Differences in Cerebral Blood Flow and Glucose Utilization in Vegetative Versus Locked-in Patients

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Positron emission tomographic studies of regional cerebral metabolic rate for glucose (rCMRGlc) and cerebral blood flow were performed in 7 vegetative and 3 locked-in patients to determine objectively the level of brain function underlying these clinical states. Cortical gray rCMRGlc in the vegetative patients was 2.73 ± 0.13 (mean ± SEM) mg/100 gm/min, less than half the normal value of 6.82 ± 0.23 ($p < 0.001$). Cerebral blood flow exhibited similar but more variable reductions. By contrast, cortical rCMRGlc in the locked-in patients was 5.08 ± 0.69, a 25% reduction ($p < 0.02$) from normal. The massive reduction in vegetative rCMRGlc involved not only the cerebral cortex but also the basal nuclei and cerebellum. Such metabolic hypoactivity has precedent only in deep anesthesia and supports clinical evidence that cerebral cognitive function is lost in the vegetative state, leaving a body that can no longer think or experience pain.

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Recent technological advances make it possible to rescue many critically ill patients who only a few years ago might have died. Some recover completely, but for others, survival means spending years or decades limited by severe brain damage. The vegetative state [1, 2] following severe cerebral disease or injury is the worst degree of functional brain damage compatible with prolonged survival. Behavioral evidence of learned cerebral function is lost, and only automatic, reflex brain activity remains. Published pathological studies [3, 4] have shown extensive neuronal loss in the cerebral hemispheres, especially affecting the cortex, hippocampus, and thalamus. Except for cerebellar Purkinje cells, subtentorial structures are relatively spared. The distribution and severity of postmortem anatomical damage to the cerebral hemispheres can vary considerably in vegetative patients [4], making it difficult to infer on pathological grounds alone whether or not all self-awareness was lost during life. Such uncertainty can be resolved only by additional objective measures of brain function in these patients.

The locked-in state [5] superficially resembles the vegetative state but raises additional questions about diagnostic accuracy and clinical management. Well-informed families sometimes ask whether a patient who clinically appears vegetative might instead be locked in. The clinical distinction is almost always straightforward and based on the ability of locked-in patients to communicate using coded eye movements. Objective laboratory evidence distinguishing cerebral function in vegetative versus locked-in patients would provide valuable reassurance to clinicians and families alike.

The present study involved positron emission tomographic (PET) measurements of regional cerebral blood flow (rCBF) and glucose metabolic rate (rCMRGlc) in 7 vegetative and 3 locked-in patients. The results indicate that cerebral metabolism and, to a less consistent degree, blood flow in the vegetative state fall to an extremely low level. Cerebral metabolism in the locked-in state, by contrast, was significantly higher and approached that of the normally working

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Table 1. Clinical Features of Patients with Altered Consciousness

Patient No.	State	Age	Sex	Cause	Interval[a]
1	Vegetative	43	F	Arrest[b]	3 wk
2	Vegetative	25	F	Anesthesia-hypoxia	68 mo
3	Vegetative	57	F	Arrest[b]	5 wk
4	Vegetative	54	M	Arrest[b]	8 wk
5	Vegetative	27	F	Asphyxia	30 mo
6	Vegetative	17	M	Trauma	9 wk
7	Vegetative	40	M	Arrest[b] and Wernicke's encephalopathy	4 wk
8	Locked in	39	F	Central pontine myelinolysis	5 mo
9	Locked in	29	F	Trauma	14 wk
10	Locked in	45	F	Trauma	13 mo

[a]Time from the insult to the positron emission tomographic scan.
[b]Cardiac and/or pulmonary arrest.

F = female; M = male.

forebrain. The results provide strong support for the clinical diagnosis of these conditions and have important humanistic and ethical implications.

Patient Material

Table 1 lists the diagnoses of 7 vegetative and 3 locked-in patients. The median interval from insult to PET scan was 12 weeks (range, 3 weeks to 68 months), and the median age was 39 years (range, 17 to 57 years). All vegetative patients had intact corneal and pupillary light reflexes, all opened their eyes and blinked spontaneously, and all had sleep-wake cycles. Three (Patients 1, 3, and 4) had roving conjugate eye movements at the time of the scan, and 4 (Patients 2 and 5 to 7) appeared at times to direct their gaze toward auditory or visual stimulation. No vegetative patient could maintain eye contact or consistently follow movement. Some had localizing (Patient 7) or withdrawal (Patients 1 and 3) responses to pain, but 4 patients (Patients 2 and 4 to 6) still postured abnormally. No vegetative patient followed commands, mimicked movements of the examiner, or signaled by eye movements. No vegetative patient spoke, and only 1 (Patient 3) vocalized. The Appendix contains individual details of the patients. Normal subjects recruited from the medical and neighboring community served as controls. All subjects underwent physical and neurological evaluation, and those found to be normal then underwent a series of psychological tests to confirm the lack of any cognitive deficit. The median age of 18 subjects used as rCMRGlc controls was 26 years, and the median age of the 6 rCBF control subjects was 24 years.

Methods

The experimental protocol was approved by institutional review boards at New York Hospital–Cornell Medical Center and at Memorial Hospital Sloan-Kettering Cancer Center, where the PET scanner and cyclotron are located. With informed consent from responsible guardians and with the assent of normal subjects and patients 8 through 10, studies of rCMRGlc and (for Patients 1 through 6 and 8, and normal subjects) rCBF were obtained as follows.

Catheters were first inserted into a distal artery for blood sampling and into an arm vein for administration of radiopharmaceuticals. Patients and normal subjects were placed in a custom-molded polyurethane head holder to ensure accurate and reproducible head positioning. The head was positioned by centering the intersection of two perpendicular Gammex lasers at the intercanthal midpoint. The intersection of the horizontal laser with the head holder was marked, and the position and height of the mobile scan table were measured in millimeters to facilitate repositioning for a subsequent coplanar computed tomographic (CT) scan. Nine transaxial PET sections 10 mm thick and measuring 11.5 mm center to center were reconstructed with a resolution of approximately 10 mm [6]. A CT scan was subsequently obtained using the same head position, section thickness, and section separation. Subsequent region of interest (ROI) analysis was performed on 128 × 128 PET reconstructions with corrections for random coincidences, tissue attenuation (using a transmission scan), and electronic dead time. The scanner was corrected for inhomogeneities, and a cross-calibration factor reflecting relative sensitivity of the scanner and well counter was determined before each study. The following 15 irregular ROIs were drawn with reference to the CT images: cerebellum, brainstem, midbrain, basal ganglia, thalamus, hippocampus, lateral temporal lobe, operculum, posterior temporal lobe, medial frontal lobe, lateral frontal lobe, calcarine cortex, cuneus, inferior parietal lobe, and paracentral frontal lobe. Values for the last 10 ROIs from each hemisphere were combined as representative of cortical gray matter, which is known [4] to be damaged in posthypoxic vegetative patients.

rCBF was measured first because of the short half-life of ^{15}O (2 minutes) relative to that of the ^{18}F (2 hours) used in the subsequent rCMRGlc measurement. $CO^{15}O$ mixed in air was administered via nasal prongs or, when necessary, an endotracheal tube, at a flow rate adjusted to deliver 15 mCi/min. The eyes were covered, and music was played through acoustically isolated earphones. After 8 minutes of inhalation, when a steady state was approached, blood sampling and scanning began. Arterial $CO^{15}O$ activity was measured

in 2-ml specimens collected automatically at a rate of 0.1 ml/sec throughout the sampling time. Four PET frames were acquired at 1-minute intervals using the PC 4600 positron camera. Midway through the imaging sequence, blood was sampled for arterial blood gas measurement.

For rCBF, a composite 4-minute scan was constructed. Count rate images were converted to units of rCBF using the algorithm of Lammertsma and co-workers [7]. To represent the maximal rCBF for each ROI and minimize noise, the rCBF assigned was the mean of the pixel values in the upper portion (20%) of the range from zero to the maximal pixel value for that region, a modification of a thresholding technique described previously [8, 9]; for our patients this yielded 30 to 40 thresholded pixels in most of our ROIs.

After a time equal to six ^{15}O half-lives beyond the end of $C^{15}O$ inhalation, ^{18}F-fluorodeoxyglucose (FDG) in 10 ml normal saline was infused intravenously over 30 seconds. ^{18}F-FDG was produced by a method described by Ginos and associates [10]. The ^{18}F-FDG was always greater than 97% radiochemically pure, with a specific activity of 5 to 7 mCi/μmole. Approximately 5 to 10 mCi ^{18}F-FDG was administered to each patient. Throughout the ^{18}F-FDG study patients and normal subjects remained blindfolded; music and occasional verbal briefings were delivered to the earphones, a paradigm that reduced the chance that normal subjects might sleep and enhanced compliance by avoiding total sensory deprivation.

Blood radioactivity was measured by counting 10 2-ml arterial blood samples collected automatically at a rate of 0.1 ml/sec every 18 seconds for the first 3 minutes, followed by manual sampling at minutes 5, 7, 10, 15, 20, 25, 30, 40, 50, and 65. For computation of compartmental rate constants, 21 serial PET images were obtained from all but 2 patients (5 and 9): the first 10 were 1-minute scans, and the next 5 were 2-minute scans, followed by 3 5-minute and 3 10-minute scans. Three plasma glucose samples were measured during the study. Compartmental rate constants k_1 (influx), k_2 (efflux), and k_3 (phosphorylation) were determined from the time course of blood and regional brain activity [11] using a thresholding strategy in the final 10-minute (minutes 55 to 65) scan similar to that described above.

For rCMRGlc, count rate images in the 45 to 55-minute scan were converted to units of rCMRGlc using a standard value of the lumped constant (0.42) and the mean of each patient's own cortical rate constants, according to the algorithm of Phelps and co-workers [12]. The rCMRGlc assigned to each ROI was calculated using a thresholding method. For Patient 5, the mean rate constants for Patients 1 through 4 were used, and for Patient 9, those from Patient 8 were used.

Most statistical analyses used the two-tail Student's *t*-test. When individual ROIs were compared, a Bonferroni correction based on 15 ROIs was applied to the data. As a measure of regional variability, the population standard deviation for rCMRGlc measurements in each patient's cortical ROIs was normalized by dividing by the mean cortical gray rCMRGlc for that patient. Regional variability in the different groups was then compared using Student's *t*-test applied to these normalized statistics. As a measure of interpatient variability, the *F* test for variance was applied to the mean cortical gray rCMRGlc. Linear regression was used to test for correlations between rCMRGlc and interval between insult and PET study and between rCBF and $PaCO_2$.

Results

In the 18 normal volunteers stimulated with music, rCMRGlc in the cortical gray matter (all brain ROIs except posterior fossa structures, the thalamus, and basal ganglia) was 6.82 ± 0.23 (mean ± SEM) mg/100 gm/min. The cortical gray rCMRGlc in the 7 vegetative patients was reduced by more than 60% to 2.73 ± 0.13 mg/100 gm/min ($t = 10.7$, $p < 0.001$; Table 2). Each individual value fell several standard deviations below the range of normal, consistent with profound reduction of metabolic activity in the cerebral hemispheres. The highest cortical gray rCMRGlc in the vegetative population was 3.18 mg/100 gm/min (Patient 7), 45% lower than the lowest of the 18 normal cortical rCMRGlc measurements (5.69 mg/100 gm/min). There was no relationship between rCMRGlc and the interval from insult to PET study ($r^2 = 0.02$, not significant [NS]). The overall depression of rCMRGlc reflects a generally uniform reduction in rCMRGlc in individual brain regions (Figs 1, 2). The cerebellum in the 7 vegetative patients had a higher rCMRGlc (3.46 ± 0.40) than did the cortical gray matter, but even this structure showed a reduced rCMRGlc (normal, 5.63 ± 0.19; $t = 5.5$, $p < 0.02$, Bonferroni).

By contrast with the vegetative patients, the locked-in patients showed only moderately depressed rCMRGlc (5.08 ± 0.69; $t = 2.8$, $p < 0.05$; Table 2 and Figs 1, 2). Patient 8, who was most cognitively intact by bedside testing, had normal rCMRGlc in every region, with a mean cortical gray rCMRGlc value of 6.45; Patients 9 and 10 had depressed rCMRGlc values, but their cortical gray values for rCMRGlc of 4.38 and 4.40, respectively, were still higher than the highest value in the 7 vegetative patients (3.18 in Patient 7).

Figure 1 suggests that the regional cerebral variability for rCMRGlc in the locked-in patients was similar to that of the 18 normal subjects and that regional variability was blunted in the 7 vegetative patients. The normalized population standard deviation, however, was the same for both vegetative patients and normal subjects. Similarly the interpatient variability in the mean cortical gray values for vegetative patients and normal subjects was not significantly different.

Metabolic rate constants were determined for Patients 1 through 4, 6 through 8, and 10 (Table 2). The phosphorylation rate constant, k_3, in 6 vegetative patients (0.040 ± 0.003) was significantly lower than that in 18 normal subjects (0.083 ± 0.007; $t = 3.5$, $p < 0.01$). The rate constant for influx (k_1) was also lower than normal, although this difference was less marked (0.064 ± 0.008 in 6 vegetative patients versus 0.084

Table 2. Cortical Gray Metabolic Rate Constants, Glucose Metabolic Rate, and Cerebral Blood Flow in Patients with Altered Consciousness

State/ Patient No.	K_1[a]	K_2[a]	K_3[a]	rCMRGlc (mg/100 gm/min)	rCBF (ml/100 ml/min)
Vegetative					
1	0.058	0.184	0.048	2.27	22.1
2	0.052	0.114	0.049	2.80	18.8
3	0.053	0.142	0.035	2.74	18.8
4	0.075	0.136	0.035	2.94	29.5
5	...	...	...	2.27	17.7
6	0.049	0.135	0.041	2.89	23.8
7	0.072	0.128	0.032	3.18	22.1
Mean	0.064[c]	0.140	0.040[d]	2.73[e]	21.8[e]
SEM	0.008	0.010	0.003	0.13	1.5
Locked in					
8	0.093	0.134	0.081	6.45	31.9
9	...	...	...	4.38	...
10	0.069	0.125	0.063	4.40	...
Mean	0.081	0.130	0.072	5.08[c]	31.9
SEM	0.012	0.004	0.009	0.69	...
Normal[b]					
Mean	0.084	0.108	0.083	6.82	42.7
SEM	0.004	0.013	0.007	0.23	1.2

[a]Kinetic rate constants used in calculating rCMRGlc.
[b]Based on 18 subjects for kinetic constants and rCMRGlc and on 6 subjects for rCBF. Significance versus normal controls (Student's *t*-test): [c]$p < 0.05$; [d]$p < 0.01$; [e]$p < 0.001$ (without a Bonferroni correction).

rCMRGlc = regional cerebral metabolic rate for glucose; rCBF = regional cerebral blood flow.

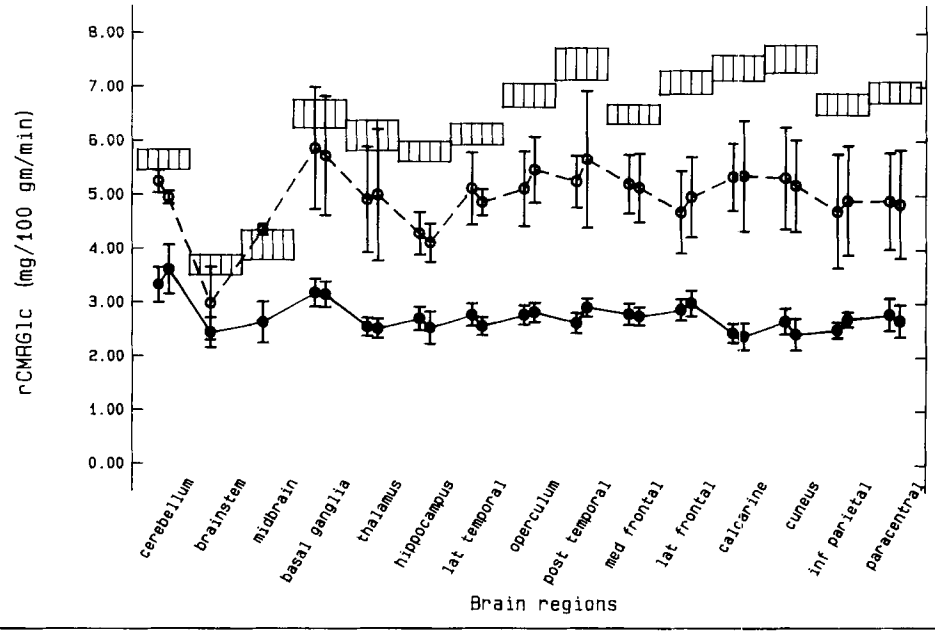

Fig 1. Cerebral metabolic rate for glucose (rCMRGlc) *in different brain regions of normal, vegetative, and locked-in patients. For all regions except the brainstem and midbrain, the symbol to the left represents the left-sided structure and that to the right, the right-sided structure. The hatched boxes are mean ± SEM for 18 normal subjects. Circles and error bars are the mean ± SEM; solid circles represent 7 vegetative patients and open circles, 3 locked-in patients. lat = Lateral; post = posterior; med = medial; inf = inferior.*

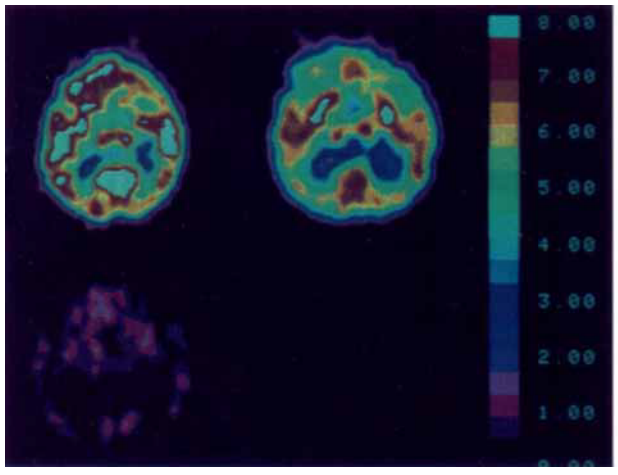

Fig 2. Regional cerebral metabolic rate for glucose (mg/100 gm/min) shown in transverse sections through the thalamus and basal ganglia of a normal brain (top left), *locked-in brain* (top right; *Patient 8), and vegetative brain* (bottom left; *Patient 1). Note the marked depression of metabolic rate in the vegetative patient.*

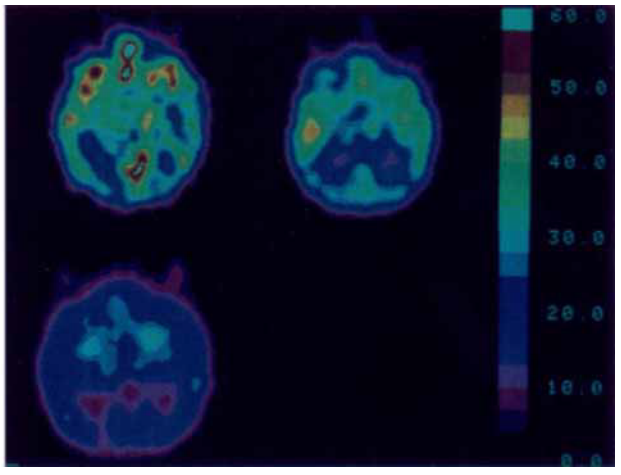

Fig 4. Regional cerebral blood flow (ml/100 ml/min) shown in the same transverse sections as Fig 2 through the thalamus and basal ganglia of a normal brain (top left), *locked-in brain* (top right; *Patient 8), and vegetative brain* (bottom left; *Patient 1).*

± 0.004 in 18 normal subjects; $t = 2.4, p < 0.05$). By contrast, the rate constant for efflux (k_2) was similar in vegetative and normal subjects.

rCBF (Table 2, Figs 3, 4) was depressed in the vegetative patients but not in the single locked-in patient studied (no. 8). Cortical gray rCBF in 6 normal subjects was 42.7 ± 1.2 ml/100 ml/min, whereas the cortical rCBF of 7 vegetative patients was reduced by nearly 50% to 21.8 ± 1.5 ($t = 10.7, p < 0.001$). There was no relationship between rCBF and $PaCO_2$ ($r^2 = 0.02$, NS). $PaCO_2$ in the 7 vegetative patients was 37.3 ± 1.7 torr, a value similar ($p > 0.05$) to that in our 6 normal subjects (41.5 ± 1.1 torr). There was greater interpatient variability (F statistic 41.6, $p < 0.001$) in the vegetative cortical gray rCBF than in the vegetative cortical gray rCMRGlc. The locked-in pa-

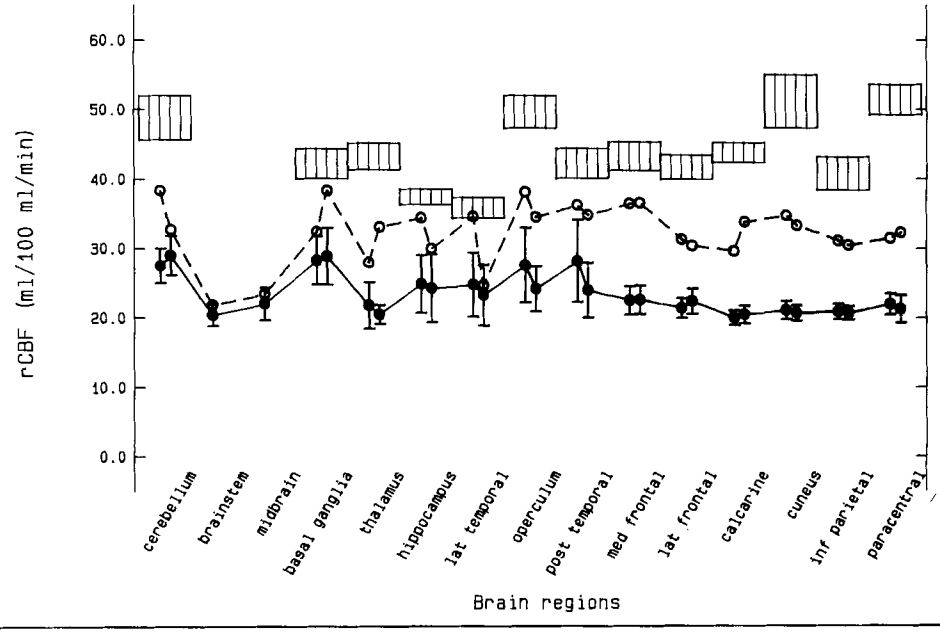

Fig 3. Cerebral blood flow (rCBF) *in different brain regions of normal, vegetative, and locked-in patients. For all regions except the brainstem and midbrain, the symbol to the left represents the left-sided structure and that to the right, the right-sided structure. Hatched boxes are mean ± SEM for 6 normal subjects. Circles and error bars are means ± SEM; solid circles represent 7 vegetative patients and open circles, one locked-in patient (thus no error bars). No determinations of brainstem or midbrain rCBF were made in the normal subjects. lat = Lateral; post = posterior; med = medial; inf = inferior.*

tient had a cortical gray rCBF of 31.9 ml/100 ml/min ($PaCO_2$ 42 torr), a value midway between the vegetative patients and normal subjects.

Discussion

These PET results demonstrate a profound reduction of cerebral glucose metabolism in vegetative patients. The changes involved not only the cerebral cortex but also the basal nuclei and the cerebellum, with which these higher centers normally intereact. Furthermore, no metabolic overlap occurred between vegetative patients and either normal or locked-in persons.

Several factors could affect interpretation of these data. Our thresholding technique minimizes the influence of cerebrospinal fluid (CSF) spaces and thus cerebral atrophy on calculated values for rCMRGlc and rCBF. In fact, correction methods for cerebral atrophy suggested by Herscovitch and associates [13] could not be applied to individual regions of interest, as used in our calculations [14]. Although the degree of CT-estimated cerebral atrophy in the vegetative patients varied widely (minor in Patients 3 and 6, studied 1 month after the insult, to marked in Patient 2, studied after 68 months), the low rCMRGlc was similar among our patients and correlated neither with the duration of the vegetative state nor the size of the CSF spaces. Even for patients with marked cerebral atrophy, the size of the CSF space on CT scan was not great enough to account for the reduction in rCMRGlc.

Although several patients were febrile, this appears not to have influenced the results. Patient 6 had a temperature of 39.8° C during the scan but an rCMRGlc within 1 SEM of the mean of the entire group (Table 2). In most biochemical systems, metabolism increases by about 10% with each degree Celsius [15], and one might expect such a biochemical effect even in organs with marked damage. Although most investigators studying temperature effects on brain metabolism have investigated body temperatures no higher than 38° C [16], a study by McCulloch and coworkers [17] showed increased rCMRGlc in rats subjected to core temperatures above 40° C. Temperature was not measured during the PET study in all patients, but we found no apparent relationship between rCMRGlc and temperatures measured the same day. A correction for temperature in our febrile vegetative patients would have lowered the calculated rCMRGlc even more than reported. For example, such a correction in Patient 6 would have lowered the cortical gray value from 2.89 to 2.00 mg/100 gm/min.

One must emphasize the importance of comparing results in the study patients directly with those in normal control subjects examined under similar environmental conditions using the same experimental protocol. Different laboratories calculate rCMRGlc and rCBF values in different ways, under different conditions, and for different regions, but our normal values generally lie within the range reported previously. Thus our cortical rCBF of 42.7 ml/100 ml/min in normal subjects is similar to normal values obtained with inhaled $CO^{15}O$ by Lebrun-Grandié and associates [18] and with intravenous $H_2{}^{15}O$ by Perlmutter and associates [19]. Likewise, our cortical rCMRGlc of 6.8 mg/100 gm/min compares closely with cortical gray values of 6.41 to 6.80 reported by Kuhl and coworkers [20] and whole brain values of 36.2 μmol/100 gm/min (6.52 mg/100 gm/min) reported by Heiss and co-workers [21].

Until recently, technical considerations have precluded obtaining information about the regional pattern of rCBF and metabolism in altered states of consciousness. Shalit and associates [22] measured global cerebral metabolic rate for oxygen at multiple times in 6 chronically vegetative patients after trauma or diffuse cerebral anoxia; values were 1.3 to 2.0 ml/100 gm/min (40 to 60% of normal). In a 1977 symposium [23], Ingvar and co-workers published results of supratentorial and infratentorial xenon blood flow measurements in a single vegetative patient, but no three-dimensional reconstruction was possible. Recently the Cologne group published a PET scan illustrating supratentorial metabolic rate in 1 vegetative patient depressed by about 30% [24] and in another lethargic and possibly vegetative patient with bilateral thalamic infarctions depressed by about 40% [25]. We [26] reported a mean rCMRGlc value of 3.83 mg/100 gm/min in a 23-year-old patient with aplastic anemia who became vegetative and died after whole body irradiation and systemic amphotericin B prophylaxis. Two recent reports of rCBF in coma [27, 28] using ^{133}xenon washout techniques cannot easily be compared to the present data because the patients were studied within only a few days of head trauma. In these studies, variability of rCBF was noted; some patients had reductions in flow and others had hyperemia.

The residual low level of cerebral metabolism in the vegetative state could reflect several conditions. One is that a common proportion of all parenchymal elements, including neurons, glia, and blood vessels, are spared and functioning. More likely, however, is that the activity largely reflects the nutrient requirements of residual glial and vascular elements. Herz and Schousboe [29] suggested that neuronal activity might account for 50 to 60% of normal brain metabolism. Our rCMRGlc data are consistent with substantial loss of functioning neurons, and our kinetic rate constants further support this inference. The cortical gray phosphorylation rate constant (k_3) in our vegetative patients (0.040) differs markedly from the gray matter k_3 in our 18 normal subjects (0.083; $p < 0.01$) but is not significantly different from the white matter k_3 in our 18 normal subjects (0.063). It is even closer to the white matter k_3 reported by Heiss and co-workers

[30] (0.039 to 0.051). Similarly, the cortical gray influx rate constant (k_1) in our vegetative patients (0.064) lies midway between our normal gray matter k_1 (0.084) and our normal white matter k_1 (0.044); it is even closer to the k_1 of Heiss and associates [30] (0.048 to 0.059). With both k_1 and k_3 moving closer to white matter values in our vegetative patients, these changes are consistent with pathological evidence [3, 4] of extensive neuronal loss in gray matter.

rCBF in cortical gray matter was also depressed in the vegetative patients but with more interpatient variation. This greater variability of rCBF than rCMRGlc could reflect either dissociation between parenchymal flow and metabolism as observed in patients in acute coma [31] or different patterns in response to injury, which are known, for example, to include neovascularization.

No relationship of blood flow or metabolism to interval after insult emerged in this study. The two vegetative patients examined more than one year after onset had the lowest and the median rCMRGlc values, respectively, and two of the three lowest rCBF values. The two vegetative patients studied within 4 weeks of insult had the lowest and highest rCMRGlc values, respectively, and the median rCBF values. Similarly, variability in $PaCO_2$ cannot explain differences in rCBF.

The results of this metabolic study of vegetative and locked-in patients have important clinical implications. Behavioral criteria buttressed by knowledge of the nature and extent of neurological injury gained from clinical and laboratory studies indicate that patients in the vegetative state lose all conscious awareness, including the capacity to experience pain and suffering. Nevertheless, some of these patients can display a considerable amount of organized behavioral activity in response to sudden or noxious stimuli. Nearly all regain sleep-wake cycles; many display the facial appearance of interest; and some even show emotional fluctuations with occasional infant-like tearing or smiling in response to nonverbal stimuli. Although none follow moving objects consistently, some occasionally move the eyes slowly toward visual stimuli. Others blink inconsistently to visual threat, startle or close the eyes in response to sudden noises, or demonstrate reflex groping or sucking. Uncertainty among families and even some professionals that such behavior originates entirely in instinctive reflexes can be difficult to counter solely on the basis of clinical experience and known facts about prognosis [2, 32, 33].

The clinically diagnosed vegetative state was accompanied in this study by profound cerebral metabolic depression, with no overlap in cortical gray rCMRGlc between vegetative and normal subjects. The mean cortical rCMRGlc reduction of 60% in our vegetative patients far exceeds the 13% decline reported during nondreaming sleep in normal persons [21]; it even exceeds the 30 to 50% decline seen in most experimental [34–36] and clinical [31, 37] studies of anesthesia. The finding offers little support to therapeutic enthusiasts who claim that the vegetative state is simply a form of sleep that constant stimulation can reverse. Similar degrees of cerebral metabolic depression have been reported previously only in deep barbiturate anesthesia [31]. When taken together with clinical evidence of chronicity, the 50 to 60% reduction in metabolic rate found in vegetative patients offers strong evidence that such bodies can no longer either think or experience pain or suffering.

The present data reemphasize the dreadful plight of locked-in patients. Behavioral evidence has always suggested that despite their profound motor loss, these persons feel, think, and experience anguish in close to a normal way. The metabolic findings support that inference and stress the need for great compassion and sensitivity when caring for such unfortunate persons.

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Appendix: Case Reports

Patient 1

A 43-year-old woman suffered cardiopulmonary arrest several days after a gynecological procedure. Intubation and ventilation were started at home by paramedics. In the hospital, her pupils reacted to light at 3 mm, and she withdrew from noxious stimuli bilaterally. Corneal reflexes were present, but spontaneous eye movements were absent, and she gave no response to command or verbal stimuli. Spontaneous breathing returned within several days, and her eyes opened spontaneously on the third hospital day, but she did not improve further. PET study was performed 3 weeks after the arrest, at which time she was receiving no neuroactive medications. At that time, she had intact pupillary light reflexes, corneal reflexes, oculocephalics, and breathing but had only roving conjugate eye movements and neither spoke nor obeyed commands. An electroencephalogram (EEG) showed generalized disorganization and a background of theta activity with some superimposed sharp activity. A CT scan showed mild cerebral atrophy. She died unchanged 3 weeks after the PET study. Postmortem examination showed diffuse neuronal loss in the cerebral cortex and thalamus.

Patient 2

A 25-year-old woman suffered cardiopulmonary failure during a gynecological procedure. Initially, she had no motor response to noxious stimulation, but the pupils reacted, and she breathed intermittently. On day 2, she developed extensor posturing to stimuli, and oculocephalic responses returned. By day 3, she showed roving conjugate eye movements and grimaced in response to supraorbital pressure. Phenytoin was given to treat myoclonus beginning 2 weeks after the onset of coma. Her neurological status changed little in the ensuing 68 months. At the time of her PET scan, she breathed regularly, opened her eyes spontaneously, and blinked normally. She occasionally shifted her eyes toward movement in the room but made no eye contact and neither vocalized nor followed command. Her pupils were 4 mm, regular, and light reactive; corneal reflexes were present.

Oculocephalic stimulation elicited conjugate but only partial contraversive eye movements, and oculovestibular testing elicited tonic deviation with a few beats of superimposed nystagmus (what we have called a tonic atypical response [32]). Noxious stimuli elicited flexion in all extremities except her right leg, which extended. Her phenytoin level at the time of the PET study was 23 μg/ml. An EEG was slow and disorganized, and brainstem auditory evoked responses (BAERs) showed bilateral absence of the first wave, suggesting end organ damage. Magnetic resonance and CT scans showed generalized cerebral atrophy. She remains unchanged one year later.

Patient 3

A 57-year-old woman with two past mitral valve replacements collapsed pulseless on the street but responsed to cardiopulmonary resuscitation and mechanical ventilation. At the hospital, she exhibited no motor response to noxious stimuli. Pupillary light reactions and corneal reflexes were present, and she had full oculocephalic responses. Spontaneous breathing soon returned, and by 3 weeks she appeared to look toward visitors in the room and was vocalizing sounds but no words. At the time of her PET scan, 5 weeks after the arrest, her eyes opened spontaneously and she made noises, but despite hours of observation, no words could be identified. She did not follow commands, and noxious stimuli caused only withdrawal. She had roving conjugate spontaneous eye movements, full oculocephalic reflex responses, and intact pupillary and corneal reflexes. She received no neuroactive medications. A CT scan showed multiple white matter lesions consistent with infarcts plus enlarged ventricles and cerebral sulci. Two months after the PET study, she began to speak recognizable words but no comprehensible phrases. She neither followed commands nor responded emotionally to family members. She died elsewhere 6 months after the PET scan without ever having recognized or interacted with anyone, including family members. No postmortem examination was performed.

Patient 4

A 54-year-old man was revived from asystole during a surgical procedure. Within days, his eyes opened spontaneously and he blinked. His pupils and corneas reacted sluggishly, and he had no motor response to noxious stimulation. Oculocephalic and oculovestibular maneuvers produced only full conjugate lateral eye deviation. At the time of PET scan 8 weeks after the arrest, he had roving conjugate eye movements, but he did not follow environmental movement. Pupillary and corneal responses were active, and noxious stimuli elicited only a partial flexion response in both arms. He was on no neuroactive medications. A CT scan showed moderate ventricular and sulcal enlargement but no focal abnormalities. An EEG showed background disorganization with diffuse theta and delta activity. On a BAER study, there were no discernible waves after wave III, indicating an abnormality rostral to the midpons. The patient died 2 weeks after the PET scan; permission for postmortem examination was denied.

Patient 5

A 27-year-old woman attempted suicide by hanging but responded to cardiopulmonary resuscitation. Within hours, she made respiratory efforts but had no motor responses to noxious stimuli. Her pupils were 3 mm, irregular, and reacted sluggishly to light. Corneal reflexes were diminished, and there were no spontaneous eye movements, but her eyes moved laterally to oculocephalic stimulation. By 12 hours, her eyes opened and she blinked spontaneously, and by 2 days, she developed spontaneous roving conjugate eye movements. Her arms flexed to nail bed compression and extended to supraorbital pressure. At 6 months and thereafter, her eyes appeared intermittently to follow movement in the room. At the time of PET scan, 30 months after the hanging, the neurological signs remained unchanged. EEG was disorganized but contained some posterior alpha activity. She was on no neuroactive medications. Reports from another institution indicate that her condition has not changed in the 2 years since the study.

Patient 6

A 17-year-old man suffered head trauma from a motor vehicle accident. At a local hospital, he was unresponsive, had no corneal reflexes, and had midposition pupils that were fixed to light. Extensor posturing was observed. A CT scan showed punctate hemorrhages in the brainstem, left thalamus and occipital horn, and right basal ganglia. Corneal reflexes appeared on day 3, pupillary reaction to light was first recorded on day 7, and roving conjugate eye movements on day 16. An EEG after 4 weeks showed generalized slowing over both cerebral hemispheres, and a BAER 2 weeks later was normal. At the time of the PET scan, 9 weeks after trauma, his eyes opened and sleep/wake cycles were observed. He responded to neither verbal nor written commands and failed to manipulate environmental objects placed in his hands. His eyes moved conjugately, and they inconsistently appeared to be directed toward noise on either side of the bed. Pupillary, corneal, and oculocephalic reflexes were present. His arms were tonically flexed, and his legs, extended. Supraorbital pressure elicited flexor posturing in both arms, but locally delivered noxious stimuli produced no response. No clinical change has been noted after a further 3 months.

Patient 7

A 40-year-old man had received renal hemodialysis for 5 years after rejecting a transplanted kidney. During a dialysis in the hospital, he suffered asystole and was resuscitated. Initially, the effect of diazepam and barbiturates given to control generalized seizures and multifocal myoclonus interfered with clinical evaluation. He did, however, have round, 4-mm light-reactive pupils and brisk oculocephalic responses. He had extensor posturing to noxious stimuli, but he lacked corneal reflexes until day 3. At the time of the PET scan, 4 weeks after the arrest, clinical seizures had stopped, but occasional stimulus-bound myoclonic jerks remained. He had Cheyne-Stokes respirations, brisk pupillary, corneal, and oculocephalic responses, and nonlocalizing responses to noxious stimuli. He followed neither written nor oral commands. At times, he appeared to gaze briefly toward auditory or visual stimuli. At the time of the PET scan, a phenytoin level was 9.4 μg/ml, and a clonazepam level was 12.8 ng/ml. The ^{18}F-FDG and rCBF scans were done on successive days for technical reasons. He died 5 days after the ^{18}F-FDG scan. At postmortem examination, hyperacute ischemic changes

were found in the cortex, more chronic changes in the cerebellum, and neuronal loss and gliosis in the mamillary bodies and thalamus, suggesting Wernicke's encephalopathy, a condition recently described [38] in patients undergoing dialysis.

Patient 8

A well-nourished, healthy 39-year-old woman acutely developed fever and headache and over several days lapsed into coma. Examination elsewhere showed roving horizontal conjugate eye movements, intact pupillary responses, and bilateral extensor posturing. A lumbar puncture was normal, but a subsequent CT scan revealed a lesion in the right pons. Within several days, she became afebrile and opened her eyes. Gradually she regained voluntary eye movement and, by way of codes using eye movements, was found to have an intact memory and the capacity to read. Her pupils reacted normally to light, and she voluntarily opened her mouth but had bifacial pareses and lacked tongue movement. She was unable to move her limbs to command. Noxious stimuli produced flexor posturing, but she perceived pain in all extremities. Magnetic resonance scans demonstrated a low pontine lesion, consistent with central pontine myelinolysis (Fig 5). She underwent a PET scan 5 months after the onset of her illness. At that time, she had no control of movement in the face, tongue, or limbs and could not vocalize. By eye movement code, she could demonstrate full orientation and the ability to read and calculate. She had intact pupillary light reflexes and facial sensation. CSF was normal. Except for dexamethasone, 0.75 mg/day by gastrostomy (started elsewhere), she was on no neuroactive medications. She was discharged to a rehabilitation facility. After 18 months of further treatment she remains quadriplegic and aphonic; laughter has been noted at times. She communicates by directing her gaze to letters on a letterboard and has demonstrated full orientation and intact, syntactically correct language. Her attention span is limited to 15 minutes, and she has difficulty solving problems.

Patient 9

A 28-year-old woman lost consciousness in a motor vehicle accident. Examination on day 3 showed coma, a left third nerve palsy, preserved corneal reflexes, and extensor posturing to noxious stimuli. A CT scan showed hemorrhage in the midbrain tegmentum and subthalamic region. Twelve weeks after the head injury, she grimaced to supraorbital pressure and had flexor posturing on the right and extensor posturing on the left. Her left pupil was fixed at 7 mm, and the right pupil was 6 mm in diameter but reacted to direct and consensual light. She had no corneal reflexes but had good oculocephalic responses with her right eye. After another week of observation, she began to move her right eye horizontally on command and smiled to song. Within another few days, she was able, intermittently, to signal yes/no with an eye code or to blink when asked. She never developed consistent responses to command. The PET scan was performed 14 weeks after the accident; only rCMRGlc was measured. At the time of PET study, she was on antibiotics and had been on atenolol (which was withheld for 24 hours before the PET scan). She died 3 weeks later; permission for postmortem examination was denied.

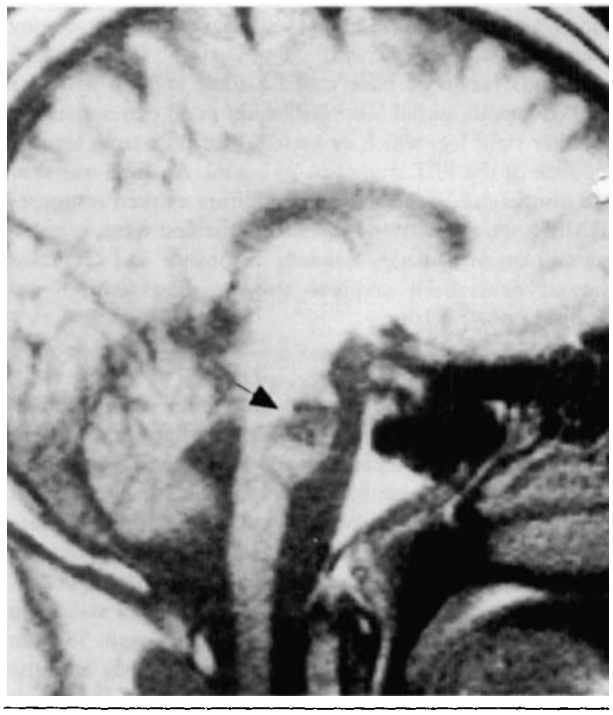

Fig 5. Magnetic resonance image (T1-weighted; TE = 32 msec, TR = 500 msec) in the midsagittal plane of Patient 8 showing an area of decreased signal intensity in the basis pontis (arrow), *consistent with central pontine myelinolysis.*

Patient 10

A 44-year-old woman, as a result of a motor vehicle accident, had a Glasgow coma score of 4 and a CT scan that showed diffuse edema and a brainstem hemorrhage. She was reportedly in a vegetative state for at least 6 months, but after approximately eight to ten months, health workers noted that she intermittently followed commands using her left arm or eyes. When we evaluated her 13 months after the accident, she had a spastic quadriplegia but retained some voluntary movement in the left hand. Her pupils were 3 mm and reacted briskly to light. Corneal reflexes were present, as were full horizontal oculocephalic responses. Nevertheless, to command, she gazed to the right or left, intermittently blinked, and protruded her tongue. Using code, she could select her name from a list of names and within one day of establishing the code, could protrude her tongue 4 times when asked to indicate the square root of 16. She rapidly learned to manipulate a letter board with her left hand and was soon spelling syntactically correct sentences. She complained of diplopia, which was apparently a premorbid strabismus. Cognitive testing was limited by her physical impairment, but she scored well on most verbal tests, with a scaled score of 12 on the similarities subtest of the Wechsler Adult Intelligence Scale (bright average to low superior); however, she had difficulty with nonverbal tests such as Ravens Progressive Matrices. An EEG showed bilateral theta activity, but BAERs were normal bilaterally. A PET scan for rCMRGlc was performed 15 months after the accident. In the subsequent 10 weeks, the tracheostomy tube has been removed, the patient has become more facile using the letter board, and has produced markedly dysarthric speech.