Chronic "brain death": Meta-analysis and conceptual consequences

D. Alan Shewmon

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Meta-analysis and conceptual consequences

D. Alan Shewmon, MD

Article abstract—*Objective:* One rationale for equating "brain death" (BD) with death is that it reduces the body to a mere collection of organs, as evidenced by purported imminence of asystole despite maximal therapy. To test this hypothesis, cases of prolonged survival were collected and examined for factors influencing survival capacity. *Methods:* Formal diagnosis of BD with survival of 1 week or longer. More than 12,200 sources yielded approximately 175 cases meeting selection criteria; 56 had sufficient information for meta-analysis. Diagnosis was judged reliable if standard criteria were described or physicians made formal declarations. Data were analyzed by means of Kaplan-Meier curves, with treatment withdrawals as "censored" data, compared by log-rank test. *Results:* Survival probability over time decreased exponentially in two phases, with initial half-life of 2 to 3 months, followed at 1 year by slow decline to more than 14 years. Survival capacity correlated inversely with age. Independently, primary brain pathology was associated with longer survival than were multisystem etiologies. Initial hemodynamic instability tended to resolve gradually; some patients were successfully discharged on ventilators to nursing facilities or even to their homes. *Conclusions:* The tendency to asystole in BD can be transient and is attributable more to systemic factors than to absence of brain function per se. If BD is to be equated with death, it must be on some basis more plausible than loss of somatic integrative unity.

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The equivalence of "brain death" (BD) with death is one of the few bioethical issues of this decade considered relatively settled.[1(p 115)] (Together with Veatch,[2] I prefer to place "brain death" in quotation marks on account of its semantic ambiguity.[3] For purposes of this paper, the term will be taken to mean "whatever most people understand by the term 'brain death' [with whatever ambiguity and inconsistency that entails]," or equivalently, "a clinical neuropathologic state fulfilling official diagnostic algorithms and legally equated with death in most jurisdictions [regardless of the rationale for, or validity of, that equation].") What has been settled, however, is merely statutory definition and diagnostic protocols.[1,4,5] Beneath this superficial consensus there is tremendous confusion about the fundamental rationale for equating the death of one particular organ with death of the entire organism.[2,3,6-10] In the United States and most other countries where a quasi-official rationale has been articulated, the rationale is that the brain is the "central integrator" or "critical organ" of the body, and its destruction or irreversible nonfunction entails a loss of somatic integrative unity, a thermodynamic "point of no return," a literal "dis-integration" of the organism as a whole.[1,11-15]

One line of evidence usually cited is that BD bodies cannot be maintained indefinitely; rather, they inexorably and imminently deteriorate to cardiovascular collapse despite the most aggressive therapy and resuscitative efforts. The BD literature, right up to the present, is replete with statements to this effect,[16-21] such as the following (emphases added):

> Even with extraordinary medical care, these [somatic] functions cannot be sustained indefinitely—typically, *no longer than several days* (President's Commission) (p. 35).[13]
>
> Despite all efforts to maintain the donor's circulation, irreversible cardiac arrest usually occurs *within 48 to 72 hours* of brain death in adults, although it may take as long as *10 days* in children. Indeed, general acceptance of the concept of brain death depended on this close temporal association between brain death and cardiac arrest (p. 816).[22]
>
> What was clearly established in the early 1980s was that no patient in apneic coma declared brain dead according to the very stringent criteria of the United Kingdom code . . . had ever failed to develop asystole *within a relatively short time*. That fundamental insight remains as valid today as it was 20 years ago—and not only in the United Kingdom but throughout the world (preface to second edition).[23]

It is important to distinguish between this line of reasoning and a conflation of prognosis of eventual death with diagnosis of present death. As David Lamb eloquently explained:

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From the Department of Pediatrics, Division of Neurology, UCLA Medical School, Los Angeles, CA.

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Address correspondence and reprint requests to D. Alan Shewmon, MD, Department of Pediatrics, Division of Neurology, UCLA Medical Center, MDCC 22-474, Box 951752, Los Angeles, CA 90095-1752.

When evidence is cited to show that, despite the most aggressive support, the adult heart stops within a week of brainstem death and that of a child within two weeks, one is not marshalling empirical support for a *prediction* of death. What is being said is that a point has been reached where the various subsystems lack neurological integration and their continued (artificial) functioning only mimics integrated life. That structural disintegration follows brain death is not a contingent matter; it is a necessary consequence of the death of the critical system. The death of the brain is the point beyond which other systems cannot survive with, or without, mechanical support (emphasis in original; pp. 36–37).[24]

Recent literature and collective personal experiences, however, cast serious doubt on this long-standing doctrine.

Methods. An attempt was made to compile all known cases of BD with survival of 1 week or longer through personal experiences of the author and other professionals, collection of articles, and systematic database searches. Melvyl Medline (UCLA) was searched on the key word "brain death" over the entire history of BD (1966 to 1997), yielding 12,219 articles. An article was examined if either title or abstract suggested a possible case of prolonged survival. News media were surveyed through the World Wide Web and Lexis-Nexis on key words "brain death," "pregnancy," and "life support," using a variety of search engines and Lexis-Nexis libraries.

Cases were selected if BD was formally diagnosed according to customary criteria. In the medical articles and personal sources the basis for diagnosis was usually thoroughly documented. From the news stories great care was taken to include only cases in which BD had been formally declared by (presumably) competent physicians, not merely journalistic hearsay in which the reporter might have confused BD with vegetative state or coma. Articles typically stated physicians' names, specialties, and institutions. Often the diagnosis was confirmed by multiple physicians, including at least one neurologist or neurosurgeon. Many articles mentioned results of confirmatory tests or described circumstances comprehensible only if the cases truly involved formal declarations of BD (e.g., that organ donation was proposed to the family).

Despite the internationality of cases, diagnostic criteria were fairly uniform. In most, a US-style "whole-brain" standard was employed. A few cases involving the British "brainstem" standard were nevertheless included because the intrinsic survival capacity of a BD body should not be affected by possible residual cortical function in the context of a dead brainstem. Moreover, the purported imminence of asystole is cited as much by British proponents of "brainstem death" as by US proponents of "whole-brain death."

As much information as possible was collected about each case and compiled into an Excel (Microsoft; Seattle, WA) spreadsheet for statistical analysis and graphical representation. The following data categories were of particular interest: survival duration, age at BD, etiology, clinical signs essential to the diagnosis, confirmatory tests, associated clinical findings (e.g., diabetes insipidus, nonpurposeful movements), terminal event (spontaneous asystole versus treatment withdrawal), reason for prolonged support, miscellaneous details (e.g., pregnancy outcome, transfer from hospital), city, patient identification, and source(s) of information. If patient names were public knowledge, they were included; otherwise, cases were identified as in their original reference or by code.

To study the extent to which associated systemic injuries, rather than brain destruction per se, might limit survival potential, etiologies were divided into two categories depending on whether the primary insult was restricted to the brain or also affected multiple organs.

Data were analyzed with Kaplan-Meier survival curves. Terminal event (spontaneous asystole versus treatment withdrawal or ongoing survival) distinguished "deaths" from "censored data" according to Kaplan-Meier methodology. Survival curves of age and etiology subgroups were statistically compared using the Mantel-Haenszel (log-rank) test. Some partitionings of data were also evaluated by the chi-square test. There is no pretension that these cases constitute a random or representative sampling of the entire BD population; the statistical techniques were strictly for exploratory purposes within the set of cases collected.

Results. Combined sources yielded approximately 175 cases of BD with survival of at least 1 week (the approximation stemming from two articles that reported survival durations grouped as mean and standard deviation[25,26]). The data for these cases, which constitute an integral part of this article, are available in two tables, along with references and 270 footnotes, from the National Auxiliary Publications Service (NAPS) (see Note at end of text). The distribution of sources was as follows: author's personal experience (2 cases), other professionals (6 cases), medical literature (approximately 154 cases), nursing literature (2 cases), bioethics literature (2 cases), court transcripts (2 cases), and newspapers or news wire services (17 cases, about which 79 articles were obtained). The stated total of approximately 175 is less than the sum of the foregoing numbers because of overlap among sources.

For purposes of meta-analysis, three cases were excluded due to extreme paucity of information and one due to lack of certainty of diagnosis (Rosemarie Maniscalco, whose case occurred before diagnostic standardization by the President's Commission[13] and in whom some residual EEG activity of uncertain significance reportedly returned). An additional approximately 115 cases with reliable diagnoses, though of considerable interest for survival duration, were unsuitable for meta-analysis because of insufficient individual data (most reported as grouped statistics). One table on file with NAPS itemizes these approximately 119 segregated cases, whereas the other contains the remaining 56 cases subjected to meta-analysis (see Note at end of text). The case of Tracy Bucher, known through the news media, and that of "Sheila" (a pseudonym) in a nursing article had so many features in common that they were assumed to be the same patient. Although itemized separately in the NAPS table, they were analyzed as a single case.

A few cases featured diagnostic controversy at the time of occurrence but were nevertheless included for meta-analysis because, in the author's opinion, the evidence strongly favored BD. These controversies arose many days into the clinical course and revolved around the interpretation of return of muscle tone or certain spontaneous or

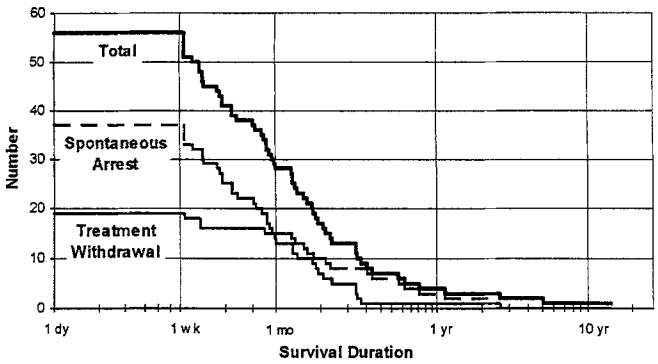

Figure 1. Survival curve for the 56 cases subjected to meta-analysis ("Total") subdivided according to terminal event—spontaneous cardiac arrest or treatment withdrawal.

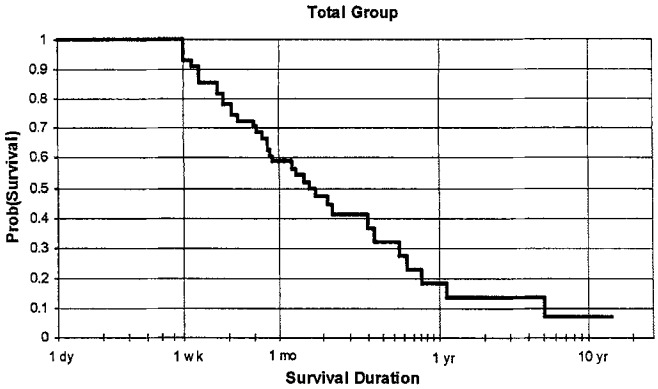

Figure 2. Kaplan-Meier survival curve corresponding to figure 1 (with the 19 treatment withdrawals and 1 still surviving patient analyzed as "censored" data) representing probability *of survival as a function of duration of brain death.*

reflex movements (Camp, Rader, "TK"), including ineffectual respiratory-like movements on rare occasions ("Baby A," "TK"). Both spontaneous trunk and limb movements[27-29] and respiratory-like movements[30,31] have been described as spinal cord-mediated phenomena in well-documented cases of BD and are explicitly compatible with the diagnosis according to the American Academy of Neurology.[4] Therefore, the diagnostic disputes engendered by such movements were not considered in themselves sufficient grounds to reject a case from the current study, especially because criteria for BD were incontrovertibly fulfilled early in the patients' courses (when organs could have been legally removed or life-support terminated and the later controversies never have arisen).

Survival durations. Of the approximate total of 175 BD patients surviving at least 1 week, approximately 80 survived at least 2 weeks, approximately 44 at least 4 weeks, approximately 20 at least 2 months, and 7 at least 6 months. Even excluding the 14 cases known only through news media or mentioned merely in passing in medical articles, there remained approximately 161 documented survivals of at least 1 week, approximately 67 at least 2 weeks, approximately 32 at least 4 weeks, approximately 15 at least 2 months, and 7 at least 6 months.

The 56 cases with sufficient individual information for meta-analysis are shown in figure 1 as actuarial survival curves for the whole group and for the two subgroups distinguished by terminal event: those supported indefinitely until spontaneous cardiac arrest (36 cases plus 1 still surviving) and those from whom treatment was withdrawn (19 cases). The longest survivals were so great (up to 14.5 years) that a logarithmic scale was required to fit everything meaningfully on a single chart. The drop-off of all three curves was biphasic, with an initially rapid exponential decay followed by a very slow decline, the transition occurring around 4 to 6 months.

Most treatment withdrawals (15/19; 79%) occurred after 4 weeks, whereas spontaneous arrests were widely distributed across survival durations, with slightly more than one-half (21/37; 57%) before 4 weeks. Chi-square testing revealed a window of statistical significance for placement of the survival-duration partition between 21.5 and 38.5 days, with maximum significance at 28.5 days ($p = 0.006$). If support had hypothetically been continued in the withdrawal subgroup, the overall survival curve would have been shifted up and to the right by unknown extents. This uncertainty can be taken into account statistically by regarding the treatment withdrawals as "censored" data in Kaplan-Meier methodology, analogous to patients lost to follow-up or still alive at data collection in a typical survival study. Accordingly, the three curves of figure 1 transformed into the single Kaplan-Meier curve of figure 2, in which the 36 spontaneous arrests constitute the vertical steps and the 20 censored cases (19 withdrawals and 1 still surviving) modify the probability level at each step. The resulting curve is a better indicator of intrinsic survival *capacity* than those of figure 1. Note that it has shifted markedly to the right, with the first phase (still nearly linear on the semilog plot, but with shallower slope corresponding to a half-life of 2 to 3 months) extending as long as 1 to 2 years, before the second, more gradual, phase sets in.

Age effect. Figure 3 shows a scatter plot of age at BD versus log(duration) for all 56 cases. The longest survivors (2.7, 5.1, and 14.5 years) were all young children, two of whom were newborns, and all nine survivors beyond 4 months were younger than 18 years. Conversely, all 17 patients over age 30 survived less than 2½ months. The inverse relationship between age and maximum survival duration was nearly linear on the semilog plot.

Age also influenced the proportion of treatment withdrawals, most of which involved adult patients. An age-partition

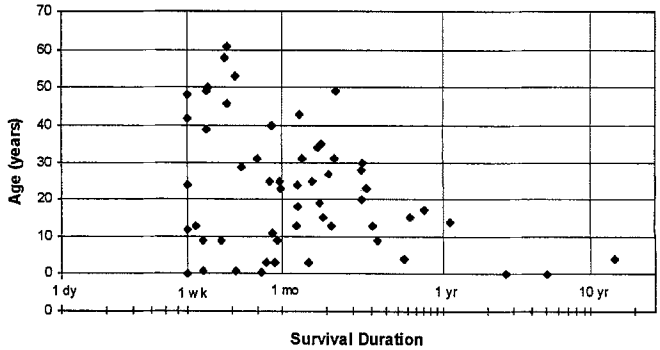

Figure 3. Scatter plot of age at brain death versus log-(survival duration) shows inverse relationship between maximum survival and age.

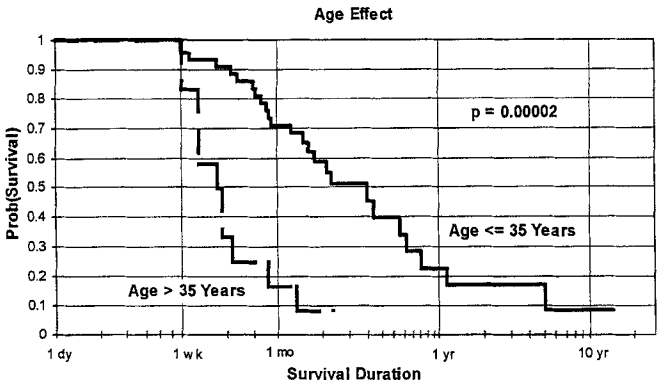

Figure 4. Kaplan-Meier curves show the effect of age at brain death on survival capacity: patients at or below age 35 years survived significantly longer than did those over 35.

anywhere between 13 and 22 years yielded a statistically significant chi-square test, with maximal significance at age 14; older than this, 47% of cases (16/34) ended by treatment withdrawal compared with only 14% (3/22) for age 14 or younger ($p = 0.01$).

Upon defining treatment withdrawals as censored data, Kaplan-Meier curves for "young" and "old" subgroups differed significantly for age-partitions placed anywhere between 27 and 57 years. The higher the partition, the more divergent the survival curves (that of the older subgroup shifting more to the left). Figure 4 exemplifies this with a partition at 35 years, where statistical significance was greatest ($p = 0.00002$).

Etiology. The distribution of etiology category was as follows: primary brain pathology (24), diffuse systemic insult (24), and uncertain (8). Chi-square testing revealed a region of statistical near-significance ($p = 0.07$) for survival-duration partitions placed between 40.5 and 48.5 days, below which the majority of cases with known etiology category (17/28; 61%) had multisystem insult and above which the majority (12/18; 67%) had primary brain pathology. This etiology effect was not accounted for by age as a proxy variable because a separate plot of etiology versus age revealed no relationship between the two.

Nevertheless, age and etiology interacted as determinants of survival probability. Figure 5 shows a scatter plot of log(age) versus log(duration) according to etiology category. The association of primary brain pathology with longer survivals and diffuse pathology with shorter survivals is evident; but the two extremes of age clearly constitute notable exceptions to this general trend. The two newborns (lower right corner) had very long survivals despite etiologies of severe hypoxia-ischemia. By contrast, older adults had shorter survivals regardless of etiology.

Because the age effect was statistically overpowering at both ends of the age spectrum, the contribution of etiology was best appreciated in the large age group between these two extremes. Exploratory analysis was performed by systematically varying its upper and lower bounds and comparing the Kaplan-Meier curves for the two known etiology categories within it. There was a broad region approximately defined by a lower age limit between 1 month and 2 years and an upper age limit anywhere from 13 to 48 years within which primary brain pathology was significantly associated with longer survival than multisystem insult.

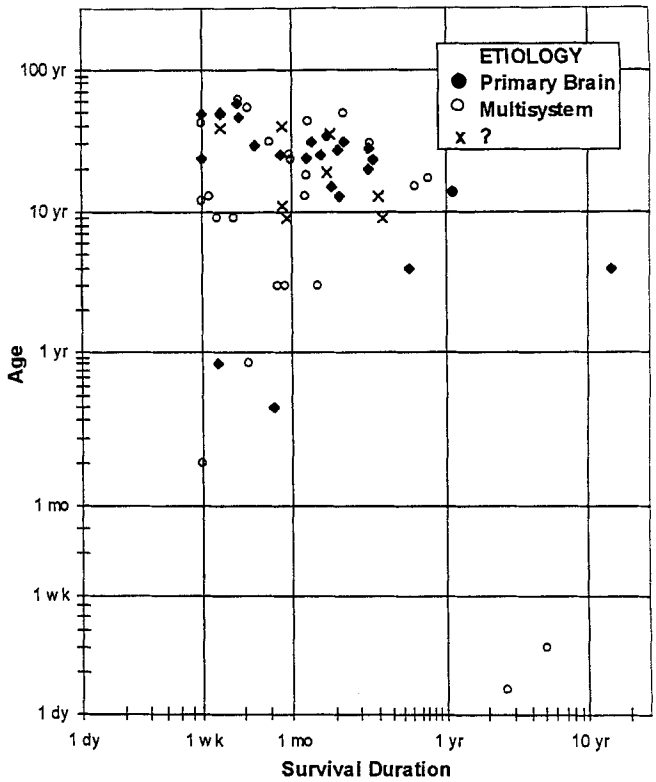

Figure 5. Scatter plot of log(age) versus log(duration), broken down according to etiology category, illustrating the interaction between age and etiology of brain death as co-determinants of survival capacity. Overall, primary brain pathology was associated with longer survivals and multisystem insult with shorter, but at the extremes of age, the effect of etiology was overshadowed by that of age.

The greatest significance was for an age group between a lower bound of 5 to 9 months and an upper bound of 43 to 45 years ($p = 0.005$), as illustrated in figure 6.

Within the category of primary brain pathology, the independent effect of age was even more powerful than it was across combined etiologies. Comparisons of survivals above and below an age-partition placed anywhere between 22 and 49 years were statistically significant (maximally so between 34 and 45 years, $p = 0.0000003$), with

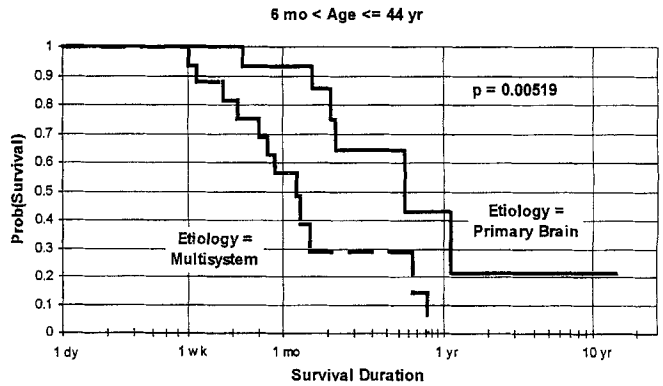

Figure 6. Etiology effect abstracted from age effect by excluding extremes of age. Kaplan-Meier curves show that primary brain pathology is significantly associated with longer survival capacity than multisystem insult.

the younger subgroup manifesting considerably longer survivals than the older subgroup. This striking effect remained even after excluding extremes of age. Parallel comparisons within the multisystem category could not be meaningfully accomplished due to small numbers and excessive inhomogeneity of data.

Discussion. Contrary to popular belief, there are many well-documented BD cases with survival beyond the "few days" typically cited as maximum possible. An exhaustive search yielded approximately 175 cases surviving 1 week or more.

Validity of cases. Naturally, the amount and quality of information varied tremendously, inviting the criticism of possible misdiagnoses. But even in cases with least information, formal diagnoses were unquestionably rendered by presumably competent physicians, usually including at least one neurologist or neurosurgeon. If patients were "brain dead" enough to qualify as organ donors, they were surely "brain dead" enough to qualify for this study. To dismiss the cases as presumptive misdiagnoses would imply that organ donors are also often misdiagnosed and that BD declarations are inherently unreliable. Even excluding news stories, many striking examples remain of unequivocal BD confirmed by multiple clinical examinations, EEGs, intracranial blood flow, and necropsy findings.

Undoubtedly, more cases of prolonged survival have occurred than have been reported, and many more *potential* cases have never been manifest because BD is nearly always a self-fulfilling prophecy of somatic demise through organ harvesting or discontinuation of support.[18,32] (Thus, the small proportion of prolonged survivals among all BD cases in no way diminishes their conceptual importance. The relevant denominator—the number supported maximally until asystole—is unknowable but surely also small; therefore, the meaningful ratio is not nearly so tiny as it might initially seem.)

Enough information was available on 56 cases for meta-analysis of factors affecting survival capacity. Although detailed inferences must be viewed cautiously, the general conclusions are robust and extremely relevant to whether BD represents loss of somatic integrative unity.

Durations of survival. Of the meta-analyzed cases, one-half (28/56) survived more than 1 month, nearly one-third (17/56) more than 2 months, seven (13%) more than 6 months, and four (7%) more than 1 year, the record being 14½ years (and still going).

If many of these cases have been in the medical literature for some years, how did the "few days at most" dictum ever become so firmly entrenched? Frequently cited is a 1978 multidisciplinary conference, in which:

> No investigator contributing to this volume has presented evidence that irreversible cardiac arrest may be postponed more than a week (exclusive of that in infants and children), and most often these final irreversible changes occur prior to 48 and even 24 hours after brain death (p. 27).[12]

That observation carries little weight, however, given the lack of systematic attempt to maintain BD patients aggressively to determine survival capacity. The same disclaimer applies to the landmark review article that same year by Black,[33] one section of which equated the very *essence* of BD with "inevitable bodily death."

Another oft-cited study involved 609 BD cases from three neurosurgical units during the 1960s and 1970s.[34] Again, it is difficult to draw conclusions regarding intrinsic survival capacity from this and from similar but smaller studies[23(p 30)] because patients who did not succumb quickly to asystole (nearly one-half of the 609) were typically disconnected from support. Unfortunately for BD research, ethical patient management is incompatible with optimal scientific methodology. Studies permitting organ donation are particularly unhelpful because the best donor candidates have the most intact organs and therefore also the greatest survival potential, which never becomes manifest; by contrast, patients with very unstable hemodynamics or multisystem failure are typically rejected as donors, thereby biasing outcomes toward early asystole.

Furthermore, neuro-intensive care has improved substantially since those pioneering studies. Some aspects then would be considered substandard today[20,35]; therefore, the apparent imminence of asystole is no evidence for limited *intrinsic* survival capacity.

Given that BD pregnant women have been maintained for months and that Japanese teams have supported BD patients extensively as far back as 1984[36] and virtually indefinitely with hormonal therapy,[25,26,37,38] it is difficult to interpret the dismal survival data from a recent Taiwanese prospective study of "brain-stem dead" patients given "full cardiorespiratory support."[39] Perhaps more interinstitutional variation in "fullness of support" exists than is generally recognized.

Finally, one cannot help wondering to what extent philosophical bias and sheer inertia of tradition may have contributed to perpetuating the anachronism despite increasingly abundant published counterevidence.

Terminal event. The data collected here actually *underestimate* BD survival potential because in one-third of cases support was withdrawn. Approximately 4 weeks into BD there was a statistically significant transition in the proportion of treatment withdrawal versus spontaneous asystole, with 79% of withdrawals after, and 57% of spontaneous arrests before, that time.

The most straightforward reason could be called "somatic plasticity." The acute loss of all brain-based somatic regulation predisposes to cardiovascular collapse. But those who survive gradually stabilize: homeostasis adjusts, hemodynamic status improves,

enteral nutrition can be resumed, and overall management simplifies. This may be largely attributable to recovery from spinal shock, with return of spinally mediated autonomic tone and reflexes. Such tendency to stabilization seems strong evidence for integrative unity.

There also may be two subpopulations of BD patients: those absolutely unstable (possibly although not necessarily because of lack of integrative unity) and those relatively stable (implying some minimal degree of integrative unity). Supporting evidence, inferred from the relationship between etiology and survival duration, will be considered in the following.

Perhaps the circumstances of treatment withdrawal in many cases (especially cesarean delivery of a fetus brought to viability) merely happened to entail a several week latency.

Regardless of the interpretation, the main point remains incontrovertible: BD does *not necessarily* lead to imminent asystole. At least *some* bodies with dead brains have survived chronically, and many others must have an unrealized potential to do so.

Age factor. Age and survival capacity were inversely related. Adults treated indefinitely all succumbed to spontaneous arrest within 4 months. By contrast, children seemed capable of surviving virtually indefinitely. The three most spectacular survivors—with durations of more than 2 years—were all young children, two being newborns. This age effect is not surprising. In general, children have more robust health than do the elderly, and if the concept of somatic plasticity is valid, children must have more of it than adults, just as they have more neuroplasticity.

Complexity of care required. Seven very unusual cases prove that complex technology and extraordinary clinical effort are not always necessary for prolonged survival.

Of the two cases known personally to the author, "BES" was an almost-14-year-old head-trauma victim who, after several weeks in an intensive care unit (ICU), was transferred at the parents' request to a skilled nursing facility. There he received nothing more than mechanical ventilation, desmopressin acetate, parenteral fluids, and basic nursing care. Hardly any laboratory tests were obtained. Survival was cut short at 65 days by untreated sepsis.

The other ("TK") is now an 18½-year-old boy who contracted *Haemophilus influenzae* meningitis at age 4. Cerebral edema was so extreme that the cranial sutures split. Multiple EEGs have been isoelectric, and no spontaneous respirations or brainstem reflexes have been observed over the past 14½ years. Multimodality evoked potentials revealed no intracranial peaks, magnetic resonance angiography disclosed no intracranial blood flow, and neuroimaging showed the entire cranial cavity to be filled with disorganized membranes, proteinaceous fluids, and ghost-like outlines of the former brain. He is fed by gastrostomy, and for the last 6 years has been thriving *sui generis* on a ventilator at home.

Five other cases transferred to nursing facilities (Chamberlain, "Baby A") or home (Hamilton, the case of Pinkus, "Baby Z") similarly exemplify how chronic survival in BD does not necessarily require "heroic," "aggressive," or "sophisticated" technology.

Several Japanese studies teach a similar lesson. By merely adding vasopressin to epinephrine, mean survival times in BD increased to 23 days.[38] With pressor rather than antidiuretic doses of vasopressin, stable hemodynamics were maintainable in all patients seemingly indefinitely, and the epinephrine requirement gradually decreased.[25,37] Similar results have been obtained with cortisol and triiodothyronine.[26] Because these studies were prospective, prolonged survivability seems representative of BD patients in general, not merely rare anecdotal exceptions. For such simple treatments to permit virtually indefinite survival, the underlying somatic substrate must be considerably integrated already.

Even in the acute phase, the effort required to sustain most BD patients is not particularly extraordinary for contemporary ICU standards. That many actually need much less sophisticated management than many other ICU patients who are nevertheless quite alive argues strongly that the former possess integrative unity to at least the same degree as the latter.

Such relative simplicity of treatment contrasts markedly with the technologic tour de force typically described with pregnant BD women. Plausible explanations for the discrepancy are differences in clinical stage (before versus after recovery from spinal shock) and therapeutic goal. The treatment regimen for a pregnant woman is not merely the minimum to sustain her own body, as in other BD cases (often with minimal enthusiasm of the health care team); rather, it is directed toward maintaining an optimal physiologic environment for the developing fetus (and with great enthusiasm). Thus, complexity of management in the pregnancy cases does not indicate lack of unity in BD bodies in general.

Etiology factor. If some BD patients can survive apparently indefinitely with relatively simple interventions, why do others deteriorate quickly to asystole despite aggressive therapy? The heterogeneity suggests a difference in *somatic* substrate, contradicting the brain-as-somatic-integrator hypothesis, because the difference between two subgroups (imminence versus nonimminence of asystole) cannot derive from what is common to both (lack of brain function).

Apart from age, one possible somatic factor is direct multisystem injury. Listings of etiologies in the BD literature often obscure this. For example, "head trauma" is a commonly stated category, but motor vehicle accidents or severe falls are much more likely to damage internal viscera than are gunshots to the head. Similarly, one should not attribute to "loss of neural integration" a downward hemodynamic spiral actually caused by cardiac contusion or hypovolemic shock.

For current purposes, therefore, etiologies were

classified as either "primary brain" or "multisystem." Longer survivals (more than 6 weeks) were associated with primary brain pathology, and shorter survivals with multisystem insults. Excluding age extremes, etiology and age were independent and additive determinants of survival capacity. (At extremes the age effect predominated. Thus, babies "A" and "Z" had very long survivals despite an etiology of perinatal asphyxia. Conversely, older adults had shorter survivals regardless of etiology.)

A second possible somatic factor is systemic pathology secondarily induced by sympathetic storm from the process of brain herniation *before* BD and not attributable to mere absence of brain function afterward. Complications include transient severe hypertension, neurogenic pulmonary edema (manifested by difficulty maintaining oxygenation), and subendocardial infarctions (manifested by refractory hypotension, cardiac arrhythmias, and arrest).[40,41] These are common with serious neurologic injuries in general, so they are hardly surprising in cases culminating in BD. Neurogenic pulmonary edema and subendocardial microinfarcts have been described in experimental BD,[42,43] human BD autopsies,[44] and ICU management of organ donors.[21,35] Additionally, disseminated intravascular coagulation occurs commonly with severe head injury and in 25 to 65% of BD organ donors.[21,45] Gastrointestinal hemorrhage from neurologically induced stress ulcers can also complicate management.

The rapid, inexorable deterioration in a minority of BD patients (only approximately 10% of prospective organ donors[21,35]) is therefore less attributable to absence of brain function per se than it is to supracritical damage to *multiple organs*, especially the heart. Indeed, transplant specialists ironically consider cardiovascular stability a relative *requirement* for heart donation.[20,35] Conversely, BD patients with least hemodynamic stability have the least usable hearts due to intrinsic cardiac pathology.

These considerations are elegantly summarized in a book chapter entitled "Multisystem sequelae of severe head injury" (significantly *not* about BD):

> Head injury cannot be considered an isolated, single-system injury. Head-injured patients frequently sustain other organ trauma. Equally important are the multisystem effects of trauma to any part of the body and the unique effects of head trauma on the hypothalamic-pituitary axis, which influences such diverse pansystemic functions as blood coagulation, pulmonary venular tone, gastric acid secretion, renal water conservation, and glucose metabolism . . . quality functional survival obviously depends on attention to these multisystem derangements (p. 702).[45]

Ironically, in a chapter on head injury these "multisystem derangements" are interpreted as therapeutic challenges to keep a critically injured patient alive, whereas in a typical chapter on BD the same derangements are cited as evidence that the patient had already died.

Conclusion. The phenomenon of chronic BD implies that the body's integrative unity derives from mutual interaction among its parts, not from a top-down imposition of one "critical organ" upon an otherwise mere bag of organs and tissues. If BD is to be equated with human death, therefore, it must be on some basis more plausible than that the body is dead. Whether other rationales, such as loss of "personhood" from a biologically live body, might be conceptually more viable or desirable for societal endorsement is beyond the scope of this physiologic inquiry.

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