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MRI and Neuropsychological Correlates of Carbon Monoxide Exposure: A Case Report

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A 45-year-old woman experienced long-term, chronic exposure to carbon monoxide in the restaurant kitchen where she was employed as a cook. After returning to the restaurant after 5 days off work, she noticed that her symptoms returned immediately; she then aired out the room and called the gas company. Approximately 6 hr after a leak was detected, the patient went to the hospital, where her carboxyhemoglobin was found to be within normal limits and results of a neurologic examination were described as normal. Based on her symptoms, the patient believed she had been exposed to CO for at least 1 year before the leak was discovered. Initially, she experienced flu-like symptoms, which eventually resolved. At the time of her first neuropsychological evaluation (17 months after the exposure was identified), her persisting complaints included difficulties in reading, writing, speaking and word retrieval. The test results were consistent with secondary frontal lobe dysfunction associated with subcortical disorders such as those seen after CO exposure. Results of a subsequent neuropsychological examination (29 months postexposure) showed slight improvement in performance, but her performance was still consistent with mild frontal/subcortical dysfunction. Although the initial screening of a brain magnetic resonance image (MRI) performed 15 months after the exposure was interpreted as being within normal limits, two subsequent blind reviews of the same scans identified multiple bilateral lesions in the basal ganglia, which were consistent with chronic CO exposure. We present this case as an example of the utility of MRI and neuropsychological examinations in detecting central nervous system dysfunction secondary to CO exposure. *Key words:* carbon monoxide, neuropsychology, toxicant-induced encephalopathy, neuroimaging, MRI, neurobehavioral methods. *Environ Health Perspect* 110:1051–1055 (2002). [Online 6 September 2002]
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Case Presentation

A 45-year-old white, college-educated, right-handed woman was referred to the Boston University Neurology Associates Neuropsychology Service by her neurologist. She was reportedly exposed to carbon monoxide while at work in a restaurant and suffered from subsequent changes in behavior and cognition. She was referred for an evaluation to rule out CO-associated central nervous system (CNS) dysfunction. She was initially seen on 15 April 1998.

According to the patient, she discovered that she had been exposed to CO in November 1996, when she came to work early, noticed the smell of gas, and called the gas company. She said that the gas company employee informed her that there were extremely high levels of CO in the kitchen where she worked as a restaurant cook. The patient went to the hospital approximately 6 hr after leaving her workplace on the day she called for help, but, at that time, her carboxyhemoglobin was reportedly not elevated and no focal neurologic signs were noted. She explained that she had been off work for 5 days and, immediately upon arriving at work the morning the leak was detected, she sought fresh air and did not have further exposure. The restaurant was then closed for 2 weeks so the furnace, which was the source of the CO fumes, could be replaced. The patient believed that CO had been leaking into her workplace for at least a year, given the duration of her symptoms.

We were unable to obtain a copy of the gas company reports on levels taken on the day that the leak was identified (the company refused to release them to us). Because no records were available on the levels of CO before the gas leak was identified, it was impossible to model the apparent chronic, long-term exposure to CO experienced by the patient. However, correspondence in the medical record and communication with the insurance company for the building in which the exposure occurred documented the existence of exposure.

The patient was not certain when her symptoms began, but she said that they peaked in January–April 1996. She reported feeling as though she had a severe case of flu (influenza). Her symptoms included being unable to walk straight, bumping into things, balance problems resulting in several falls, severe headaches that persisted 24 hr/day, exhaustion, ear problems (especially on the right), a "cloudy" sensation, an inability to talk clearly or to produce a full sentence, tingling or numbness in both thighs, difficulty hearing, irritability, brittle teeth, and pain in her face. The patient reported taking echinacea and golden seal to treat her symptoms, but in May 1996 she decided to consult a physician, who diagnosed a sinus infection and prescribed amoxicillin. She indicated that she stopped the herbs at that time, but when her symptoms became so severe that she could not finish the amoxicillin, she resumed taking the echinacea. The patient stated that the echinacea allowed her to "get through the day."

The patient said that after the identification of the CO exposure, most of her symptoms resolved. The only symptoms that continued to cause distress at the time of neuropsychological testing (17 months later) were difficulties in reading, writing, and speaking. She stated, for example, that she sometimes omitted a letter while writing a word. She also said that she sometimes had trouble finding a word that she wanted to say, and she sometimes mispronounced words.

The patient reported that her neurologist had ordered a magnetic resonance image (MRI) of the brain, which was read as normal, and that he then informed her that he could find no evidence that she had suffered a CO-induced encephalopathy; her neurologic examination was described as being normal.

Relevant History

The patient denied any history of birth trauma, hypertension, closed head injury, loss of consciousness, seizures, diabetes, or thyroid problems. She also denied ever having had asthma; although she reported being allergic to ragweed and grasses in her teens, she indicated that this allergy disappeared when she was in her 20s. She reported having had two allergic episodes after being exposed to chemical fumes; both episodes occurred after exposure to paint stain. She denied sensitivity to perfume, gasoline, or foods.

The patient provided the following information on her education and skills: she had received a full scholarship to college and had earned a bachelor's degree in fine arts; her best subjects in school were languages, reading, and writing, and her most difficult subject was higher math; her employment history included teaching and cooking. The patient reported that she had worked for 2 years at the restaurant where she was reportedly exposed to CO.

At the time of the evaluation, the patient stated that her mood was "good." The only medication she reported taking was ibuprofen, as needed, for knee pain, and she denied any significant history of drug or alcohol use.

Summary of neuropsychological functioning. **Time 1.** The patient's performance on neuropsychological tests on 15 April 1998 (Time 1; 17 months after exposure) was within the superior-to-very-superior range across most cognitive tasks. However, her performance was below expectations for estimated premorbid abilities on demanding tasks that assessed attention, learning, memory retrieval, and mood. Occasional attentional lapses, perseveration, sequencing problems, and slight concreteness were seen throughout testing. Some word retrieval problems were noted on confrontational naming, but her performance was generally aided by cues. Initial learning and retrieval of new information on tests of short-term memory was below expectation, given the patient's intellectual potential, and she displayed sensitivity to interference when completing memory tasks. Her responses to a mood inventory raised the possibility of some unacknowledged depressive symptomatology (Table 1).

Test results were suggestive of subtle frontal lobe dysfunction and were of the type seen in secondary frontal lobe deficit associated with subcortical disorders such as those involving the basal ganglia. The deficits observed were typical of those we have seen residually in patients with histories of chronic low level CO exposure not producing loss of consciousness.

Time 2. Neuropsychological testing was repeated on 28 April 1999 (Time 2; 29 months after exposure). Some variability was seen on Time 2 testing relative to Time 1, with increases in some scores and decreases in others. The patient continued to score below expectations for her premorbid very superior intellectual potential on challenging memory tasks that involved interference and on complex verbal reasoning tasks with executive system components. In addition, executive system signs, such as perseveration, pull to stimulus, and poor development of strategies, continued to be evident. Her performance diminished significantly on a test of psychomotor speed. Test results again revealed mild frontal/subcortical dysfunction. If anything, the pattern of frontal/subcortical difficulties was slightly improved from prior testing (Table 1).

Neuroimaging. An MRI of the brain performed on a GE Signa 1.5 Tesla scanner (General Electric Medical Systems, Milwaukee, WI) 26 February 1998 (15 months after detection of CO exposure) was read as normal by the radiology department where it was performed. We requested the original films for additional analyses because the neuropsychological findings were abnormal. The scan was independently read blind to history by two MRI experts at the VA Boston Healthcare System (Jamaica Plain campus), a board-certified neuroradiologist and a neuroscientist who does neuroimaging research. They concurred that the Fast Spin Echo MRI

Table 1. Neuropsychological test results.

Domain and neuropsychological test	Time 1	Time 2
General intelligence (premorbid estimate = very superior)		
WAIS-III		
Verbal IQ	135	130
Performance IQ	121	128
Full Scale IQ	132	133
Mini Mental Status Examination	29	30
Attention, executive function		
Attention Index, WMS-R	127	118
Digit Span		
WAIS-III		
Age-scaled score	17	17
Forward span (backward span)	8 (8)	9 (8)
Wisconsin Card Sorting Test		
Completed sets/number of trials	6/70	6/73
WAIS-III		
Arithmetic (age-scaled score)	14	15
Comprehension (age-scaled score)	16	13
Similarities (age-scaled score)	12*	12*
Letter-number sequencing (age-scaled score)	13	NA
Trail making test		
Trails A time (errors)	22 sec (0)	15 sec (0)
Trails A (percentile)	90th	> 90th
Trails B time (errors)	75 sec (1)*	48 sec (0)
Trails B (percentile)	50th–75th[a],*	75th–90th
Continuous performance test		
A errors	0	0
XI errors	0	0
Trails errors	1	0
Verbal, language		
WAIS-III		
Information (age-scaled score)	14	14
Vocabulary (age-scaled score)	18	16
Controlled Oral Word Association Test		
Number of words	56	40
Percentile	> 95%	60–64%
Categories (total, percentile)	NA	34, 10th–25th*
Motor (handedness: right)		
Finger tapping		
Right	59.8	58.0
Left	54.8	54.0
Grooved pegboard		
Right	55	67
Left	61	74
WAIS-III		
Digit symbol (age-scaled score)	15	11*

Continued, next page

[TR (time to radio frequency) = 6000; TE (time to echo) = 105/Ef] revealed multiple small lesions bilaterally in the basal ganglia (more severe in the globus pallidus than the putamen), which the radiologist reported to be consistent with chronic CO exposure (Figure 1).

Discussion

Carbon monoxide is a highly toxic, odorless, colorless, tasteless, and nonirritating gas. The most common causes of CO exposure are fires, faulty combustion heating systems, exhaust from internal combustion engines, and heating gases other than natural gas (1). When breathed in, CO competes with oxygen in the blood, binding to hemoglobin in place of the oxygen and interfering with the oxygenation of tissues. The affinity of CO to hemoglobin is approximately 200 times greater than that of oxygen, making it a very effective mechanism to displace oxygen (2). Although the neurotoxicant effect of CO exposure was initially believed to be a result of hypoxia secondary to the displacement of oxygen, it is now believed that additional mechanisms are involved, including the suppression of mitochondrial oxydatic respiration and cardiomyopathy, with the associated hypotension and systemic acidosis (1).

The most common pathological findings on MRI for patients with CO exposure include bilateral necrosis in the globus pallidus and bilateral hyperintensities in periventricular white matter (3,4). The white matter changes are thought to represent reversible demyelination (3). Vieregge et al. (5) reported that the white matter changes were more predictive of outcome than the globus pallidus changes. Although the vast majority of lesions reported in the literature are in the globus pallidus and white matter, lesions in other brain areas have been reported, including the hippocampus (6), thalamus, medial temporal lobe, cerebellum (1), parietal lobe, occipital lobe, and frontal lobe (7).

The early symptoms of CO exposure are not easily identified because they are nonspecific (1). Symptoms include nausea, headache, weakness, irritability, confusion, visual disturbances, parkinsonism, persistent vegetative state, akinetic mutism, agnosia, apraxia, confabulation, depression, delirium, and psychosis (8). Patients may present with flu-like symptoms or symptoms consistent with a bacterial or viral infection, and may, therefore, be misdiagnosed (8). As the level of exposure to CO increases, the level of consciousness decreases, further jeopardizing quick and accurate identification of the exposure (1) and potentially leading to coma or death. The relation of CO levels, serum carboxyhemoglobin levels, and symptoms were outlined by O'Donoghue (9) (Table 2).

CO exposure is somewhat unusual in that a person may have an initial change in consciousness due to the exposure, recover from the acute stage (or show no initial symptoms), be asymptomatic for several days to several weeks, and then have an exacerbation with neurologic and/or psychiatric symptoms. Choi (10) reported that of 2,360 patients examined for CO intoxication, 2.75% had delayed neurologic sequelae, and of the 549 of those patients who were admitted to the hospital, 11.8% had delayed neurologic sequelae. Choi (10) reported that the the patients were symptom-free for 2–40 days, with a mean of 22.4 days and a mode of 1–4 weeks. (It is noteworthy, however, that the patients in Choi's report were not administered neuropsychological tests, which are now generally regarded as being more sensitive to sequelae than physical/neurologic examinations.) The delay of onset of neurologic and neuropsychological symptoms is believed to be due to a progressive demyelination in the white matter (3).

The identification of CO exposure by laboratory tests is imprecise, making it difficult to determine the degree of exposure. The most commonly used physical marker is blood carboxyhemoglobin (HbCO) levels. The half-life of HbCO is 4–5 hr in room air free of CO (11) and 45–80 min when an individual has been at rest breathing 100% oxygen (11), making the utility of HbCO testing largely ineffective. Although serum HbCO levels, if elevated, do provide evidence of exposure to CO and, if precise time measurements are known, it can suggest the level of CO exposure, it does not reveal how severe the poisoning was, nor does it predict delayed sequelae (12). First, HbCO measurements reflect only the blood levels and do not indicate the degree of tissue involvement (13). Second, a longer-term exposure to one level

Table 1. Continued.

Domain and neuropsychological test	Time 1	Time 2
Visuospatial		
WAIS-III		
Picture completion (age-scaled score)	9*	14
Picture arrangement (age-scaled score)	10*	13
Block design (age-scaled score)	17	15
Matrix reasoning (age-scaled score)	14	17
Boston Visuospatial Quantitative Battery		
Qualitative findings	Large; poor spatial planning; sometimes works right to left*	
Rey-Osterreith complex figure test, copy		
Raw score (percentile)	35 (75th–99th)*	34 (75th)*
Memory		
WMS-R		
Attention index	NA	118*
General memory quotient	NA	128
Verbal-verbal paired associate learning, immediate recall		
Learning trials	2-0-0-4*	0-1-3-5*
Verbal-verbal paired associate learning, delayed recall		
Learning trials	2/10*	6/10
Delayed recognition span test, verbal		
Span, total	14, 14	14, 14
Recall (15 sec, 2 min recall)	6, 6*	7, 8
Forced choice recognition	12/14	12/14
Word Triads (Peterson)	15-14-7-7*	15-11-8-9*
Rey-Osterreith Complex Figure		
Immediate recall		
Raw score (percentile)	27 (75th)*	26.5 (50th–75th)*
Delayed recall		
Raw score (percentile)	25 (50–75%)*	25.5 (50–75%)*
California Verbal Learning Test		
Learning	6-9-9-14-13 (Total = 39)*	7-10-12-12-15 (Total = 46)*
Recognition (free recall, forced choice)	15,* 16	15,* 16
Clusters	3-3-1-5-4*	1-2-3-3-5*
Qualitative	Performance below expectation, perseverations; poor strategy*	
Motivation		
Test of memory malingering		
Trail 1	47	50
Trail 2	50	NA
Trail 3	50	NA
Minnesota Multiphasic Personality Inventory		
Description of results	Unacknowledged depression (all scales < 60)	

Abbreviations: NA, not available; WAIS-III, Wechsler Adult Intelligence Scale, Third Edition; WMS-R, Wechsler Memory Scale, Revised. Time 1, 15 April 1998; Time 2, 28 April 1999.
[a]Perceptual error. *Scores and impressions are below expectation.

of HbCO may result in more severe effects than a shorter-term exposure at the same level (11). Third, in clinical practice, patients do not always reach the hospital within 4–5 hr of exposure and precise time measurements are rarely known, making the assessment of HbCO levels insignificant. Indeed, Myers et al. (14) asserted that HbCO levels are "of little value in diagnosing either acute or chronic CO poisoning" (p. 564).

A second physical marker sometimes used to evaluate CO exposure is CO in exhaled air (11). This measurement can then be used to approximate HbCO levels in cases where a blood sample cannot be obtained.

A third physical marker involves brain MRIs. MRI findings can help to confirm that brain damage consistent with CO exposure has occurred, but the lesions are nonspecific and,

often, exposed individuals have lesions in brain areas other than globus pallidus or the white matter, complicating diagnosis. In addition, as was seen in the current case study, the small lesions resulting from CO exposure can be overlooked or interpreted as normal in a generalized radiologic evaluation. Neurologic examinations, too, often do not reveal the subtle changes in functioning that may be seen in CO exposure (12,14). A reliable physical marker to determine the extent of CO poisoning has yet to be found (13). Neuropsychological evaluation, however, has been advocated as a more sensitive and thus potentially useful tool to help with differential diagnosis of CO-induced encephalopathy (12–14).

A specific, distinctive pattern of deficits on neuropsychological testing has not been identified in patients with CO exposure (8,15,16).

Rather, a wide range of deficits has been reported. However, the majority of case reports have described deficits in memory (8,14–20), visuospatial functioning (8,14,16,17,21) and executive system functions (8,16,17), as well as depression (15). Additional neuropsychological findings in case reports of individuals exposed to CO include deficits in abstraction (8,14,19), tactual apprehension of complex stimuli (8), fine manual motor control (8,14), attention (8,15), cognitive processing speed (14,19,20), and psychiatric and behavioral symptoms (14,17,22–24).

Few case reports have been published regarding the neuropsychological effects of low-level (< 20% HbCO level), short-term exposure to CO, and those that have been reported show no effects or nonreplicable effects (8). McNulty et al. (13) reported that HbCO rates of < 10% are associated with exposure to CO that was too low to cause clinical symptoms. However, experimental studies have revealed transient deficits in functioning that are correlated with the severity and duration of exposure (2), even at low levels of exposure (5–10% HbCO; 100 ppm over 1–8 hr). These deficits can be detected in memory and subjective mood states (25); performance on divided attention tasks (26); driving skills (27); visual vigilance (28); performance on manual tasks (29); reaction times (30); and memory, visuomotor coordination, visuospatial functioning, and attention (31). Benignus et al. (32) asserted that none of the dose-effect studies of HbCO using behavioral responses have been replicated. However, they also pointed out that the studies of HbCO were mainly done with healthy young males at rest and may not generalize to other populations (32).

Although chronic (as opposed to short-term) low-level exposure may produce more notable neuropsychological deficits, it is rare to find reports in the literature of patients who
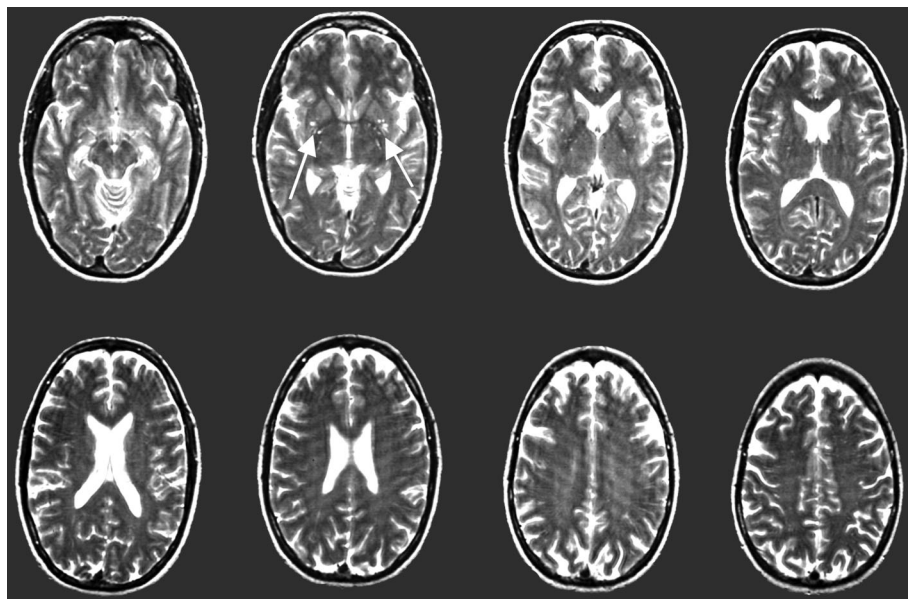

Figure 1. MRI of a 45-year-old woman exposed to CO. The MRI was performed 15 months after CO exposure was reported and revealed multiple small lesions bilaterally in the basal ganglia (arrows) consistent with chronic CO exposure.

Table 2. Human responses and approximate ambient CO air levels at various carboxyhemoglobin concentrations.

%HbCO	CO concentration producing HbCO saturation (ppm)[a]	Human responses and situations associated with HbCO levels
0.3–0.7	1–3	Normal range due to endogenous CO production
1–5	5–30	Selective increase in blood flow to compensate for reduced blood oxygen-carrying capacity; with advanced cardiovascular disease, cardiac reserve may be insufficient to compensate; major urban expressway CO levels may reach 25 ppm during peak traffic levels
5–9	30–60	Visual light threshold increased; chest pain occurs with less exertion in patients with angina pectoris; one to three pack per day cigarette smokers have similar HbCO levels
10–20	65–150	Slight headache; visual evoked response abnormal; may be lethal for those with severely compromised cardiac function; CO levels may exceed 100 ppm during weather inversions
20–30	150–300	Throbbing headache; fine manual dexterity abnormal; dizziness, hypernea, and palpitations with exertion
30–40	300–700	Severe headache; nausea; vomiting; confusion; increased heart and respiratory rates especially with exertion; syncope
40–50	500–700	Progressive worsening of all symptoms; vision, hearing, and intellect impaired; incoordination
50–60	700–1,000	Coma and convulsions
60–70	1,000–2,000	Coma, cardiorespiratory depression, lethal if untreated
94	10,000	Coma without headache, nausea, and vomiting
99	50,000	May induce fatal cardiac arrhythmia and death without significantly elevating carboxyhemoglobin

%HbCO, carboxyhemoglobin blood saturation. Data from O'Donoghue (9).
[a]Approximate CO concentrations producing sated blood HbCO saturation (ppm).

have CO exposure without loss of consciousness (*15*), which is more likely the case in a low-level exposure situation. Ryan (*15*) reported a case of a woman with a 3-year history of low-level CO exposure who demonstrated likely effects of the exposure including depression, difficulty tracking verbal information, and difficulty retrieving newly learned verbal and visual information. It may be that few clinical case reports of low-level exposure to CO are in the literature because, without loss of consciousness or independent identification of CO leaks, patients are misdiagnosed.

Recovery from CO exposure is variable, depending on the degree and chronicity of exposure (*8*). Although patients may recover spontaneously, it is rare (*15*). Smith and Brandon (*33*) reported that only 8 of 63 patients with acute CO poisoning improved after an average of 3 years, and 17 indicated that their memory had worsened. In contrast, Choi (*10*) reported that 59% of the 549 hospitalized patients with CO intoxication had recovered "without any sequelae," and 27 of the 36 hospitalized patients (75%) who showed delayed sequelae displayed recovery after 1 year, although 5 had persistent mild memory problems and 1 had parkinsonism. However, as mentioned above, the patients in Choi's study (*10*) were not administered neuropsychological tests, which may have revealed persistent deficits that were missed in a neurologic evaluation.

Conclusion

Although CO poisoning manifests itself in a variety of neuropathologic, neurologic, and neuropsychological sequelae, the most consistent findings include bilateral necrosis in the basal ganglia, bilateral hyperintensities in the periventricular white matter, headaches and other flu-like symptoms, memory disturbance, deficits in visuospatial functioning, and executive system signs. As discussed above, our patient displayed many of these more common signs and symptoms, including bilateral basal ganglia lesions, headache and flu-like symptoms, memory difficulties (specifically retrieval of newly learned information), and executive system dysfunction. Deckel (*17*) asserted that the frontal lobe deficits often seen in patients with CO exposure may be caused indirectly by disruption in the functioning of the basal ganglia as well as the white-matter tissue that connects the frontal lobes with other brain areas. The patient was seen in follow-up 1 year after the first testing to monitor any progression; at that time, no significant evidence of progression was seen.

This case provides further evidence that routine neurologic examinations may miss sequelae to CO exposure that can be picked up by careful neuropsychological evaluation. Even the routine clinical MRI reading missed the evidence of CO exposure. By administering a complete battery of neuropsychological tests to this patient with chronic, low-level exposure and no history of unconsciousness at exposure, a pattern of deficits was revealed that was similar to that often reported in the literature in cases of more severe CO exposures.

Findings in this case are typical of those we have seen in our clinic among patients with chronic CO exposure, no loss of consciousness, and positive MRI findings. The absence of documentation of chronic or acute levels of CO exposure is also typical, with detection of a leak leading to identification of faulty ventilation and CO exposure at home or in the workplace. In most of these cases, reliable documentation of acute levels of exposure on the day of detection are unavailable; in virtually none of these cases are chronic exposure levels available. In such situations, one must rely on clinical outcomes to document health effects of such exposures. This case is somewhat unusual in the clarity of the neuropsychological and neuroimaging findings, which we see in only a minority of patients referred for evaluation of possible effects of chronic or acute CO exposure without loss of consciousness.

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