal injury").[24]

How can this technologically produced unnatural state of affairs be reconciled with the Aristotelian view of the human soul as the organizing principle or "substantial form" of the body? I propose that the situation following SCI is similar to a human embryo with a severe (or even fatal) developmental defect. An embryo with such a defect is clearly a human organism and not a mere collection of human cells or a disorganized tumor, and therefore it must possess a human organizing principle. Yet in the case of embryos with developmental defects, the proper function of this organizing principle is blocked by a material deficiency,[25] and the embryo is prevented from exercising its full human capacities. For example, failure to develop a nervous system capable of supporting rational thought (one of the defining characteristics of a human being) in an embryo that is otherwise undergoing an organized pattern of maturation does not preclude the embryo from being a human being. It merely indicates this particular embryo is a severely impaired human that cannot exercise its natural capacity to produce those neurological structures required for rational thought. This indicates that while the *capacity* to develop as a rational being is a metaphysical power inherent to all humans, the *exercise* of this capacity is not necessary for existence of a human substantial form (i.e., for a human soul or organizing principle). Yet, so long as an embryo with a developmental defect functions as an organism (criterion #2 above), it is a living human being.

Similarly, in the case of SCI, the organizing principle of the body must persist (otherwise the individual would be dead), but the full function of this principle is blocked by an injury-induced material deficiency—in this case, the severing of the connections that would enable the brain to communicate with the rest of the body below the site of injury. This results in a human being who only exercises a subset of their natural abilities and who is no longer able to exercise his capacity to function as an organism. In nature, SCI would be completely incompatible with continued existence of the organism, and would rapidly and inevitably result in the total loss of the capacity (rooted in the soul) for organismal integration. In nature, therefore, SCI would rapidly and inevitably result in the death of the organism. Yet, due to artificial interventions substituting for the vital functions that have been blocked, the individual remains alive, despite his inability to function as a completely self-integrated biological system (i.e., without functioning as an organism). Just as the immediately exercisable capacity for reason can be lost without loss of the substantial form "human" (despite the fact that humans are rational animals), the immediately exercisable capacity for organismal function can also be lost while the human individual nonetheless persists. So long as SCI patients exhibit brain function (criterion #1 above), there is reason to believe that the human soul (which is also the principle of the capacity for organismal integration) persists, and that such patients are therefore *alive*.[26]

Objections to Brain Death as Evidence for Human Death

The conclusion that death of the brain is a valid criterion for determining the death of a human being has been criticized by those who assert that sufficient bodily integration remains following death of the brain (table 1) to view such individuals as living human organisms. This view denies that any higher metaphysical or functional level is relevant to the consideration of death (i.e., it asserts that all the mental, sensory, motor, and involuntary functions of the brain can be lost without the loss of a human being), and it turns critically on the question of whether the bodily functions observed following death of the brain rise to the level required for a human organism to persist. This requires us to revisit the levels of organization seen in living systems (fig. 1) and consider in detail how the highest level of organization (that of a living human being or organism) is accomplished.

In the human body, biologic functions are coordinated or "organized" in three basic ways. The most extensive and most sophisticated means of control is through the activity of the nervous system, most especially the brain. In a healthy individual, the brain receives diverse types of information from all parts of the body. In addition to the five primary senses (sight, sound, taste, olfaction, and touch), the brain receives information from the entire body—continuously reading out factors as diverse as body temperature, pH, fluid balance, hormone levels, gravity, pain, vibration, mechanical load, muscle contraction, electrical fields, inflammation, blood sugar, and many other aspects of the overall metabolic state. The brain is then responsible for *integrating* this diverse information to generate a comprehensive representation of the status of the body as a whole—including the environmental and social context in which the body is operating—and to craft an adaptive, global, biologic response that appropriately reflects this status.

For example, when an individual exercises, the brain receives information regarding the state of the body from multiple sources, including an exercise-induced drop in blood pH and direct neural signals from both the muscles and from the vessels leading out of the heart. The brain integrates this information to generate a complex, multifaceted, global, and adaptive response that involves and serves the entire body. It drives an increase in both heartbeat and respiratory rates to increase oxygen and reduce carbon dioxide in the blood, thereby bringing blood pH back into a healthy range. The brain also signals blood vessels in the muscles to widen and those in the gut to constrict, thereby shifting blood to where it is most needed. Finally, the brain initiates the release of adrenaline to increase blood glucose levels and modulate the function of cells throughout the body in a coordinated manner that is appropriate to strenuous activity. These adaptive responses would not occur (or would occur only partially) in a SCI patient who was mechanically or electrically stimulated to exercise; bodily function would rapidly become unbalanced, potentially resulting in a state of medical shock or even in death.

In addition to controlling these *involuntary* responses, the brain is also the source of *voluntary* adaptation to exercise, including conscious regulation of breathing, relaxation of the muscles not being utilized, and (e.g., if playing tennis) visual tracking of the ball and deliberate physical behaviors to keep the ball in play. While these actions do not directly sustain the health of the body, they are clearly an important component of what makes playing tennis a highly coordinated and uniquely *human* physical activity.

An important aspect of the integrating activity of the brain is that it is *context dependent*, and that this context dependence is *global*, reflecting the net balance of information from the body as a whole as well as from the environment. If blood pH drops due to a medical condition unrelated to exercise (e.g., renal acidosis), the brain responds adaptively by increasing breathing rate to restore normal blood chemistry, but it does not initiate the full complement of responses seen during exercise. The brain does not react in a *unitary* way to blood pH, but rather it determines the overall state of the body and responds appropriately to the particular context.

A far less sophisticated form of bodily coordination occurs via soluble signaling molecules that are released by specific cells into the bloodstream. Because blood circulates throughout the body, chemical signals are systemic (whole-body), and such signals can therefore mediate a coordinated bodily response to specific stimuli. Chemical signals can elicit a single type of response throughout the body, or they can have different effects on different cell types. Yet, because chemical signals are regulated by specific triggers to serve specific functions, they are inherently restricted to these functions. Adrenaline (a chemical-signaling molecule) affects many bodily systems, yet it has exactly the same effects whether it is released in response to exercise, stress, or any other stimulus. Therefore, chemical signals mediate a *coordinated* response to one or more triggering stimuli, but they do not *integrate* multiple factors to craft a global response that reflects the diverse conditions present in the body as a whole.

Finally, on a local level, coordination of function can also occur through cell contacts or soluble-signaling molecules that diffuse over short distances. This kind of communication can control the activity of cells within a particular tissue, but does not regulate the body in a systemic manner. Similar to long-range chemical signaling, local signals are induced by a narrow range of local conditions to generate a *coordinated* cellular response, but they do not *integrate* multiple sources of information from the body as a whole or regulate the activity of systems throughout the body in response to that information.

The difference between the *integrating* activity of the brain and the more limited *coordinating* activity of other signaling systems is critical to the interpretation of brain death. *Merriam-Webster* [27] defines "integrate" as "to combine two or more things to form or create something; to form, coordinate or blend into a functioning, unified whole," with a synonym being "unite." In contrast, "coordinate" is defined as "to bring into a common action, movement, or condition; to act or work together properly and well," with a synonym being "harmonize." Thus, integration combines two or more elements to result in a single, unified whole, whereas coordination simply involves communication of parts in order to achieve an effective outcome. On a biological level, these terms can be defined as follows:

Integration: The compilation of information from diverse structures and systems to generate a response that (1) is multifaceted, (2) is context dependent, (3) takes into account the condition of the whole, and (4) regulates the activity of systems throughout the body for the sake of the continued health and function of the whole. Integration is (by definition) a global response and during postnatal stages of human life is uniquely accomplished by the nervous system, most especially the brain.

Coordination: The ability of a stimulus, acting through a specific signaling molecule, to bring responding cells into a common action or condition. Coordination can reflect either (1) a single type of response that occurs simultaneously in multiple cells or (2) a set of synchronous, but cell-type specific responses. Coordination can be local or global and is accomplished both by the brain and by other signaling systems.

All chemically mediated biologic functions, including those that persist after death of the brain (table 1), involve a specific signal and a unitary response. There is coordination of the response across all of the cells capable of receiving the signal, but there is no modulation of that response to reflect differences in circumstance regarding the condition of the whole; i.e., there is no integration. Processes due to coordinated cellular responses can be very complex, often resembling the behavior of a living organism. Yet, despite the apparent "unity" of such coordinated events, they do not necessarily reflect the action of an integrated whole. Like the behavior of swarming bees or a school of fish, coordinated processes persisting after death reflect only the behavior of individual, autonomous cellular units that are responding to a limited number of stimuli to generate the semblance of a unified whole.

Unlike mere coordination, the brain can modify, enhance, or suppress components of a multifaceted response that involves many parts of the body at once, and that depends on the balance of information it receives from throughout the body as well as from the environment. It *integrates* body-wide information to craft an appropriate (and, when needed, body-wide) response that serves the organism as a whole, depending on the details of the situation.[28] After death of the brain, the lower levels of cell communication remain, but the body is no longer capable of compiling multiple sources of information to produce an integrated, global response.

Importantly, while only organisms exhibit integration and integration is necessary for a biological system to function as an organism, partial or limited integration is not sufficient for organismal function (fig. 3). For example, SCI patients maintain limited integration (primarily involving functions of the head and those bodily functions mediated by endocrine signaling or by undamaged cranial nerves), yet this level of integration is not sufficient to sustain the vital activities of the body as a whole. Therefore, SCI patients do not function as organisms, despite the persistence of higher mental functions and the limited integration that persists (fig. 2; "Patients with high cervical spinal injury").

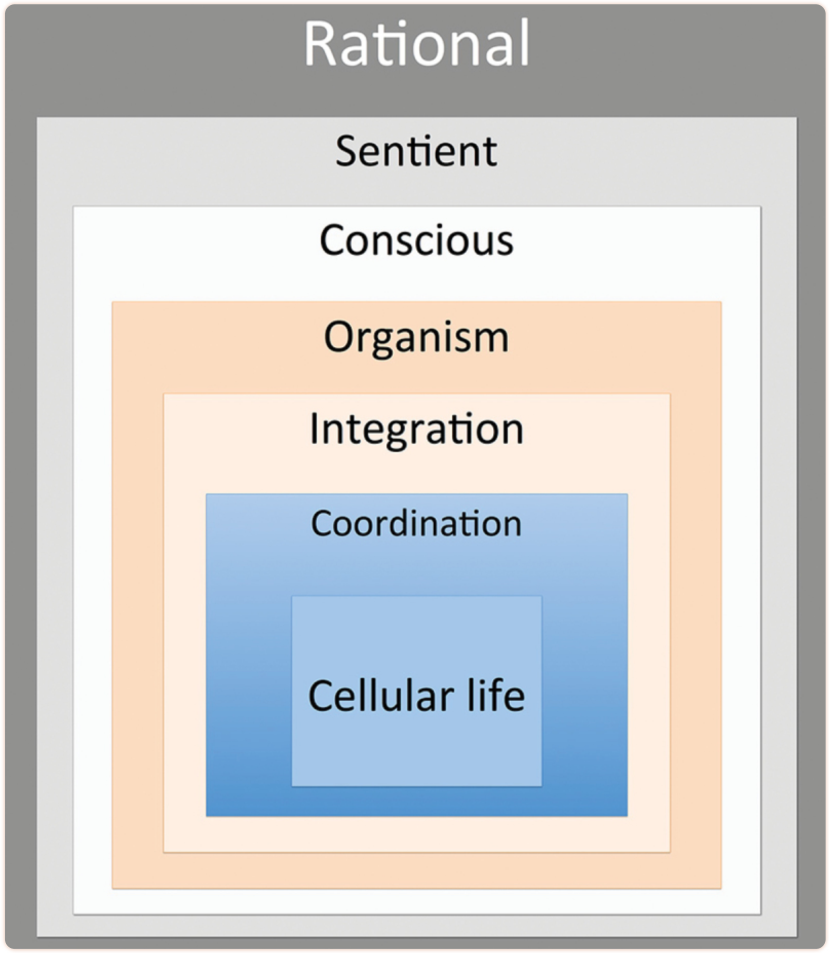

Fig. 3.

Integration is not sufficient for human organismal function. At the lowest level (blue), cells are alive and show coordination (cell communication). At the next level (orange), there is a system capable of integration, which, at postnatal stages, requires a brain. If integration is sufficient to sustain life, the system functions as an organism. At the highest level (gray), the brain is capable of supporting consciousness, sentience, and rationality.

Interpreting the Persistence of Order after Brain Death

Following death by any means, the body does not instantaneously turn into a pile of dust or a disaggregated collection of single cells. Consequently, cells within a corpse retain their inherent, ordered properties that were established during life, including their contacts with neighboring cells. The heart continues to beat, due to the intrinsic electrical properties of cardiac cells and the connections between cells within cardiac tissue. Blood continues to travel to all parts of the body via the circulatory system—a sophisticated network of cell-contacts that was established during embryonic life. Respiration ceases because it requires signals from the brain, yet if oxygen is artificially supplied, cells in the body will remain alive and continue to function normally for some time, just as they would in laboratory culture.

Under these conditions, functions that are mediated by chemical signaling and by local cell contacts will persist (table 1). Yet *none* of these activities involves the *integration* that is characteristic of a living organism. Rather, the bodily functions that persist after the death of the brain reflect the properties of individual cells, functioning as autonomous cellular organisms within a pre-existing system that provides efficient distribution of long-range signaling molecules to other, independent cellular organisms. Coordination persists, but integration is lost.

The persistence of what may *appear* to be integrated function after brain death can be better understood by considering the following, simple analogy. If a marching band with red, white, and blue hats assembles on a field in the shape of an American flag—this is clearly an integrated activity requiring global communication of all members of the band for the sake of the performance as a whole. And if, after the performance has concluded, the marchers simultaneously throw their hats into the air, the image of the flag will persist for a short time as the hats rise above the field. But once the hats have left the direct control of the marchers, adaptive integration is no longer possible. The hats are ordered only by their own intrinsic properties and by the forces of physics. The fading and imperfect image of the flag is merely a remnant of the prior order; a projectile of the past, with no ongoing integration to sustain it.

Just so for the persistence of order after death, living cells (similar to hats) are able to intrinsically sustain their own properties and (unlike hats) are also able to maintain their ordered connections with neighbors. Consequently, cells will persist in their natural functions for some time in the absence of global integration. Yet, without an overriding organizing principle that can respond adaptively and globally to changing circumstances, the residual order seen in a corpse rapidly decays. Despite aggressive life support, the great majority of brain dead bodies suffer irreversible cessation of cardiopulmonary function within 7 days (Jennett, Gleave, and Wilson, 1981; Hung and Chen, 1995; Al-Shammri et al., 2003). In contrast, SCI patients, who typically retain at least some degree of brain-mediated integration following injury,[29] show far better survival, with more than 90% remaining alive for at least 30 days (Shao et al., 2011). Global integration is required for sustained organization above the level intrinsic to cells, and at postnatal stages of human life, integration is uniquely accomplished by the brain.

As a final point, it is important to consider the assumptions underlying the argument that coordinated cell communication (table 1) is sufficient for a living human being to persist. Clearly, coordinated functions exist in continuously varying degrees at all levels of life from cells up to organisms (fig. 1). If the *integrated* function that is uniquely provided by the brain at postnatal stages is not required for human life, distinguishing the living from the dead is simply a matter of degree. And if any arbitrary level of coordination is sufficient to conclude that a human organism remains alive, then an organism is nothing more than the sum of its constituent parts; i.e., if parts remain and their functions persist, then a human organism also persists, at least *partially*. The view that a body remains alive after the death of the brain is fundamentally a reductionist argument that denies the existence of an integrated human whole beyond the properties of the cells and organs that comprise the body.[30] If this view were correct, then human death would not occur until every single cell in the body had died.

VI. CONCLUSIONS

The beginning and end of human life are naturally defined by the onset and cessation of organismal function. Organisms autonomously and globally integrate all bodily activities for the sake of the whole, and at postnatal stages of life this integration critically and uniquely requires a functioning brain. Living cells persist in the human body for some time following death and maintain their natural properties and relationships. Although communication between cells can provide a *coordinated* biologic response to specific signals, it does not provide evidence for *integrated* function that is characteristic of a human organism. Modern technology has produced a wide range of challenging situations in which some elements of biological coordination can persist, uncoupled from the natural biological hierarchy. In particular, individuals such as severe SCI patients, who are no longer able to function as organisms, can (under some conditions) be maintained in a living state. In these cases, the persistence of brain function, and therefore the potential for mental function, is sufficient evidence for persistence of a living human being. Conversely, in cases of severe brain damage, individuals may be unable to exercise mental function, yet so long as they continue to autonomously and globally integrate their own biologic activities (i.e., so long as they continue to function as an organism), they remain alive. By contrast, after total brain death mental function clearly ceases and none of the evidence produced thus far has conclusively demonstrated that genuine organismal integration (as opposed to mere coordination) can persist. While these facts do not *prove* the claim that brain death is a valid criterion for human death, they strongly support this claim. At the very least, these facts show that the documented biological observations about brain dead bodies and their (artificially supported) capacities do not *disprove* the claim that brain death marks the death of a human organism as a whole.

NOTES

1. Catholic and other religious traditions hold that this transition occurs in an instant. For example, St. John Paul II described death as "a single event, consisting in the total disintegration of that unitary and integrated whole that is the personal self. It results from the separation of the life principle (or soul) from the corporal reality of the person" (John Paul II, 2000).

2. The list of functions persisting after death of the brain is taken from Shewmon (2001).

3. The work of Alan Shewmon has been particularly influential in this regard (Shewmon 1998, 2001). Based largely on Shewmon's evidence, the President's Council on Bioethics issued a report in 2008 (The President's Council on Bioethics, 2008) rejecting the loss of somatic integration rationale for considering brain death to be a sign of human death. Nonetheless, the Council did reaffirm the validity of brain death as a criterion for death on other grounds. Others, however, believe that Shewmon's evidence proves that brain death does not necessarily mark the death of the human being. See, for example, Miller and Truog (2008); Truog et al. (2013).

4. Given the somewhat mysterious nature of death (see, e.g., Spaemann, 2011), it is not reasonable to expect absolute scientific certainty on this matter. The only absolute certainty that a human being has died would be when all of the cells of the body have died. What is needed, rather, is moral certainty, or the certainty sufficient to guide action.

[5] I recognize that determining the criteria for human death also requires answering fundamental philosophical questions, such as what distinguishes an aggregation of individual substances from a single complex substance composed of many parts. The biological analysis presented here does not address these questions directly, but rather is complementary to the philosophical analysis presented in Moschella's paper in this issue.

[6] The medical dictionary maintained by the U.S. National Library of Medicine and the National Institutes of Health defines an organism as "an individual constituted to carry on the activities of life by means of organs separate in function but mutually dependent: a living being" (http://www.merriam-webster.com/medlineplus/organism [accessed 29 January, 2016]).

[7] Some have suggested that there is no meaningful distinction between the processes within a cell and the information and materials it receives from the environment (e.g., Oyama, 2000), but this argument requires that all features of the environment needed for life (oxygen, gravity, etc.) are intrinsic features of cells, not extrinsic factors to which the organism has evolved to respond, thus abolishing the ability to speak of any entity as a distinct thing.

[8] For a more extensive discussion of what distinguishes an embryo from a cell, see Condic, 2014a.

[9] For a more detailed discussion of molecular programs in development, see Condic, 2011; Condic and Flannery (2014).

[10] For example: Massetti et al., 2005; Nusbaum et al., 2014; Gaieski, Boller, and Becker, 2012.

[11] For further philosophical elaboration and defense of this point, see Moschella, 2016.

[12] Rationality itself is not directly observable. Therefore, to err on the side of caution, I take the presence or absence of mental function as sufficient evidence to indicate that the basic natural capacity for rationality (even if not immediately exercisable) may still be present.

[13] There is substantial evidence from animals that "consciousness" and "emotion" are broadly distributed in the brain, and depend critically on subcortical structures (see Bennett and Hacker, 2005; Edelman and Seth, 2009; Butler, 2012; Fabbro et al., 2015). Similarly, humans without large regions of the cortex remain conscious (see Shewmon, Holmes, and Byrne, 1999; Beshkar, 2008; Denton, 2009; Morsella, 2010; Aleman and Merker, 2014), suggesting mental function is also broadly distributed in the human brain.

[14] The precise level of brain function that must be lost unambiguously to conclude to the loss of the basic natural capacity for mental function is unknown, and (indeed) may be impossible to determine. However, irreversible loss of function of the entire brain is clearly an unambiguous indication that the capacity for mental function has been lost. The precise level of brain function required to result in total loss of either organismal function or mental function has yet to be determined.

[15] Cases where individuals in a persistent vegetative state require support for vital functions (dialysis, pacemaker, etc.) are no different from cases where conscious individuals require such support: (1) if the intervention is temporary or partial, the patient still integrates his own function, albeit in an impaired manner or

(2) if the intervention is permanent and complete, the patient no longer integrates his own function.

16. The argument that an individual with SCI is no longer able to exercise the capacity to function as an organism is considered in more detail in the next section.

17. For example, humans who lack cortical structures responsible for "higher" brain functions such as language are clearly conscious, and therefore capable of some degree of mental function. See citations given in footnote 20.

18. Although (2016) some authors such as Shewmon and Austriaco believe that bodily integration can persist even after brain death, my analysis (see below) indicates that the evidence on which their belief is based shows only that *coordination between cells and tissues* can persist after brain death, not that genuine *organismal integration* can persist.

19. Some advocates of a systems biology approach would appear to deny this premise (see, e.g., the Austriaco (2016) paper in this issue and Shewmon, 2001), or at least its insistence on the need for *global* self-integration. Yet, as I have already noted and argue further below, the logic of this approach would imply that death does not really occur until all of an organism's cells have died.

20. For a defense of this premise, see Moschella's paper in this issue.

21. See, for example, President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1981); Bernat, Culver, and Gert (1981); Tonti-Filippini (2012).

22. For more on this point, see Moschella, 2016.

23. Nor is this a technologically trivial matter. Individual cells were not sustained in culture until the 1950s, with the successful cultivation of so-called "HeLa" cells, which were taken from the cervical cancer biopsy of Henrietta Lacks. Human cells do not naturally or easily live when removed from the whole of which they are a part.

24. Since the capacity for organismal function is rooted in the soul, so long as a human remains alive, he remain the kind of entity that is an organism. However, just as a human being who no longer exhibits "rationality" can nonetheless remain a rational animal (i.e., an animal with a rational nature, rooted metaphysically in the soul as the principle of rational capacities), an individual who no longer functions as an organism (i.e., an animal) can nonetheless remain a rational animal. Biologically, an organism is a self-sustaining integrated whole; and clearly following SCI, neither the head nor the body below the injury functions as an organism (while metaphysically, they remain an organism).

25. Developmental biologists would see this deficiency in terms of a perturbation of a normal developmental pathway, due to an internal genetic or other biological defect.

26. For a more in-depth analysis of the status of a SCI patient from a philosophical perspective, and an explicit response to Shewmon's analogy between SCI patients and brain dead patients (Shewmon, 2010), see Moschella, 2016.

[27] Merriam-Webster, s.v. "integrate," http://www.merriam-webster.com/dictionary/.

[28] While other body organs can have complex and graded responses that affect many tissues, they cannot directly control the body as a whole. While the activities of the liver (for example) have global effects on many body functions, the liver qua liver cannot directly control the activity of the eyes or the hands.

[29] In most SCI patients, brain-mediated endocrine functions and those functions controlled by the 9th and 10th cranial nerves persist, along with any residual functions mediated by "spared" spinal fibers that continue to communicate with the body through the damaged spinal column.

[30] I am indebted to Fr. Ignacio de Ribera Martin for this important insight.

REFERENCES

1. Al-Shammri S., Nelson R. F., Madavan R., Subramaniam T. A., Swaminathan T. R. 2003. Survival of cardiac function after brain death in patients in Kuwait. *European Neurology* 49:90–3. [PubMed] [Google Scholar]
2. Aleman B. and Merker B.. 2014. Consciousness without cortex: A hydranencephaly family survey. *Acta Paediatrica* 103:1057–65. [PubMed] [Google Scholar]
3. Austriaco N. P. G. 2016. The brain dead patient is still sentient: A further reply to Patrick Lee and Germain Grisez. *Journal of Medicine and Philosophy* 41:315–328. [PMC free article] [PubMed] [Google Scholar]
4. Bennett M. R. and Hacker P. M.. 2005. Emotion and cortical-subcortical function: Conceptual developments. *Progress in Neurobiology* 75:29–52. [PubMed] [Google Scholar]
5. Bernat J. L., Culver C. M., Gert B. 1981. On the definition and criterion of death. *Annals of Internal Medicine* 94:389–94. [PubMed] [Google Scholar]
6. Beshkar M. 2008. The presence of consciousness in the absence of the cerebral cortex. *Synapse* 62:553–56. [PubMed] [Google Scholar]
7. Bliss L. A., Sams M. R., Deep-Soboslay A., Ren-Patterson R., Jaffe A. E., Chenoweth J. G., Jaishankar A., Kleinman J. E., Hyde T. M. 2012. Use of postmortem human dura matter and scalp for deriving human fibroblast cultures. *PLOS One* 7:e45282. [PMC free article] [PubMed] [Google Scholar]
8. Butler A. B. 2012. Hallmarks of consciousness. *Advances in Experimental Medicine and Biology* 739:291–309. [PubMed] [Google Scholar]
9. Carter D. A., Mayer E. J., Dick A. D. 2007. The effect of postmortem time, donor age and sex on the generation of neurospheres from adult human retina. *British Journal of Ophthalmology* 91:1216–18. [PMC free article] [PubMed] [Google Scholar]
10. Condic M. L. 2008. When does human life begin? A scientific perspective. *The Westchester Institute for Ethics & the Human Person*. White Paper Series 1:1–18. [Google Scholar]
11. ———. 2011. A biological definition of the human embryo. In *Persons, Moral Worth, and Embryos: A Critical Analysis of Pro-Choice Arguments*, ed. Napier S., 211–237. New York: Springer. [Google Scholar]
12. ———. 2014. a. Totipotency: What it is and what it is not. *Stem Cells and Development* 23:796–812. [PMC free article] [PubMed] [Google Scholar]