The Signs of Death
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THE APNEA TEST AND RATIONALE FOR BRAIN DEATH AS DEATH*

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I have been asked to address two subjects that are importantly related. One is a technical one on apnea, and because of this knowledgeable audience and the fact that it is essentially a technical issue, I am going to move through it fairly quickly. There are a few open questions in the apnea test, but they are essential to address. It is the last step in defining death and therefore requires the careful attention of clinicians. The second part of my paper is broader and addresses the medical and neurological reasons to consider brain death as death. It is largely a recapitulation of our talks over the past two days on this subject and I would hope to emphasize the central points and develop one or two particular themes.

The Special Significance of Apnea

Apnea has special significance in all discussions about death because it indicates that the medulla, the most rudimentary part of the brain, is damaged and implies that other vital functions that require a degree of central nervous system control will be likewise damaged. In the proper context, apnea is the last technical step in the diagnosis of brain death. Apnea is further essential to the medical argument for the equivalence of brain death and death, because ultimate cardiopulmonary collapse is driven by the notion that the bodily systems cannot sustain themselves indefinitely without a form of gas exchange and that, with the withdrawal of the artifice of a ventilator, the rest of the corpus will dissolve. This argument is based on 'ventilation' as the last step in death, not on 'respiration', a point I to which I will return. Neurologists, from their own observations, can emphatically state that removing the ventilator, if the apnea test has been performed properly, inevitably leads to cardiovascular collapse. For this reason, the loss of ventilation leads to the loss of cellular respiration, and then to death of the entire organism.

* The views expressed with absolute freedom in this paper should be understood as representing the views of the author and not necessarily those of the Pontifical Academy of Sciences. The views expressed in the general discussion are those of the participants and not necessarily those of the Academy.

Context of the Apnea Test

The test is performed only after all other features of complete unreceptivity (the inability to perceive environmental change) and unresponsivity (the inability to volitionally alter the environment) have been established and all other brain stem reflexes have been demonstrated to be abolished. As it is a technically demanding, and not a casual test, individuals who are highly familiar with brain death, not surrogates, should perform it, a point emphasized further on.

Conduct of the Apnea Test

There are a few technical issues in apnea testing but they have given rise to considerable study and some controversy. The first is that the current recommendations of the American Academy of Neurology suggest that there be apneic oxygenation to denitrogenate the alveoli, and thus create a pool of high concentration alveolar oxygen that causes passive diffusion of oxygen into the blood. I was a little bit disappointed to hear that an inspired fraction of 100% oxygen was recommended. The concern is that this kind of extreme denitrogenation rapidly leads to alveolar collapse and a degree of atelectasis that may itself lead to hypoxemia and cause the test to be shortened. I will not argue with this component of the technique since it is usually possible to get away with it if the test goes no longer than several minutes. I do, however, encourage some clinical investigation on the 100% preoxygenation approach and would expect that the patient's pulmonary status, length of time on a ventilator, recent inspired oxygen fraction and ventilator tidal volumes, and degree of humidification, would all contribute to the rapidity of atelectasis.

Another option in the apnea test is to determine the initial carbon dioxide tension in the blood. The ventilator is then removed for a period that is anticipated to produce a partial pressure of carbon dioxide that is high enough to drive the medulla and at the conclusion of the test. The end level of carbon dioxide is measured in order to demonstrate that it has exceeded a threshold that is believed to stimulate spontaneous breathing, even in a sick brain, but not in a brain that is dead. A third option relates to accelerating the test by insufflating carbon dioxide at the outset so that the starting level is closer to the desired end level. Both of these approaches would benefit from more investigation but they are in common use at this time and do not alter the larger perspective on

whether brain death and death are equivalent. Leaving the patient on continuous positive airway pressure or on a very low ventilator rate seem reasonable, rather than entirely disconnecting from the machine, but these techniques could benefit from further study. While there have been series of patients that suggest otherwise, I am concerned about the delivery of oxygen by a T-piece since there is potential for a Venturi-effect to pull oxygen out of the endotracheal tube and cause desaturation. Perhaps this concern is excessive. The potential for pneumothorax caused by a tracheal cannula should also be mentioned here.

I think that most physicians would agree that there is no conventional way to make the diagnosis of brain death until after this test is done and after some pre-specified threshold of arterial carbon dioxide has been exceeded. Therefore, the patient should be reconnected to the ventilator while the clinician waits for the result of the ending arterial carbon dioxide tension. It is a little bit paradoxical to carry out the test in this way but it is mainly for reasons of certainty that an adequate stimulus has been reached.

One could imagine circumstances in which the patient's prior wishes, the family or the clinician have determined that no transplantation will take place and that continuing ventilation is futile in view of brain death. In this case the ventilator could simply be left off to observe the absence of spontaneous breathing until cardiovascular function fails. While not strictly a technical issue relating to apnea, this latter scenario speaks to the essential equivalence of death and brain death since, had the ventilator not been initiated in the first place, there would be little need to go through the intermediate step of documenting the extreme degree of brain damage that characterizes brain death; the patient would simply die in what would gave been considered a more conventional cardiovascular manner.

To address concerns of risk from apnea testing, and in part to balance what have been disingenuous arguments against brain death, there is general agreement that the test should be stopped if there is profound blood oxygen desaturation or if the blood pressure drops. There is always, of course, an intent to prevent inadvertent harm to what still might be a living patient, until it is clear that the medulla is damaged as reflected by apnea. Finally, one of the most curious things that I have observed is a lack of visual and tactile attention to the patient's thorax and abdomen during the test. Causal inspection of movement of the ventilator needle is not enough to determine if the patient is breathing. These are self-evident but perhaps need to be said.

Additional Concerns Expressed About the Apnea Test

The singular significance of the apnea test makes it desirable that it not be fallible, in other words that it not give a false positive result. The best protection against this is to emphasize to all physicians who might be participating in determining brain death that there are guidelines for the conduct of the test and they should be followed. Moreover, the proper personnel should perform the test after all of the usual exclusions have been addressed. Preferably, these are neurologists, neurosurgeons or intensivists who have experience with the test. Whether individual hospitals, local medical societies or other official entities should identify or certify such individuals is uncertain.

There should however be no ambiguity about the result of the test; the patient either breathes or does not breath. The result is binary. There are numerous potential misinterpretations and false negatives. The most common of these, and the one I think has created a degree of public fear, is the peculiar and stunning movements of the thorax, shoulders, arms that are known to occur minutes after the ventilator has terminally removed but may rarely occur at the end of the apnea test, most often associated with a degree of hypoxemia or hypotension. The intercostal muscles appear not to be involved because we have put EMG electrodes into them and do not find activity. These bizarre movements, which I coined in a 1984 Archives of Neurology paper as 'Lazarus phenomena', do not represent breathing. They do not provide ventilation and are not medullary in origin since they are seen in spinal man.

The second concern that has been expressed is that somehow the test could lead to death, or is risky or cruel. Again, this is ostensibly avoided by attending to details and to guidelines. After thirty-five years of studying the apnea test and refining the guidelines, they by and large prevent harm to somebody who may not yet have a totally destroyed brain.

The third misconception that is worth brief comment has been that apnea is itself death. This would be an extension, or an extreme, of the brain stem definitions of death as opposed to the whole brain definition of death. This view accords roughly with a classical view that loss of breath is loss of life. Virtually all clinicians, with some exceptions, have a larger context of brain death. The significance of the apnea test in this larger context, however, is limited to indicating that there is overwhelming medullary damage and the absence of self-sustainable breathing.

Adequate Threshold of $PaCO_2$ to Stimulate Breathing

This technical aspect of the apnea test has a long history but scant data. Dr. Plum's early work on post-hyperventilation apnea in brain damaged patients set the bar at 60 mm Hg as an adequate stimulus. As best I am able to determine, this is where the number 60 originated. In his work, patients with very large strokes who were hyperventilated, and then had the ventilator stopped, in a few cases did not breathe again until the arterial CO_2 tension exceeded 60 (actually, it was 65). I would point out that this model of medullary stimulation by CO_2 has little to do with brain death. The patients he studied had intact medullas and cerebrums, both structures participating in the control of breathing.

In the case of brain death we have some systematic experience with the CO_2 threshold, the biggest one being Rudolf's study that showed no advantage to going above 60 in the apnea test. Our own paper in the 1980s studied four patients with overwhelming brain damage but who were not brain dead solely because they had residual signs of medullary function. They had deep unresponsive coma, unreactive pupils, and no caloric-induced eye movements. For these reasons, we considered them to be as close as possible to brain death but they clearly breathed. It seemed that it was this ideal configuration to determine the CO_2 threshold that separated brain dead patients from those who 'almost' qualified for brain death and the group to study in order to prevent false positive apnea tests that would misclassify a patient as brain dead. We posed the question: What does it take to make a very damaged brain breathe? The result was that they all breathed in the range of $PaCO_2$ in the mid-30s mm Hg. Dr. Wijdicks has given his own experience in a previous lecture here. The patients he studied breathed at levels below 40 or into the low 40s. Based in these observations, and acknowledging perhaps 3 exceptional published cases in which a stimulus of 65 was apparently required, I think 60 is a safe target. We can perhaps have a discussion about that.

An associated question is when to stop the test and draw an arterial blood sample. What is the appropriate time to leave the patient off the ventilator? I have no particular recommendation, but my practice has been to calculate an endpoint based on the starting $PaCO_2$ (which requires that an initial gas be drawn) and use the formula that carbon dioxide goes up 2.5 mm Hg, on average, per minute in a euthermic patient. The rate needs to be adjusted for hypo- or hyperthermic patients. This model allows a reasonable estimation of the duration of the test, and determines when to check the CO_2, return the patient to the ventilator, and establish that the preselected adequate thresh-

old has been met. If the arterial pCO_2 is found to be too low at the end of the test, it allows new calculation based on the rate of change observed in that individual and the test must be repeated.

A final technical question is what to do in patients with COPD (chronic pbstructive pulmonary disease). This is an issue that relates to the fact that these people chronically require or are accommodated to high CO_2 and therefore need a hypoxic drive and a higher CO_2 drive to stimulate breathing. We have studied several such patients and if they had been on a ventilator for 12 hours, their pH returned to normal and it no longer appeared that an excessive respiratory drive was necessary. If an apnea test is required before about twelve hours on the ventilator with normal $PaCO_2$, then there may be a problem and a target above 65 mm Hg should be chosen.

Potential Serious Complications of Apnea Testing

Hypotension is the most common complication and it is probably the result of hypoxia, and generally relates to inadequate preoxygenation. This can be eliminated for the most part by careful preparation as I have already discussed. Goudreau, Wijdicks and Emery from the Mayo Clinic indicated said that there was some degree of hypotension in 24% of patients overall and 15% had inadequate preparation. Twelve percent in Saposnik's series had hypotension and 1 had a cardiac arrest during the apnea test in 129 cases. Hypotension was said not occur if the pH was kept above 7.2 in a study from the Canadian Journal of Anaesthesiology. Hypercarbia and acidosis do not, however, seem to reach a severity that they become physiologic problems. I mention them because there is a paper that suggests them as theoretical problems.

Why Brain Death?

The reason we are here, is why brain death? And why death? I am not presumptuous enough to give an answer but maybe to guide one with the group. If we take the perspective that medicine has nothing, or little, to say about death, then there is not much point to further discourse. However, there is and always has been a medical perspective on death and it is sensible to attend to the medical perspective from a personal, societal, and technical point of view. Furthermore, brain death, being a contrivance brought about entirely by modern medicine, demands that a perspective be given by from physicians, even if this is only to be integrated with a philo-

sophical and theological perspective. Medicine is in a position to give an opinion on whether brain death is *equal* to death and whether brain death is *equivalent* to death. These are, of course, subtly different, and the differences in these phrases has led to terminological or semantic confusion that continues in part because there is a difference between being brain dead, as an event, and being on the way to dying. I do not know if medicine will be able to get at the precise moment of death as discussed below but medicine is a practical science and society needs medicine to be practical. Medicine, however, is not meant to be expedient; in other words care must be taken not to frame brain death as driven by transplantation.

Medical Meaning of Death

The definition of death has continuously changed as has been elaborated by previous speakers. Someone whose heart stopped before 1947 was dead because external defibrillation had not yet been applied. In fact, many people, right up to 1969, when defibrillation was widely available, were dead. Someone with overwhelming brain injury prior to 1948, when Drinker introduced the negative pressure ventilator, or 1953 when Ibsen's mechanical positive pressure ventilator was applied, was essentially dead. An individual with overwhelming brain injury in the future might theoretically be resuscitated by some extraordinary scientific discovery but medicine has not evolved to that point. In fact these inceptions are not gradual, but stepwise change the definition of death by necessity. Medicine has done what it must adapt to by the changing of technology that is able to sustain bodily function.

The Time of Death

It may be difficult to accept that the time of death has an element of arbitrariness. One hopes for a definition of death that is not arbitrary. We are adapting to our ability to measure survival of components of the organism that we deem are necessary for persistent life, the opposite of persistent death. John Paul II in 2000, in fact, said the exact moment cannot be precisely determined but there are biological signs that a person has indeed died. This is the practical medical view and is a reasonable starting point. I would repeat that the 'problem' of brain death has been created solely as the result of artificial ventilation and associated intensive care technology, as Dr. Hacke and other speakers have indicated. It is a given that artificial ventilation and other supportive techniques, including fluid and hormone

replacement and pressors, the medications that support blood pressure, are interposed elements between life and death, without which there would quickly be a complete cessation of ventilation and then very quickly, thereafter, complete loss of cellular respiration and the dissolution of the corpus.

So there is a dual medical rationale for brain death as death. The first is the idea that technology, and in particular the ventilator, of which apnea is the measure, 'masks' the cardiovascular collapse of the body, which is an inevitable, inexorable first step towards the loss of all cellular metabolism and all life. The second and perhaps more important rationale, and the one that needs to be articulated, is that this is irreversible AND inevitable. It is more than just permanent. Permanent means indefinite for now; until some extraordinary advance comes along brain death is inevitably and inexorably equivalent to death. With regard to the exact time of this event, I do not find appealing the idea that it occurs when a physician walks over and writes a note in the chart that the patient is brain dead, but I have no better way of defining the timing of death.

The medical-philosophical backdrop to this is deeper. It does indeed have to do with unity and integration of the organism and to the personhood and consciousness that goes along with the functioning of the brain. The brain must define, in some way, this personhood, and it must embody it. If it does not, then medicine has no starting point in the discussion of brain death and all further polemic is non-medical. Therefore, there are two durable, technical, current, temporal reasons to think of brain death as death and there is a larger philosophical backdrop.

I would make note also of the 1989 address by Pope John Paul II, to the Pontifical Academy of Sciences that '(Death) occurs when the spiritual principle, which ensures the unity of the individual, can no longer exercise its functions in and upon the organism, whose elements, left to themselves, disintegrate'. To me there are two elemental phrases here: 'the unity of the individual' and 'cannot exercise its functions whose elements, left to themselves, disintegrate'. That is indeed the medical view. You cannot say it any better. It is a disintegration predicated on this interposed technology.

Brain Death is Unique

Brain death, of course, is unique, as we have heard repeatedly. The brain dead body in a medical view is just a collection of artificially supported organs and cardiorespiratory collapse occurs in almost most cases in some fixed period, that is, even without removing the ventilator. Dr.

Wijdicks expressed the opinion in our conversation the night before last that it happens in *every* patient. Without getting into this uncertainty, and acknowledging that it is very difficult to sustain a brain dead body for any length of time, if the artifice of the ventilator is removed, death is inexorable. I would remind everyone that we have arrived at a point where the differentiation between withholding (initiating) and withdrawing care in a critically ill patient has no distinction, morally, ethically and medically. Socially, it is harder to persuade lay people of the equivalence. Since the collapse is inevitable, arguing about the interval, the precise moment, is really not practical for the physician, because the goal posts of the football game are just moved and moved and moved, based on current technology.

Technical Issues and Misdirection

Dr. Shewmon has made some excellent points but I believe that there is misdirection and in two slides I would like to summarise why, but again I cannot speak for the group, so I am just going to create the theme. Let me address some of the arguments that have been made against brain death as death.

If one argues that people are constantly making mistakes in the application of brain death criteria and in the apnea test, that is a problem. Does it negate brain death? Of course not; it is a competency and professional issue. We have to educate our colleagues and insist on the highest standards. The risk of the apnea test as a refutation of brain death similarly makes no sense. Posturing and bodily movements have been pointed out as part of the common sense evidence that brain death is not death. How could a dead body move? I think we have had that discussion. You can cut the head off and the body can move; the brain is not required. The necessity for the entire brain to be necrotic has been raised as an objection to brain death. The example that is given is the retention of the antidiuretic hormone made in the posterior hypothalamus and elaborated in the back of the pituitary and so on and so forth. This would indicate that the entire brain, every cell, is not dead. Again, in medicine we make practical distinctions that are useful and valid and we acknowledge that it is not possible to know if very cell is dead. If every cell in the brain is not dead now, it surely will be very soon, but in any case, the brain is not working as the organ is meant to, in a unitary way. This issue of every cell not being dead is not valid as an objection to brain death. If one brings this argument to the reductionist level of every cell being dead, then we are similarly obliged to

await the cessation of all bodily cellular respiration before declaring death has occurred and this is a practical impossibility. We would be sitting in the mortuary with patients for a day or two. And if you put them in a cooler, for maybe longer.

There has been an argument that different definitions or criteria for brain death in different jurisdictions point to the fact that we are in disarray and the definitions are arbitrary. The differences are subtleties; they are not about brain death as death. They have instead to do with minor criteria and perhaps the pride of medical societies that need to have their say in the matter.

The purported 'awakenings' from brain death I think we can all dismiss. These are reported in the press by persons ill equipped and ill informed about the criteria for brain death. At the risk of sounding glib, I would say it is nonsense. I will dwell for a moment on the lack of validity of published statements that cardiovascular collapse is easy to prevent. I can attest to the fact that these claims are not correct as presented by one of our colleagues in his writings. One virtually has to live at the bedside of these patients to keep them going. Sustainability is contrary to the experience of neurologic intensivists. I will return to the meningitis case in a moment. Are there instances where younger patients with very healthy myocardial tissue can have cellular survival, can have a heart beat that goes on, on a ventilator for a long period of time (days, weeks)? The record I alluded to in my own intensive care unit is 45 days. Yes, perhaps they can. Does that negate brain death? I do not see how it does.

Shewmon's Rejection of All Brain-Based Criteria for Death

Shewmon is entitled to reject all brain-based criteria for death. I want to make it clear this is not an *ad hominem* attack on Alan Shewmon, quite the contrary, he is offering us the opportunity to refine, clarify, bring to a fine point brain death as a medical entity. The starting point of his discomfort appears to be the issue of the appearance of a warm body. That is a reasonable starting point but we have heard that medicine is allowed to have a logical progression based on evidence, not on thought experiments, and medicine is permitted, if not obliged, to change our notions of death over time.

An essential diversion here is the idea that the body is dying but not yet dead, and that an irreversible phenomenon occurs when we recognise brain death, the same way that a physician who stops cardiopulmonary resuscitation recognises that he has reached the point of no return. I find this idea of 'dying but not dead' appealing but, either way, it creates an entity which is

de facto dead. The Repertinger meningitis case, which Dr. Shewmon utilizes, ironically demonstrates that it is possible to keep a body and organs perfused for a long period of time. I would like to point out that that patient did not have an apnea test, at a time when you could have presumed that he was brain dead. We know that some time, perhaps in a brief epoch before the autopsy, there was necrosis of the lower brain stem, completing the brain death notion, but there is no testing to confirm that. One possibility, although I am uncertain, is that that patient may not have been brain dead for a long period of time.

Another problem that has caused people to reject brain death is the operational motivation in transplantation. We are familiar in medicine and in society with withdrawal of supportive care to avoid the prolongation of suffering of the corpse, or 'beating a dead horse', as it were. It is cruel. I think there is a point at which one can remove the ventilator and can take out the organs but the two are disconnected and really remain so. Shewmon says that he can imagine going about transplantation in a different way, so that removal of the vital organs neither kills nor harms the donor, I do not really understand that. There is not a lot of middle ground: either the patient is dead, and all you are doing is taking the organs, which is seemingly permissible societally, or they are not dead and you have to make a whole new conceptual system around it.

Thought Experiments All Lack Context

All of the thought experiments that have been proposed by Shewmon and others lack context. The first is the apnea-coma idea, namely that brain death is simply coma and apnea, or destruction of the top and the bottom of the brain. These thought experiments are querying why a cervical section is not dead, or if somebody has cortical damage and is comatose and they happen to have a cervical cord transection that we are claiming that that patient is dead. Of course, no neurologist would diagnose either of such cases as dead. These are just ideas that lack neurological context. The pupils, the corneal responses, the eye movements, deep coma, and so forth are all required for the diagnosis of brain death.

An extension of the apnea-coma notion is vagotomy and cardiac denervation. This creates a different type of disconnection of the brain and the body. It again lacks context and misrepresents what we are doing when we determine that somebody is brain dead. Further extensions of this idea to severe Guillain-Barre syndrome or motor neuron disease in which the

patient cannot signal that he is awake, similarly have no context. There is, of course, in these instances no coma, no brain stem damage etc.

The decapitation notion is very interesting and still fascinating. It was apparently Alan Shewmon who at a Vatican meeting proposed decapitation as the most compelling reason for making an analogy of brain death to death. No one can imagine that a decapitated body is alive, so why not extend that to brain death? Now the decapitation notion is being used for the contrary argument that says a decapitated body can have vital energy of some sort, and therefore that brain death is not death. I cannot grasp this logic. Similarly, White's monkey brain transplant attempts, while complicated philosophically, are not a problem medically. Unless such work is going on somewhere in the world, I do not think we are even going to have to grapple with it and I am not going to open the conundrum of putting a new brain in somebody. Is the person in the brain or in the new body? There is a very old joke about a woman who was angry that her husband was buried in a brown suit so she argued with the funeral director until he finally got fed up. When she returned she saw her husband in the blue suit she wanted for him. She asked 'so, finally you put him in the blue suit that he liked', and the funeral director replied 'no, we just switched heads'. It has no context.

The problem of a longer time frame has been raised. By this I mean that the 'irreversibility' of death does not exist until the ventilator is withdrawn. The analogy was made weakly, that the ventilator is supportive the way dialysis is supportive and obviously we do not dismiss somebody on dialysis because they are on a machine. Again, this is the wrong context and the Harvard Commission, when it framed brain death was simply catching up to medical resuscitative science. Incidentally, from discussions with Dr. Raymond Adams, the work of the Harvard group was not meant as a way to drive transplantation. It was meant as a response to futility. If there were to be a perpetuation of the brain death idea solely for the expedient purpose of transplantation, then we have a problem. I would submit, that it simply *allows* for transplantation, and it would be tragic if we rolled back the clock and transplantation went away, but there is a curtain between them and there always has been one.

Loss of 'Somatic Integrative Function'

The loss of somatic integrative function, or the unity argument, which has been expressed in many different idioms, is medically weak. It was perhaps unfortunate that was included in the President's Commission (1981).

However, even arguing against this does not negate brain death as death. Did the commission mean something different from a higher manner of unity; were they talking about soul? I think the loss of somatic integration is best considered as a supportive element for brain death.

For Medicine, a Practical Science, Death is what Medicine Makes of it, but With Good Reason!

For medicine, which is a practical science, death is what medicine can make of it, and with good reason. All pronouncements about death are based on what is possible and not possible currently in human physiology. Ideas are based on accurate and formalised practical clinical criteria which do not tell us that every cell of the brain is dead, do not tell us that there is no blood flow to the brain (those are additional emphatic confirmatory features), but tell us that that organism is not sustainable in most cases and that that dissolution is inevitable, inexorable, not just permanent. And medicine always has had to make practical distinctions by using the cessation of observable signs such as spontaneous breathing or pulse or brain function as the sensible time to declare that the patient is dead.

Brain death can be very precisely defined from a clinical perspective. It should remain an extension of the traditional consultation by the physician to a family to confirm death. It may alter the traditional sense of death as derived from common experience but with good reason. Practical life and observation eventually trump casual notions and customs. It is not simply an expedient to declare death on brain criteria and it is neither philosophically lazy nor self-contradictory. Thank you to the Academy and to my esteemed colleagues.